CARLOS D. BUSTAMANTE, Ph.D.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

IPR2025-00028

IPR2025-00029

QIAGEN SCIENCES, LLC,
Petitioner,

v.

TECAN GENOMICS, INC,
Patent Owner.

DEPOSITION OF:

CARLOS D. BUSTAMANTE, Ph.D.

NEW YORK, NEW YORK

TUESDAY, OCTOBER 7, 2025

REPORTED BY:

SILVIA P. WAGE, CCR, CRR, RPR

JOB NO. 7619957

CARLOS D. BUSTAMANTE, Ph.D.

October 7, 2025

8:41 a.m.

Deposition of CARLOS D. BUSTAMANTE, Ph.D., held at the offices of GOODWIN PROCTER, LLP, The New York Times Building, 620 Eighth Avenue, New York, New York, pursuant to agreement before SILVIA P. WAGE, a Certified Shorthand Reporter, Certified Realtime Reporter, Registered Professional Reporter, and Notary Public for the States of New Jersey, New York and Pennsylvania.

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NO.	DESCRIPTION	PAGE
NONE		

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CARLOS D. BUSTAMANTE, Ph.D.

THE STENOGRAPHER: Dr. Bustamante, if you can please raise your right hand. 08:41:11

CARLOS D. BUSTAMANTE, Ph.D., CBD Consulting Group, 600 Grapetree Drive, Apartment 11BN, Key Biscayne, Florida 33149, after having been duly sworn, was examined and testified as follows: 08:41:18

THE STENOGRAPHER: Thank you. 08:41:18

You may proceed. 08:41:19

EXAMINATION BY MR. BILSKER: 08:41:21

Q. Good morning, Dr. Bustamante. I'm David Bilsker. 08:41:21 08:41:22

How are you currently employed? 08:41:25

A. I am currently a professor at the University of Oklahoma, in the College of Medicine and I'm Vice Dean of Research. 08:41:26 08:41:28 08:41:32

Q. And you've had your deposition taken before, correct? 08:41:36 08:41:38

A. I have. 08:41:39

Q. Alright. So I'm not going to go over that. 08:41:39 08:41:41

Are you an Adjunct Professor 08:41:41

anywhere? 08:41:43

A. I was an Adjunct Professor at Stamford until the end of last month. 08:41:44 08:41:45

Q. And are you an adjunct professor in Miami? 08:41:49 08:41:53

A. I was Adjunct Professor at the University of Miami and then I was Entrepreneur in Residence. 08:41:54 08:41:55 08:41:58

Q. So at the University of Oklahoma, you're in the medical school? 08:41:59 08:42:01

A. I am. 08:42:02

Q. And do you have a lab? 08:42:02

A. I am Professor of Molecular Genetics. I haven't started a lab yet. 08:42:04 08:42:08

Q. How much time have you spent on this case? 08:42:11 08:42:14

"The case" being -- so there's four IPRs. There's actually three IPRs in this case, but there were four at one point. 08:42:14 08:42:17 08:42:19 08:42:21

How much time have you spent on this? 08:42:22 08:42:23

A. In total, since the start? 08:42:25

Q. Yes, since the start. 08:42:28

A. I don't have an exact number; several hundred hours. 08:42:29 08:42:31

Q. And if I refer to two groups -- we're going to be talking about the enrichment patents today. 08:42:33 08:42:37 08:42:39

Do you know what I'm talking about? 08:42:40

A. Yes. 08:42:42

Q. The '012 patent and the '108 patent; so you know what that is? 08:42:42 08:42:45

A. I do. 08:42:45

Q. And tomorrow you're going to be talking about -- I don't remember the number now, but the UMI-type patent? 08:42:46 08:42:48 08:42:50

A. Yes. 08:42:52

Q. I take it you've read the '012 and '108 patent? 08:42:54 08:42:56

A. I have. 08:42:58

Q. Approximately, how much time did you spend reading those? 08:42:58 08:43:00

A. Initially or in reference -- 08:43:04

Q. Let's start with initially. 08:43:05

A. Probably spent six, seven hours. 08:43:07 08:43:10

Q. Have you read either one of 08:43:10

those recently? 08:43:12

A. I reviewed the patents in 08:43:13
preparation for the deposition. 08:43:16

Q. About how much time would you 08:43:18
say you spent reviewing those two patents? 08:43:20

A. I couldn't tell you exactly. 08:43:22

Q. Five hours, ten hours? 08:43:23

A. On the order of something like 08:43:28
that, yeah. 08:43:30

Q. And was the last time you 08:43:30
looked at those within the last few days? 08:43:32

A. It was within the last few 08:43:34
days. 08:43:36

Q. Anything in those patents that 08:43:36
you didn't understand? 08:43:38

A. I would say I understand the 08:43:41
materials in the patents. 08:43:43

Q. But was there anything in the 08:43:44
patents themselves that you didn't 08:43:45
understand, any explanations or 08:43:47
methodologies? 08:43:49

A. Not that I can point to 08:43:51
sitting here right here right now. 08:43:53

Q. Did you also review the file 08:43:58

histories for those patents? 08:44:00

A. I have reviewed the file 08:44:01
history for those patents. 08:44:03

Q. And did you review something 08:44:04
called the "Brooks Declaration"? 08:44:06

A. I did review the Brooks 08:44:08
Declaration. 08:44:10

Q. When was the last time you 08:44:10
reviewed that? 08:44:11

A. In the last month. 08:44:13

Q. Was there anything in there 08:44:15
that you didn't understand? 08:44:17

A. Not to my knowledge. 08:44:18

Q. Was there anything that you 08:44:20
disagreed with there? 08:44:21

A. Not with the Brooks 08:44:23
Declaration -- 08:44:24

Q. So -- 08:44:24

A. -- that I can point to right 08:44:25
here right now. 08:44:26

Q. So sitting here without it in 08:44:30
front of you -- you don't have it in 08:44:31
front of you yet. 08:44:32

But, as you recall, there's nothing 08:44:33

that you actually disagree with in the -- 08:44:35
A. If you can give me the 08:44:36
Declaration, I'm happy to take a look at 08:44:37
it. 08:44:39
Q. Sure. But that's why I 08:44:39
prefaced the question that way. This -- 08:44:40
A. Sitting here -- 08:44:40
THE STENOGRAPHER: You have to 08:44:40
wait for him to finish. I'm sorry. 08:44:45
Q. Sorry. 08:44:45
Sitting here without it in front of 08:44:45
you, there's nothing that you can recall 08:44:47
that you disagree with it? 08:44:48
A. Not to my recollection 08:44:50
sitting here right here right now. 08:44:52
Q. Okay. We'll pull that out. 08:44:56
It's 2026. 08:44:57
(Deposition Exhibit Tecan 08:45:01
2026, Brooks Declaration, was 08:45:01
previously marked for 08:45:01
identification.) 08:45:01
(There is a discussion off 08:45:01
the record.) 08:45:45
Q. So Exhibit Tecan 2026, which 08:45:45

is 69-page document, is a document that 08:45:49
contains the Brooks Declaration. It's 08:45:53
something that Tecan marked. 08:45:56
Do you recognize this? 08:45:57
A. Can you give me a moment here 08:46:02
to... 08:46:06
Q. Sure. 08:46:06
A. I see the Brooks Declaration, 08:46:13
which starts on Page 35, I believe, of 08:46:16
the document. 08:46:18
Q. So 35 -- if you go to the end 08:46:19
-- you can take a moment to peruse that, 08:46:23
if you would like. 08:46:25
A. Thank you. 08:46:26
MS. CIPRIANO: David, I have 08:46:54
clean copies of his declaration 08:46:56
in case he wants to reference them. 08:46:59
MR. BILSKER: Sure. That 08:47:00
makes it easier for me. I have 08:47:01
his declaration too but... 08:47:03
MS. CIPRIANO: I'm sure you 08:47:05
do; just... 08:47:05
(Deposition Exhibit Tecan 08:47:05
2107, Declaration of Carlos D. 08:47:05

Bustamante, Ph.D., was previously marked for identification.) 08:47:05 08:47:50

A. Okay, I have... 08:47:50

Q. So now that you have it in front of you and had a chance to peruse it, is there anything that you recall disagreeing with in the Declaration? 08:47:51 08:47:53 08:47:55 08:47:57

A. When I say, "disagree," I mean, I understand that at the time when Dr. Brooks wrote his Declaration in reference to the period of time that we're talking about, the priority date for the patent, I understood why he arrived at the conclusions that he arrived at and the opinions he expressed. 08:47:59 08:48:01 08:48:08 08:48:11 08:48:15 08:48:17 08:48:20 08:48:22

Q. So you're putting yourself back in the timeframe of viewing his statements as of say 2012 is what you're saying? 08:48:23 08:48:25 08:48:27 08:48:30

A. I believe the priority date on the patent is in January of 2012. 08:48:30 08:48:32

Q. So you're saying, as of 2012, with the scientific knowledge that a person of ordinary skill in the art would 08:48:39 08:48:42 08:48:44

have had, you agree with all the scientific statements that Dr. Brooks made? 08:48:45 08:48:47 08:48:49

A. I agree with how he arrived at -- I believe that the context that he put forth makes good sense scientifically given the state of the art at the time, his experience in the field and, you know, concerns around the potential utility of the technology as described. 08:48:50 08:48:52 08:48:58 08:49:04 08:49:08 08:49:13 08:49:19

Q. Okay. So maybe I'm not being clear with the question. It's kind of a -- it seems like a much shorter question. 08:49:22 08:49:24 08:49:26

A. Okay. 08:49:28

Q. Putting yourself back in this timeframe of 2012, a person of ordinary skill in the art -- 08:49:28 08:49:30 08:49:33

A. Yes. 08:49:33

Q. -- do you agree with the scientific statements that Dr. Brooks made with respect to a person of ordinary skill in the art in 2012? 08:49:33 08:49:34 08:49:36 08:49:39

MS. CIPRIANO: Objection, asked and answered. 08:49:40 08:49:42

Q. Go ahead. 08:49:42
A. I agree with the statements 08:49:43
that Dr. Brooks makes in his Declaration. 08:49:44
Q. If we look at Paragraph 14 -- 08:49:47
A. Uh-huh. 08:49:48
Q. -- it's about five or six 08:49:51
lines up. 08:49:53
A. Uh-huh. 08:49:53
Q. He says, "I thought that the 08:49:54
target-specific primers would bind to 08:49:56
off-target sites at a relatively high 08:49:58
rate." 08:50:00
Do you see that? 08:50:02
A. I do. 08:50:02
Q. You agree with that in 2012? 08:50:03
A. (The witness reviews the 08:50:09
exhibit.) 08:50:12
I think it's reasonable to suppose 08:50:12
that you're going to have off-target 08:50:20
binding. 08:50:26
Q. Alright. So let's talk about 08:50:26
exactly what I mean with respect to 08:50:29
"off-target binding." 08:50:31
A. Uh-huh. 08:50:31

Q. If I refer to a "target fragment," do you understand what I'm talking about there? 08:50:32 08:50:34 08:50:35

A. Could you clarify what you mean by a "target fragment"? 08:50:36 08:50:37

Q. Sure. 08:50:38

So, if I take, say, a sample, a genomic sample, and I fragment it, you know what I mean by that? 08:50:38 08:50:41 08:50:44

A. Yes. 08:50:45

Q. Cutting it into smaller pieces either sonically or enzymatically? 08:50:45 08:50:46

A. Yes. 08:50:50

Q. You understand that? 08:50:51

A. I do. 08:50:51

Q. Those are the fragments I'm talking about that are going to be, essentially, the templates to use for sequencing. 08:50:51 08:50:53 08:50:55 08:50:58

You understand that? 08:50:59

A. I do. 08:51:00

Q. So, when you say that you agree with the suppositions that he made that you're going to bind off target -- 08:51:00 08:51:03 08:51:06

let's talk about those fragments -- those fragments, okay? 08:51:11 08:51:14

So do you agree with the statement, if it's interpreted that your primers will "bind to off-target sites at a relatively high rate," you agree with that with respect to the fragments as a person of ordinary skill in the art would understand it in 2012? 08:51:15 08:51:20 08:51:22 08:51:25 08:51:27 08:51:29 08:51:31

MS. CIPRIANO: Objection, asked and answered. 08:51:32 08:51:33

Q. Go ahead. 08:51:36

A. I would say that in the description of the patent, when we're talking about a sequence of interest and we're thinking of off-target effects with a single primer, you're going to potentially bind to more than one location, including sites that have homology to the region of interest. 08:51:36 08:51:39 08:51:44 08:51:52 08:51:57 08:51:59 08:52:02 08:52:07

So you will have with a single primer binding to off targets. I think that's a reasonable supposition. 08:52:11 08:52:14 08:52:16

Q. At "a relatively high rate"? 08:52:18

MS. CIPRIANO: Objection. 08:52:22

A. Depends on the target of interest. 08:52:22 08:52:23

Q. So are you saying that in 2012 people of ordinary skill in the art did not know how to design primers so that they would be specific to the locations they were trying to hybridize to? 08:52:24 08:52:28 08:52:30 08:52:33 08:52:34 08:52:38

MS. CIPRIANO: Objection, foundation. 08:52:38 08:52:39

Q. Go ahead. 08:52:42

A. This is the reason we would normally use two primers, right, that are specific to the region. With a single primer, you're able to bind many more sites than just the site of interest potentially. 08:52:43 08:52:44 08:52:48 08:52:50 08:52:54 08:52:56

I mean, I think, it's a question about what we mean by "a relatively high rate." 08:52:57 08:52:58 08:53:01

Q. Well, how do you understand "relatively high"? 08:53:01 08:53:03

A. At a rate sufficient enough 08:53:06

to produce off-target effects that will yield a significant amount of sequence data that you then need to go through and sort out. 08:53:08 08:53:14 08:53:17 08:53:19

Q. So what rate would that be? 08:53:20

MS. CIPRIANO: Objection, calls for speculation. 08:53:22 08:53:22

A. Yeah, I'm not a -- 08:53:23

Q. Well, so hold on. 08:53:25

MR. BILSKER: First off, Linnea -- is it Linnea? 08:53:27 08:53:28

I want to say Lin/nay (phonetic). 08:53:30 08:53:32

MS. CIPRIANO: Linnea, yes, yes. 08:53:32 08:53:33

MR. BILSKER: You can just say "form." So you don't need to, actually, state the basis. I'm pretty familiar. 08:53:33 08:53:34 08:53:35 08:53:37

MS. CIPRIANO: Under PTAB rules, I have to state the basis. So I have to establish my record. 08:53:37 08:53:40 08:53:41

Q. Well, you're here as an expert and you've given a long Declaration 08:53:43 08:53:45

as to why you think this patent is not obvious. So I don't think it's speculation. You're here as an expert. 08:53:47 08:53:50 08:53:52

If you say, I have no idea, that's fine. You can say, I have no idea. 08:53:54 08:53:55

But I would like you to answer that based on all the facts that you know and the statements that he's made. 08:53:57 08:53:59 08:54:02

A. We know that there will be off-target effects. The degree to which different regions of the genome have more or less off-target effects, obviously, depends on the specific experiment in question and the degree of specificity of the single primer. 08:54:05 08:54:07 08:54:10 08:54:14 08:54:17 08:54:21 08:54:28

And so, I think, especially if you look at the literature, there's a real rationale for why we design dual primer PCR to target gene regions that you want to amplify. 08:54:30 08:54:32 08:54:37 08:54:42 08:54:46

Q. So were there programs that were available in 2012 and before that people of ordinary skill in the art used to, actually, design primers so that they 08:54:49 08:54:50 08:54:54 08:54:55

would -- or hybridize, specifically, to the region that you wanted them to hybridize to? 08:54:58 08:55:00 08:55:02

A. There were absolutely computer programs that you could use. 08:55:03 08:55:05

Q. Did they stink? 08:55:07

A. The degree to which they were accurate, obviously, depends on the genome that you're sequencing, whether you have a reference genome to guide your experiment. 08:55:16 08:55:21 08:55:23 08:55:25

But, you know, in general, the primer design is an area of evolving accuracy and people, certainly, used lots of different programs to design primers. 08:55:30 08:55:34 08:55:38 08:55:41

Q. Yeah. 08:55:43

And my question to you was, were they so bad that in 2012 even using the programs that were available you would expect that in designing the primers, they would hybridize off target? 08:55:44 08:55:46 08:55:50 08:55:51 08:55:53

A. You, certainly, see off-target effects with single primer experiments, such as those that are under consideration by Dr. Brooks and his statement. 08:55:59 08:56:02 08:56:06 08:56:09

Q. I don't want to talk about, quote, "off-target effects." 08:56:13 08:56:14

I'm just talking about hybridizing to the target fragment, okay? 08:56:16 08:56:18

A. Okay. 08:56:19

Q. So, again, let's say in the situation where you have a reference genome -- 08:56:20 08:56:22 08:56:24

A. Uh-huh. 08:56:24

Q. -- would the computer programs that were available at the time from 2012 and before allow you to design primers that were good at hybridizing to the target sequence that you wanted them to hybridize to? 08:56:25 08:56:26 08:56:29 08:56:34 08:56:39 08:56:42

A. There were computer programs available that would allow you to design primers at the time of the invention in question. 08:56:43 08:56:44 08:56:46 08:56:48

Q. And did you use any of those programs; you, yourself? 08:56:48 08:56:50

A. I've used them in the past. 08:56:51

Q. So pre-2012? 08:56:53

A. Pre-2012. 08:56:55

Q. Primer3, are you familiar with that program? 08:56:56 08:56:58

A. I haven't used it in a while, but if you ask me a general question, I'm happy to consider it. 08:56:59 08:57:01 08:57:05

Q. Well, I guess, the question was, prior to 2012, did you use Primer3 to design primers ever? 08:57:05 08:57:07 08:57:11

A. I can't recall if I used, specifically, Primer3. 08:57:12 08:57:14

Q. But you are familiar with it? 08:57:15

A. I'm familiar with, in general, primer design software and my lab has used multiple sources -- multiple methods to design primers. 08:57:16 08:57:19 08:57:22 08:57:25

Q. So, back in 2012 and before, so 2012 and earlier, if you had a reference genome and you were using Primer3 to design primers to hybridize to target sequences, are you saying using that program you still would expect a relatively high off-target binding with your primer? 08:57:26 08:57:31 08:57:34 08:57:38 08:57:43 08:57:45 08:57:47 08:57:52

MS. CIPRIANO: Objection, 08:57:52

incomplete hypothetical. 08:57:54

A. I cannot opine on a 08:57:56
hypothetical experiment without, you know, 08:58:01
more information and thinking about the 08:58:05
specific experiment in question, what the 08:58:09
goal is of the target region, the known 08:58:12
homology. It may or may not have the 08:58:19
design capabilities necessary. 08:58:27

But, in general, off-target effects 08:58:30
were, certainly, a concern at the time of 08:58:32
the invention. 08:58:34

Q. Sorry. Again, we're not 08:58:34
talking about off-target events, in 08:58:35
general, or "off-target effects," in 08:58:37
general. 08:58:39

We're talking about primers designed 08:58:39
by a computer program such as -- now I 08:58:43
forget the name of it -- was it Primer3? 08:58:47

2012 and earlier, would you expect 08:58:52
with a reference genome that using Primer3 08:58:54
to design your primers, you would, in 08:58:57
general, get relatively high off-target 08:59:00
binding of your primer to your target 08:59:03
sequence? 08:59:05

MS. CIPRIANO: Objection. 08:59:05
Same objection. 08:59:07
A. You may or may not. It 08:59:07
depends -- first of all, the reference 08:59:09
genome is itself a draft. It has 08:59:11
collapsing of duplicate regions. It has 08:59:13
the unmapped regions. 08:59:17
So it depends on how you are 08:59:22
designing the experiment, what reference 08:59:25
genome you're talking about, what specific 08:59:27
region you're thinking about. 08:59:29
And at the end of the day, this is 08:59:31
why we do experiments, right? Much of 08:59:34
the time it works. Sometimes it doesn't 08:59:37
work. The degree to which it doesn't 08:59:39
work depends on the region being targeted 08:59:42
and the homology across the genome. 08:59:45
And so, I think, it is reasonable 08:59:47
for Dr. Brooks who have written what he 08:59:50
wrote in his deposition -- in his report. 08:59:53
Q. So you're saying you really 08:59:55
can't tell until you do the experiment 08:59:58
whether you're going to get a relatively 09:00:00
high off-target binding or whether you're 09:00:03

going to be relatively on target; is that what you're saying 2012 and prior? 09:00:05 09:00:07

A. There is a process by which you validate primers to make sure -- especially with dual primers. 09:00:09 09:00:10 09:00:16

With single primers, it -- you'd want to optimize to ensure that you are binding the select region, specifically, as you can. 09:00:17 09:00:22 09:00:25 09:00:31

Q. So would you say that in -- I mean, Dr. Brooks wrote this Declaration in 2018. But he's putting himself back in the shoes of somebody in 2012. 09:00:31 09:00:36 09:00:37 09:00:41

Would you say he just knew a lot more than you did in 2012 and prior, a lot smarter than you are? 09:00:43 09:00:45 09:00:48

A. I'm happy to believe Dr. Brooks is an expert in his field. 09:00:49 09:00:52

I'm not sure what you -- what you're getting at with that question, sir. 09:00:57 09:01:00

Q. Well, you gave me a lot of qualifications as to, well, you wouldn't know, you'd have to look at the reference genome. You'd have to look at, like, 09:01:02 09:01:03 09:01:05 09:01:07

whether they're repeats, they're duplicate sections of homology. 09:01:09 09:01:12

But Dr. Brooks in this statement in Paragraph 14 didn't make any qualifications. 09:01:13 09:01:16 09:01:17

It's an unequivocal statement that a person of ordinary skill in the art would think that you would get off-target binding "at a relatively high rate." 09:01:17 09:01:20 09:01:21 09:01:27

He doesn't say, depending on whether you have a reference genome or looking at the level of homology and adjoining sections? 09:01:28 09:01:30 09:01:33 09:01:37

He doesn't make any qualifications, does he? 09:01:37 09:01:38

MS. CIPRIANO: Objection, compound. 09:01:39 09:01:39

A. Could you break that up for me, please? 09:01:40 09:01:41

Q. Sure. 09:01:42

Does Dr. Brooks have any qualifications in the statement that you would expect "relatively high rates" of off-target binding? 09:01:43 09:01:44 09:01:46 09:01:50

A. What he states is that in order to ensure a reduction in off-target effects, that you would use the primer pair logic to target specific primers that are around the region of interest. 09:01:56 09:01:58 09:02:08 09:02:10 09:02:18

Q. It wasn't the question. 09:02:22

The question was, does he make any qualifications with respect to you would get relatively high off-target binding using a single primer when you're targeting the fragment? 09:02:24 09:02:27 09:02:31 09:02:36 09:02:38

MS. CIPRIANO: Objection, asked and answered. 09:02:42 09:02:43

A. (The witness reviews the exhibit.) 09:02:48 09:02:49

I do not see in his Declaration specific caveats. 09:02:49 09:03:07

Although, again, "relatively high rate" I would interpret as depending on conditions. 09:03:10 09:03:12 09:03:14

Q. So "relatively high rate" -- as a person of ordinary skill in the art, would you expect 50 percent off-target binding of a primer designed -- using a 09:03:16 09:03:18 09:03:19 09:03:22

computer program with a known reference genome, 2012 and prior, a person of ordinary skill in the art designing the primers, would you expect them to bind at 50 -- at less than 50 percent, specifically? Sorry. 09:03:25 09:03:28 09:03:33 09:03:33 09:03:37 09:03:42

A. Again, it's hard for me to answer a question about a hypothetical experiment. 09:03:44 09:03:48 09:03:50

It depends really on the specifics. For some regions, you'd be able to design primers that bind more specifically than in other regions. And if you have collapsed regions of homology, then you may get -- depending on the species and depending on the target region, it's, certainly, possible to have high levels of off-target binding. 09:03:51 09:03:54 09:03:58 09:04:01 09:04:03 09:04:06 09:04:14 09:04:19 09:04:21

Q. So would you say that you, actually, don't agree with Dr. Brooks that this is a statement that applies across the board to all regions that you would be targeting, if you had a reference genome? 09:04:22 09:04:23 09:04:25 09:04:27 09:04:30

A. Dr. Brooks is not limiting 09:04:35

his statements to reference genomes or -- I think, he's speaking in what one might expect. And, again, he was surprised at the results. So it was a null hypothesis, as it were, that set up based on suspicion of whether the technology may or may not work. 09:04:36 09:04:41 09:04:45 09:04:47 09:04:52 09:04:59 09:05:02

Q. But he made a statement with no caveats, no qualifications, that just said, with a single primer, I would expect there to be relatively high off-target binding. 09:05:06 09:05:09 09:05:12 09:05:16 09:05:21

And you're saying, it depends. It depends on what you're targeting and various other things. 09:05:21 09:05:23 09:05:25

So is it fair to say that you do not agree with him, as a general matter, that this applies across the board, that you would expect relatively high off-target binding? 09:05:26 09:05:29 09:05:31 09:05:33 09:05:37

A. Again, that -- it's easy to answer this question in retrospect given that we know the technology works and it works well. 09:05:39 09:05:43 09:05:46 09:05:48

So putting ourselves back at the time of when he is considering the problem and thinking as an expert at the time, I think, it is reasonable for him to hold the opinion that he holds and that he -- and that he puts forth in his Declarations. 09:05:50 09:05:52 09:05:59 09:06:04 09:06:07 09:06:09 09:06:11

I wouldn't necessarily have written them the way he wrote it. 09:06:12 09:06:14

Q. How you would have written it? 09:06:15

A. I can't tell you right here right now. I'd like to consider -- I'd need to consider how I would have written it at the time. 09:06:16 09:06:19 09:06:22 09:06:24

Q. Well, this is like one of the big issues in the case. And you worked on it for a couple hundred hours you said and looked at this Declaration relatively recently and the patents recently. 09:06:25 09:06:27 09:06:29 09:06:31 09:06:33

And you're saying you actually are unable to think of how you would express in 2012 what you would expect in relation to off-target binding of a primer to a fragment sequence? 09:06:36 09:06:39 09:06:42 09:06:47 09:06:52

MS. CIPRIANO: Objection to form. 09:06:54 09:06:56

A. That's not what I said, but if you can simplify the question for me. 09:06:56 09:06:57

Q. Sure. 09:07:01

How would you express a person of ordinary skill in the art in 2012 or earlier how they would expect there to be off-target binding of a primer designed using a computer program to a known reference genome in 2012? 09:07:02 09:07:06 09:07:07 09:07:12 09:07:17 09:07:20

A. I believe, I address many of these issues in my Declaration. 09:07:23 09:07:25

Q. Well, I'm asking you questions. We're not here to read a novel right now. We're here to ask questions. 09:07:26 09:07:28 09:07:30 09:07:32

What's the answer? 09:07:33

A. As I said, I've addressed a lot of this in my Declaration. What I said was, I would not necessarily have written it the way he wrote it. And I'm not prepared to give a narrative without thoughtful consideration. 09:07:33 09:07:36 09:07:38 09:07:40 09:07:43 09:07:45

I'm happy to speak to what's in my Declaration, as to the statements that I put forth in the Declaration. 09:07:46 09:07:48 09:07:50

Q. So, without the crutch of your Declaration, you can't answer questions today? 09:07:53 09:07:54 09:07:56

A. That's not what I said. 09:07:56

Q. Well, then how would you express it? 09:08:00 09:08:01

You said you wouldn't express it the way he expressed it. 09:08:02 09:08:03

How would you express it? 09:08:04

MS. CIPRIANO: Objection, asked and answered. 09:08:06 09:08:07

A. As I said, I would like to rely on my Declaration to be accurate in terms of what I've written and put forth in terms of my testimony. 09:08:09 09:08:10 09:08:14 09:08:16

Q. So the question stands. 09:08:17

Without the crutch of looking at your Declaration, you, actually, can't answer the question right now? 09:08:18 09:08:19 09:08:21

A. That's not what I said. I want to be accurate in my answer and I 09:08:22 09:08:23

want to discuss the inventions and the matters before us, in light of the evidence and the materials put forth in the Declaration. 09:08:25 09:08:31 09:08:34 09:08:36

Q. So PCR was invented or discovered by Kary Mullis in, like, what 1986? 09:08:36 09:08:40 09:08:44

A. I believe it's '83. But we can look at the Mullis reference and go back to when he thought about it and when he wrote it. 09:08:44 09:08:46 09:08:49 09:08:50

Q. And PCR relies on designing primers to amplify a sequence, correct? 09:08:51 09:08:56

A. It relies in, certainly, its original form on primer pairs. 09:09:01 09:09:03

Q. And if you wanted to amplify a specific sequence with PCR from the time it was invented -- let's take until 2005. 09:09:05 09:09:07 09:09:09 09:09:13

People were designing primers to amplify very specific regions, correct? 09:09:13 09:09:15

A. They were and these were usually primer pairs. 09:09:18 09:09:20

Q. And to do that they had to 09:09:21

design the primer so they would hybridize to very specific regions and not to hybridize to other regions, correct? 09:09:23 09:09:25 09:09:27

A. That is an accurate -- that is accurate. 09:09:29 09:09:31

But we also know that it took experimental trial and error to ensure that the primers were binding and that you weren't getting off-target effects. 09:09:32 09:09:35 09:09:38 09:09:41

Q. So you can't just look at something -- so you're saying you, basically, can't just look at something on paper, a primer designed -- a primer sequence that's been designed -- 09:09:45 09:09:47 09:09:48 09:09:50 09:09:54

Even if you see the primer sequence, you can't look at it and say, ah, that's going to bind very specifically at a high rate to what I want or that's not going to bind very specifically, it's going to be highly off target, right? You have to do an experiment? 09:09:56 09:09:57 09:09:59 09:10:02 09:10:04 09:10:07 09:10:09

A. That's not what I said. 09:10:11

And -- what I said was in answer to your question that in designing specific 09:10:13 09:10:20

primers, there is often trial and error and an iterative process to ensure that you're not getting off-target effects. Sometimes they work right off the bat. Sometimes they don't. 09:10:26 09:10:31 09:10:33 09:10:35 09:10:37

It also depends on how many primers are -- how many reactions are being multiplexed, if you're doing a single reaction versus doing a thousand reactions versus doing 10,000 reactions. The combinatorial possibilities can, certainly, lead to many off-target products. 09:10:38 09:10:41 09:10:43 09:10:45 09:10:47 09:10:50 09:10:52 09:10:54

Q. So, by 2012, people had been designing primers to be specific to regions that they wanted to target for almost, what, 25 years or so, right? 09:11:03 09:11:05 09:11:07 09:11:10

A. We -- yes, that's -- PCR has a long history. 09:11:16 09:11:22

Again, I think, what we want to distinguish here is PCR in a single reaction for a single gene region where you're designing one reaction versus the technology here where you're multiplexing 09:11:23 09:11:25 09:11:28 09:11:31 09:11:37

at times a thousand or more reactions. 09:11:40
At that scale, the level of off-target 09:11:45
binding, the degree to which the reaction 09:11:51
will be efficient, the degree to which 09:11:52
you'll be able to get evenness and 09:11:54
coverage across the regions is an open 09:11:57
question. 09:12:00

Q. Alright. So let's take the 09:12:00
simpler case. Let's start with 1 loci. 09:12:04

You understand what I'm talking 09:12:07
about there, right? 09:12:08

A. Yes. 09:12:09

Q. So we're not multiplexing our 09:12:09
targets. We're just talking about trying 09:12:13
to hybridize primers to one specific 09:12:16
region of a fragment. 09:12:19

You got that? 09:12:21

A. I do. 09:12:22

I would like to caveat by saying 09:12:23
the technology here really is meant for 09:12:25
multiplexing and, I think, that's really 09:12:28
where we need to frame the discussion. 09:12:30
But I'm happy to start with a single gene 09:12:32
region. 09:12:34

Q. Alright. So let's take that situation where we're talking about a single region. 09:12:34 09:12:36 09:12:38

Are you saying that in 2012 -- let's just cabinet it. 09:12:41 09:12:45

Like, between 2000 and 2012, people designing primers, for example, using a computer program would still expect relatively high off-target rates, if they were targeting a single loci? 09:12:46 09:12:49 09:12:51 09:12:53 09:12:57

A. With two primers, it would work much of the time. 09:13:01 09:13:03

With a single primer, it depends and it depends on the species and it depends on the gene region and it depends on the primer. 09:13:05 09:13:07 09:13:09 09:13:11

Q. So, even if you had a reference genome and you were targeting 1 loci, you're saying it really depends whether you would have relatively high off-target rates or not have relatively high off-target rates, you just can't tell, you have to do the experiment, if you're using a single primer extension? 09:13:12 09:13:14 09:13:18 09:13:23 09:13:27 09:13:30 09:13:32 09:13:33

A. What I said was it depends on the gene region in question. If you're looking at a gene that's part of a gene family, tandem duplicated genes, and you're using a single primer, it is certainly possible that you would amplify more than that target, especially if you don't have two primers. 09:13:36 09:13:37 09:13:40 09:13:42 09:13:44 09:13:46 09:13:49 09:13:52

If you have two primers, you can make it specific to a given exon in Gene A and not that homologous exon in Gene B. 09:13:53 09:13:56 09:13:59

If you've got a single primer, it depends on the homology and the degree to which the reference genome has collapsed or has not collapsed gene duplicates. 09:14:05 09:14:06 09:14:10 09:14:12

Q. So you're saying it depends on whether it has collapsed or un-collapsed regions. 09:14:19 09:14:21 09:14:23

What if you size fragment? So, as a first step in doing that process, you size fragment. 09:14:24 09:14:26 09:14:29

A. Size fragment is not going to solve problems with collapsing gene regions in a reference genome. Reference 09:14:30 09:14:32 09:14:34

genome is a computational representation of the genome, right. 09:14:36 09:14:40

So, to the POSA, the reference genome only has one copy, but the real genome has multiple copies and you won't know that until you do the experiment. 09:14:44 09:14:49 09:14:51 09:14:54

Q. Got it. 09:14:56

Why is it that you believe using two primers -- well, let's take a step back. 09:14:56 09:15:01

In a situation where you use two primers, a forward and reverse, each specific to a particular sequence in the fragment -- you've got that in mind? 09:15:03 09:15:05 09:15:07 09:15:12

A. Yes. 09:15:14

Q. So you, actually, have to design each one of those primers, the forward primer and the reverse primer to hybridize very specifically to the region that you want, right? 09:15:14 09:15:16 09:15:18 09:15:20 09:15:23

You do the -- it's the same process whether you use one or two, correct? 09:15:24 09:15:25

MS. CIPRIANO: Objection, compound. 09:15:27 09:15:29

A. Could you simplify the 09:15:32

question? 09:15:32

Q. Sure. 09:15:33

When you're using one primer for 09:15:33

example, SPE, Single Primer Extension, 09:15:35

you use a computer program. That 09:15:41

computer program looks for sequence in 09:15:43

the target fragment. 09:15:46

It then says, hey, if you design 09:15:48

your primer to be this long and have this 09:15:50

sequence, there's a good chance that it's 09:15:52

going to hybridize where it wants; 09:15:54

general way that the program would work, 09:15:56

correct? 09:15:59

A. In primer design, you would 09:16:01

input the sequence of interest. You'd 09:16:06

get several options and you'd chose the 09:16:08

options based on the predicted binding 09:16:11

temperature. 09:16:13

Q. And it would use that same 09:16:14

process, the computer program would use 09:16:17

that same process for both the forward 09:16:19

primer and the reverse primer? 09:16:22

A. For the primers, yes, that 09:16:23

flank the region of interest. 09:16:25

Q. And when you use two primers, a forward primer and a reverse primer, one acts on one strand -- and we'll just do it spatially, so we can kind of keep track. 09:16:26 09:16:28 09:16:30 09:16:33 09:16:36

A. Uh-huh. 09:16:36

Q. I'll say the forward primer acts on the bottom strand and the reverse primer acts on the top strand. That's -- 09:16:36 09:16:38 09:16:40

A. I have a mental image of what with you're asking. 09:16:44 09:16:45

Q. So they, actually, act independently of one another, correct? 09:16:47 09:16:49

A. Unless they for some reason interact. But, yes, in general, as you are undergoing the preliminary chain reaction, each one is binding and extending as part of the PCR. 09:17:03 09:17:06 09:17:09 09:17:12 09:17:15

Q. So wouldn't you have all the same issues if you're using a forward primer and a reverse primer that you would have, as far as specifically binding to the target sequence, that you would have with one? 09:17:17 09:17:20 09:17:22 09:17:24 09:17:26 09:17:28

A. No, sir. Because in the single primer extension, you're using the universal primer say for the reverse. So, if you have a universal primer, it will prime everything relative to wherever the forward primer is priming. 09:17:30 09:17:31 09:17:34 09:17:36 09:17:39 09:17:42

If you have two primers, a forward and a reverse, you could choose those primers in such a way that it amplifies a known exon in one gene that shares homology with a known exon in another gene, but it can do so, specifically, because you have two ways of limiting the reaction, as opposed to one way. 09:17:44 09:17:46 09:17:48 09:17:51 09:17:53 09:17:55 09:17:57 09:17:59

Q. Alright. So let's just take the first cycle of PCR, okay, just one cycle. 09:18:01 09:18:02 09:18:07

A. Okay. 09:18:07

Q. And in that one cycle, first thing I do commonly -- and I guess it doesn't have to be 100 percent. 09:18:08 09:18:10 09:18:13

But let's say I denature my double stranded DNA -- 09:18:15 09:18:15

(There is a discussion off 09:18:15

the record.) 09:18:21

Q. So let's say you denature your double stranded DNA, okay? 09:18:21 09:18:23

A. Okay. 09:18:25

Q. So I've got a top strand and I've got a bottom strand, right? 09:18:26 09:18:27

A. Okay. 09:18:29

Q. And my forward primer is going to act on the single stranded bottom strand and my reverse primer is going to act on my single stranded top strand, okay? 09:18:29 09:18:32 09:18:34 09:18:36 09:18:39

A. I think, I follow. 09:18:40

Q. So you, actually, have two individual reactions. You're saying that -- why would you expect in those two individual reactions that -- they don't know that they're going on with respect to each other. I mean, they're acting completely independently. 09:18:41 09:18:45 09:18:50 09:18:52 09:18:54 09:18:56 09:18:58

Why would you expect in that situation the forward and reverse primers are going to anneal, specifically, but if I'm just looking at the bottom reaction, 09:18:59 09:19:01 09:19:04 09:19:06

say, in a single primer extension, it's not going to anneal or hybridize, specifically? 09:19:08 09:19:11 09:19:13

MS. CIPRIANO: Objection to form. 09:19:16 09:19:16

A. Yeah. Could you simplify the question for me? 09:19:16 09:19:19

Q. Sure. 09:19:20

A. And I -- again, we're in such a kind of hypothetical situation that I would caveat my answer by saying that, in general, a POSA in 2012 would have understood that using two primers would give more specific amplification of a gene target region than using a single primer with a universal primer. That -- I would say that statement is a clear and accurate depiction of the technology at the time. 09:19:20 09:19:24 09:19:28 09:19:33 09:19:37 09:19:39 09:19:43 09:19:45 09:19:48 09:19:53 09:19:55

Q. Well, you've changed the question. 09:19:56 09:19:58

So, again, let's stick with the question. 09:19:58 09:20:00

So let's take the first round -- 09:20:00

let's just take the extension round or it's not even a round. 09:20:06 09:20:08

Let's take the extension reaction and the single primer extension. So I denature my double-stranded DNA and my single primer anneals to one of those strands top or bottom -- let's just say top in this situation. 09:20:10 09:20:12 09:20:15 09:20:18 09:20:20 09:20:23

And what Dr. Brooks is saying in Paragraph 14 is he would actually expect "a relatively high rate" of off-target binding for that primer in that extension reaction? 09:20:24 09:20:29 09:20:31 09:20:35 09:20:37

A. That is what Dr. Brooks is saying. 09:20:41 09:20:42

Q. Do you agree with that? 09:20:42

A. Again, I would say depending on the condition and the time of question, I think, it's a reasonable opinion for him to hold at the time. 09:20:44 09:20:45 09:20:50 09:20:52

It is retrospective thinking to look back on it today and say that was an unreasonable opinion to hold. 09:20:56 09:20:59 09:21:02

Q. Alright. And you're saying 09:21:03

-- is it true that you're saying now, if we do this -- we take that same double-stranded fragment, denature it and I run two reactions, one for the same primer that I used before, the same single -- in the single primer extension reaction, I use that primer for one strand and I use a different primer for the other strand, you're saying somehow magically in that situation my reverse primer is going to actually anneal very specifically, but my forward primer, which was my single primer in the single primer extension, the POSA is still going to think that's going to bind "at a relatively high rate" off target? 09:21:06 09:21:08 09:21:12 09:21:15 09:21:19 09:21:21 09:21:25 09:21:27 09:21:29 09:21:33 09:21:36 09:21:39 09:21:42 09:21:45 09:21:46 09:21:48

A. If you carry the reaction forward and you imagine the "forward primer," as you're calling it, that's multiply binding, let's say it's binding to A and to B region, and the second primer is only binding to the B region. 09:21:50 09:21:52 09:21:55 09:21:57 09:22:00 09:22:02

As you carry out the PCR, all of the product that will be produced in 09:22:04 09:22:07

subsequent rounds will be biassed towards just those in the B region, because that's where you're getting most of the amplification, both the A and the B primer. 09:22:11 09:22:15 09:22:16 09:22:18 09:22:18

In the case when you have a universal primer, for the reverse, you'll get both A and B. 09:22:19 09:22:20 09:22:22

Q. I'm not talking about carrying through the reaction and going through multiple rounds of PCR. 09:22:24 09:22:25 09:22:27

I'm just talking about the primer design right now. 09:22:29 09:22:31

A. But the primer design is -- sorry. 09:22:32 09:22:33

Q. In the primer design running the -- the first step, the extension reaction, in that first step, do you believe that a person of ordinary skill in the art would think that they're going to be able to design one primer either the forward or the reverse where it's more specific than the other? 09:22:34 09:22:36 09:22:38 09:22:42 09:22:46 09:22:49 09:22:52 09:22:54

A. The reason to use a dual 09:22:57

primer system is because as you go through the PCR cycles, you will enrich for the -- you will amplify the target region more specifically. 09:23:02 09:23:05 09:23:12 09:23:16

If you use one single universal primer and a single primer, you will then continue to amplify the target and the off target. 09:23:19 09:23:21 09:23:23 09:23:26

Q. I don't think that answered the question. I think you changed it again. 09:23:30 09:23:30 09:23:32

But let's go back to the answer that -- what you formulated as the scenario where you had an A and a B. 09:23:33 09:23:36 09:23:38

And you said the -- we'll call it the "SPE primer" or the "single primer," what would be the single primer extended through an A and B region whereas the reverse region only extended through a B region, right? 09:23:40 09:23:46 09:23:48 09:23:51 09:23:54 09:23:56

A. Happy to consider that question. 09:23:59 09:24:00

Q. At the end of the day, your multiple cycles of PCR, you'd actually 09:24:00 09:24:02

have -- what would the bias, actually, be in that situation mathematically? 09:24:04 09:24:08

MS. CIPRIANO: Objection, form. 09:24:11 09:24:11

A. I -- it, again, depends on how many cycles of PCR you're carrying through, but you would be doubling each cycle, the specific product that you want. The other one is growing linearly. So one is growing exponentially and one is growing linearly. So, by the end, you'll have many more copies of the target of interest. 09:24:12 09:24:19 09:24:21 09:24:28 09:24:33 09:24:36 09:24:38 09:24:40 09:24:43

Q. Alright. So let's take the situation that you -- again, the A and the B situation that you identified. 09:24:45 09:24:46 09:24:48

If I'm only using one primer, single primer extension, and I'm hitting A and B, right, at the end of the day with rounds of PCR, it's going to be what mathematically? 09:24:51 09:24:55 09:24:57 09:25:00 09:25:06

What's the bias going to be there with respect to A and B? 09:25:08 09:25:10

A. It depends on how accurately 09:25:15

it binds A versus B but... 09:25:15

Q. Well, let's say it binds to A 09:25:19
but extends through B every time. Well, 09:25:21
sorry. 09:25:24

Let's say it binds A and B 50/50. 09:25:25

MS. CIPRIANO: Objection. 09:25:30

A. Would you restate that? 09:25:33

Q. Sure. 09:25:35

Let's say it binds to A just as 09:25:35
frequently as it binds to B. 09:25:38

A. In your hypothetical 09:25:41
situation, which may or may not be -- 09:25:43
it's really relevant to the multiplex 09:25:45
situation in SPET. If it's equally 09:25:49
binding A and B, then sitting here right 09:25:50
today, I would venture to guess it would 09:25:53
be 50/50. 09:25:57

But I want to caveat that, you 09:25:57
know. I need to think about it and it 09:25:59
depends on the conditions and the 09:26:01
specifics. It's a highly hypothetical. 09:26:03

Q. And let's say it binds -- so, 09:26:07
at 50/50, would you say a person -- so, 09:26:09
at the end of the day, you're going to 09:26:12

have a library created for sequencing where you've got 50 percent of the thing that you really want, which is A, and 50 percent of the thing you don't necessarily want, which is B, right? You have that in mind? 09:26:14 09:26:18 09:26:20 09:26:23 09:26:25 09:26:27

A. If we can start with that as the condition. 09:26:29 09:26:30

Q. Are you saying that a person of ordinary skill in the art prior to 2012 -- so let's say at the end of 2011 -- let's just say 2011. 09:26:31 09:26:35 09:26:36 09:26:38

Would say, ah, no way, I'm not going to put this on for, for example, an Illumina sequencer because I'm just going to get garbage, I'm not going to be able to sequence this? 09:26:41 09:26:42 09:26:45 09:26:47 09:26:50

A. In the multiplex case, if I'm only getting half of what I want and I'm multiplexing against 10 loci, then the actual targets I have is a very small fraction of all the materials that's being sequenced. Plus when you're doing NGS sequencing, you also have additional 09:26:51 09:26:53 09:26:56 09:26:59 09:27:01 09:27:03 09:27:05

off-target effects that would not just come from A and the B. 09:27:08 09:27:10

So it would be an extensive experiment, if you didn't know from the get go that you're getting good targeting. 09:27:11 09:27:13 09:27:15

Q. So I don't think that answered my question. 09:27:17 09:27:20

MR. BILSKER: Can you read it back for him, please? 09:27:21 09:27:22

(Whereupon, the question is read back as follows: 09:27:23

"Question: Are you saying that a person of ordinary skill in the art prior to 2012 -- so let's say at the end of 2011 -- let's just say 2011.

Would say, ah, no way, I'm not going to put this on for, for example, an Illumina sequencer because I'm just going to get garbage, I'm not going to be able to sequence this?") 09:27:52

MS. CIPRIANO: Objection, asked and answered. 09:27:52 09:27:52

A. Would you like me to answer that question? 09:27:56

Q. Yeah. It's, actually, a yes or no. 09:27:57

A. I think somebody may choose -- even if you sequence it, I'm not sure, again, depending on the situation, whether you'd be able to interpret and what you get off of that sequencing reaction. So some would be unwilling to take the risk of doing the sequencing. 09:28:03

Q. So let me add another factor in there. Let's say you, actually, have a reference genome -- 09:28:26

A. Uh-huh. 09:28:32

Q. -- okay, something to map it too. 09:28:32

Would a person of ordinary skill in the art in 2011 knowing that the library they created for sequencing contains at most 50 percent of what they want and the other 50 percent being things that they're not interested in, but they say, I am not going to put this on an Illumina sequencer 09:28:34

because I know that I am not going to get any kind of useful data? 09:28:52 09:28:54

A. If we are -- so, first, you probably wouldn't use a Illumina sequencer for a single amplicon, right, that would be overkill. 09:28:57 09:28:59 09:29:01 09:29:03

If you're looking to do this experiment across multiple loci and multiplexing, you'd want to know what is your on-target versus off-target efficiency. 09:29:04 09:29:06 09:29:09 09:29:11 09:29:13

And at the time, you'd want on-target efficiencies in the 80 to 90 percent. 09:29:14 09:29:17 09:29:20

Fifty percent on target not ideal. 09:29:20

If you've got 2 loci and it's 25 percent on target, even less ideal. 09:29:23 09:29:25

So I probably wouldn't have run it on my lab. I'd try to redesign, if I really wanted that specific set of targets. 09:29:27 09:29:30 09:29:33 09:29:34

Q. So you're not using the full capacity of an Illumina sequencer, if you only run 1 loci. 09:29:35 09:29:40 09:29:42

But, I mean, you've worked at universities, correct? 09:29:44 09:29:45

A. I have worked at universities. 09:29:46

Q. And universities usually have core sequencing facilities, correct? 09:29:47 09:29:50

A. They do. 09:29:52

Q. And many times when you want something sequenced, you, actually, have to wait until they have enough samples to fill up the flow cell to make it efficient to, actually, run an experiment, correct? 09:29:53 09:29:54 09:29:56 09:29:58 09:30:01

A. That is an accurate statement. 09:30:05

Q. It's very common, correct? 09:30:06

A. It happens. 09:30:08

Q. And a lot of times it's not a single professor or single lab, when they want something sequenced. 09:30:09 09:30:14 09:30:16

Actually, the thing they want sequenced doesn't even come up close to filling up the capacity of what is on a flow cell, even back 2012, which I don't remember the Illumina sequencer was then. 09:30:18 09:30:20 09:30:22 09:30:24 09:30:28

But isn't that correct? 09:30:29

MS. CIPRIANO: Objection, 09:30:32

relevance. 09:30:33

A. I would say the hypothetical 09:30:34
investigator still has to pay for it. 09:30:38
It's still coming out of -- you know, 09:30:40
they've got to -- and it's just not the 09:30:42
sequencing cost. It's the interpretation 09:30:45
costs and the time that it takes to read 09:30:47
through the experiment. 09:30:50

So I would say most investigators 09:30:52
would try to design the right amplicon 09:30:53
sequencing, the amplicon targeting 09:31:01
strategy before going to sequencing. 09:31:04

Q. Right. 09:31:05

But core facilities a lot of times 09:31:06
will pool samples from different labs, 09:31:08
correct, before running the experiment? 09:31:10

A. They can. 09:31:12

Q. Not "they can," but that's 09:31:13
actually pretty -- that's not even a 09:31:16
hypothetical. 09:31:17

That, actually, does happen 09:31:17
frequently, correct? 09:31:19

A. It depends on the core 09:31:20
facility. 09:31:21

But, sure, I'm happy to concede that core facilities will pool samples across different labs. 09:31:22 09:31:24 09:31:26

Q. And they do that and they have methods to keep track of whose sample is what. They put multiple samples on a flow cell. 09:31:27 09:31:29 09:31:32 09:31:35

So back in, I guess, it was maybe the -- back in say 2011, right, that's something that was commonly done, you pooled samples on an Illumina sequencer? 09:31:35 09:31:38 09:31:41 09:31:43

So, even if your sample was not something that would use the full capacity on its own of the sequencing run, by pooling it with other samples from other labs, you, actually, did get to use the full capacity, so you weren't paying for something that you really weren't using, right? 09:31:45 09:31:48 09:31:52 09:31:55 09:31:57 09:31:59 09:32:01 09:32:03

A. Sure. The unit costs are reduced by spreading across labs. But you still have to pay for the experiment. You still have to pay for the interpretation. 09:32:08 09:32:11 09:32:13 09:32:15 09:32:16

And why would you want to spend money on an experiment that isn't going to yield the results that you want, if you know half of it is going to be on wasted, you know -- why would you waste 50 percent of your reads on off target. It wouldn't -- again, I wouldn't do it. Maybe somebody would do it. 09:32:16 09:32:18 09:32:20 09:32:22 09:32:24 09:32:29 09:32:32 09:32:34

And if you're multiplexing more than 1 loci, then you, certainly, wouldn't do it, right. That's why you -- that's why you would like to optimize. 09:32:36 09:32:38 09:32:41 09:32:44

Q. So let's say you were looking for particular mutations in a very important cancer gene and you were just looking at 1 loci. 09:32:52 09:32:53 09:32:59 09:33:02

That could be very important and it could be worth it to run your experiment pooled with other people's experiments and pay the money to interpret the data, right? 09:33:03 09:33:05 09:33:07 09:33:08 09:33:11

MS. CIPRIANO: Objection to form. 09:33:12 09:33:14

A. Could you restate the 09:33:14

question? 09:33:16

Q. Sure. 09:33:16

If you're looking for a mutation, which is specific to some deadly form of cancer for which you might have some treatment, that would be a reason to potentially run 1 loci on a machine pooled with other people's samples and pay to interpret the data, right? 09:33:17 09:33:19 09:33:22 09:33:24 09:33:27 09:33:30 09:33:34

A. Well, that would probably not be used in a clinical setting, right, given that you'd have to wait and so on. 09:33:35 09:33:36 09:33:39

But, again, we could think of a hypothetical situation where somebody might be interested in a single locus and interested in typing one side of the gene and would NGS in this way to do it. 09:33:42 09:33:44 09:33:46 09:33:50 09:33:53

But if you couldn't interpret it because you have multiple binding, why would you use that as your basis? 09:33:55 09:33:57 09:33:59

You would redesign and use two primers to amplify the amplicon that you cared about. 09:34:00 09:34:03 09:34:07

Q. Well, why would you say you 09:34:07

wouldn't be able to interpret it, if you have a reference genome? 09:34:09

A. Because the reference genome may be collapsing homologous regions. 09:34:10 09:34:11

Q. Well, it may not be. 09:34:14

MS. CIPRIANO: Objection to form. 09:34:16 09:34:17

A. But then -- yeah. So -- but in the situation that we're talking about where you're getting 50 percent from a related gene, you'd want to make sure that you would narrow the reads to the gene that is of actual interest. So -- and you could do that in multiple ways. 09:34:17 09:34:21 09:34:23 09:34:28 09:34:30 09:34:33 09:34:37

Q. So is it your belief -- so can you quantify this at all? 09:34:43 09:34:46

If we go back to Paragraph 14, you're reading this as person of ordinary skill in the art what Dr. Brooks wrote in -- well, putting himself back in 2012, presumably. He wrote it in 2018. 09:34:49 09:34:50 09:34:52 09:34:56 09:34:58

Can you quantify what he means by "relatively high off target"? Do you have in mind what he's talking about 09:35:01 09:35:03 09:35:05

there? 09:35:06

MS. CIPRIANO: Objection, 09:35:07
compound. 09:35:08

A. Could you restate the 09:35:09
question? 09:35:10

Q. Sure. 09:35:10

Do you have any idea quantitatively 09:35:11
what he means by "relatively high off 09:35:13
target"? 09:35:17

A. I can't read Dr. Brooks' mind. 09:35:18
I can't tell you what he had in mind when 09:35:21
he wrote that, in terms of quantitatively. 09:35:23

Q. Alright. Putting yourself 09:35:25
back in 2012, what is your estimation for 09:35:26
how much off target you're going to get? 09:35:31

A. As I said, it depends on the 09:35:33
genome. It depends on the gene region. 09:35:35
It depends on a myriad of factors. It 09:35:39
could be high. 09:35:44

Q. So greater than 50 percent or 09:35:45
less than 50 percent? 09:35:48

A. It depends on the region of 09:35:49
interest. But, you know, it depends on 09:35:52
how many copies we're thinking about, 09:35:56

so... 09:36:00

Q. So, again, if we were taking 1 loci, do you think that somebody -- would having a reference genome and using a computer program to design their primers, single primer, you think it's a reasonable statement to believe that in that situation, the primer designed by a computer program with a reference genome would bind off target to the fragment 50 percent of the time? 09:36:00 09:36:02 09:36:03 09:36:06 09:36:10 09:36:13 09:36:16 09:36:18 09:36:20 09:36:24

MS. CIPRIANO: Objection, asked and answered. 09:36:25 09:36:26

A. I believe I've answered that question. 09:36:29 09:36:30

Q. Answer it again. 09:36:30

A. It depends on the conditions. 09:36:31

Q. So sometimes it might bind off target more than 50 percent of the time, sometimes it might bind 90 percent of the time? 09:36:34 09:36:35 09:36:37 09:36:40

MS. CIPRIANO: Objection, form. 09:36:41 09:36:41

A. Could you simplify the 09:36:44

question for me? 09:36:45

Q. Well, you said, "it depends." 09:36:45

Sometimes it would bind on target 09:36:47
90 percent of the time, sometimes it 09:36:49
would bind 50 percent of the time; is 09:36:51
that what you're saying? 09:36:53

A. That's not what I said. I 09:36:54
said, "It depends on the conditions." 09:36:55

It depends on the genome. 09:36:56

It depends on the gene region. 09:36:58

It depends on how many actual copies 09:37:00
there are in the genome, not how many 09:37:03
copies are annotated in the reference 09:37:04
genome. 09:37:07

There are some regions that are 09:37:07
very hard to sequence. There are other 09:37:08
regions that aren't so hard to sequence. 09:37:12
Some of the time you'll get perfectly 09:37:13
good sequence from a single primer. 09:37:15
Sometimes you won't. It depends on the 09:37:19
conditions. 09:37:21

And, again, today looking back at 09:37:22
that, we know the technology works well 09:37:24
and you can program it well. So putting 09:37:26

ourselves back at that time, I understand why he wrote what he wrote. 09:37:30 09:37:34

Q. So you say today that the technology works well. Putting yourself back in the time, it may not have worked that well. 09:37:35 09:37:38 09:37:39 09:37:42

So are you saying that Primer3, that computer design program, has substantially changed from pre-2012 to current day? 09:37:43 09:37:47 09:37:50 09:37:52

A. Yeah. The way I read the Declaration, he was suspicious the technology would work and then later on says, I was surprised to see how well it worked. 09:37:54 09:37:55 09:37:58 09:38:00 09:38:03

Q. Have you looked at the data that he purports to create? 09:38:04 09:38:06

Have you asked the folks at Tecan to look at the data? 09:38:07 09:38:10

A. I was not asked to look at the data. 09:38:11 09:38:12

Q. I'm not asking whether you were asked to. 09:38:12 09:38:14

Were you curious, as a scientist, 09:38:15

to see the data that he claimed to have generated? 09:38:17 09:38:19

A. I was not given access to the data. I was -- I don't have the data. So I can't opine on the data. 09:38:22 09:38:25 09:38:28

Q. Did you look for it? Did you ask for it? 09:38:29 09:38:31

A. I believe that is a question of privilege. 09:38:33 09:38:35

Q. The question is, did you ask for it, yes or no? 09:38:38 09:38:40

MS. CIPRIANO: You can answer. 09:38:41

A. I -- I believe I asked whether any of this was available. I don't remember if -- but I believe it wasn't available. 09:38:45 09:38:49 09:38:52 09:38:56

At one point I asked about some of this, but I don't recall ever getting access to the data or knowing whether the data was available. 09:38:57 09:38:59 09:39:02 09:39:03

Q. Reading his Declaration, what understanding do you have as to when the data was created, 2012 or sometime near when he signed the Declaration? 09:39:05 09:39:08 09:39:10 09:39:15

MS. CIPRIANO: Objection to form. 09:39:18 09:39:20

A. (The witness reviews the exhibit.) 09:39:21 09:39:22

I can't tell you when the data was generated, based on the Declaration. I don't believe it's in there. 09:39:22 09:40:00 09:40:02

Q. So, I mean, you're a biostatistician by training, correct? 09:40:05 09:40:08

A. I'm a population geneticist by training. I have taught biostatistics and I have a Master's in biostatistics -- in statistics. 09:40:09 09:40:11 09:40:14 09:40:16

Q. So, actually, one of the things you do is you look sometimes at raw sequencing data and try to figure out what it means, correct? 09:40:17 09:40:17 09:40:19 09:40:22

A. That is an area of active research in my lab. 09:40:23 09:40:26

Q. What about prior to 2012, was that an area of "active research in your lab"? 09:40:27 09:40:30 09:40:32

A. Yes, it was. 09:40:32

Q. So, as someone who, actually, 09:40:33

worked with such data prior to 2012 -- on 09:40:36
Illumina instruments, for example? 09:40:39
A. We worked a lot on Illumina 09:40:41
instruments. 09:40:43
Q. So back at that timeframe -- 09:40:43
A. Yes.
Q. -- pre 2012 --
THE STENOGRAPHER: You have to wait for him to finish. I'm sorry.
THE WITNESS: I'm sorry.
THE STENOGRAPHER: It's really difficult.
Back in that what? 09:40:48
Q. Back in that timeframe 09:40:48
pre-2012, you worked with interpreting 09:40:50
raw data from Illumina sequencers, right? 09:40:53
A. That is accurate. 09:40:55
Q. Based on your own experience 09:40:58
pre-2012, was there a level of data which 09:41:01
was representative of what you were 09:41:09
trying to sequence, which was necessary 09:41:11
for sequencing results to mean anything? 09:41:15
A. That is a really broad 09:41:19

question. 09:41:21

Q. Sure. 09:41:21

So let's say you have a situation where only 25 percent of your reads are really what you're looking for coming off of an Illumina sequencer, alright? You have that in mind? 09:41:22 09:41:23 09:41:31 09:41:33 09:41:37

A. I do. 09:41:38

Q. And would it be fair to say using Dr. Brooks's characterization that that would be representative of a relatively high off-target hybridization rate to your fragment? 09:41:38 09:41:43 09:41:45 09:41:47 09:41:50

MS. CIPRIANO: Objection to form. 09:41:53 09:41:57

A. I'm a little bit lost, in terms of the hypothetical experiment. 09:41:57 09:41:59

Are we talking hybridization? 09:42:01

Are we talking about genome sequencing? 09:42:02 09:42:04

What's the setup that you would like me to answer? 09:42:04 09:42:06

Q. We have a situation where we created a library using a single primer. 09:42:06 09:42:08

A. Okay. 09:42:10

Q. And only 25 percent of the fragments that get created that get read on the Illumina sequencer are really what you want. 09:42:11 09:42:14 09:42:18 09:42:20

A. Okay. 09:42:21

Q. And 75 percent are not what you want. 09:42:22 09:42:23

A. Okay. 09:42:24

Q. Would you say that that would be characteristic of "a relatively high rate" of off-target hybridization, as Dr. Brooks was talking about in Paragraph 14? 09:42:25 09:42:27 09:42:30 09:42:34

A. And, again, just to clarify, 25 percent are on target, 75 percent are off target? 09:42:39 09:42:42 09:42:42

Q. Correct. 09:42:42

A. That's the readout from the experiment? 09:42:43 09:42:44

Q. Correct. 09:42:45

A. I would say that's a high degree of off target. 09:42:45 09:42:47

Q. Okay. "That's a high degree of off target period"? 09:42:49 09:42:51

A. Yes. 09:42:52

Q. Okay. And as a biostatistician, somebody who has worked with raw data, would you say that that makes it not useful to be able to interpret that data -- no, I'm going to withdraw the question. 09:42:53 09:42:54 09:42:57 09:42:58 09:43:04 09:43:07

As a biostatistician or somebody who worked with raw data from a Illumina sequencer from prior to 2012, would you say that that data, which was only 25 percent of what you want, can't be used? 09:43:08 09:43:09 09:43:12 09:43:13 09:43:15 09:43:18

A. That's not what I said. 09:43:19

You can, certainly, use it and you might be able to interpret it and there might be situations where the sample is so precious that you are willing to have only a couple percent, right. 09:43:20 09:43:22 09:43:23 09:43:28 09:43:33

We did a lot of work in ancient DNA sequencing where that was the case. We've done work in other situations where, you know, the minority of the sample is what you want. 09:43:36 09:43:38 09:43:39 09:43:42 09:43:44

In general, if you had 25 percent of what you want, it's not ideal. Could you analyze it? You could analyze it. 09:43:45 09:43:49 09:43:52 09:43:54

Q. Absolutely, you can analyze it, especially if you have a reference genome to map it to, correct? 09:43:55 09:43:57 09:43:59

MS. CIPRIANO: Objection to form. 09:44:01 09:44:02

A. You could analyze it. You may not be able to distinguish depending on the mapping, right, because we saw this all the time where you map reads and they either map to multiple locations, so you don't know where the read, actually, belongs, or if you have a collapsed duplicate region and you have high coverage relative to some other region, what's actually going on. So whether or not you could interpret it really depends on the situation, the scenario and how accurately it worked. 09:44:02 09:44:04 09:44:06 09:44:08 09:44:11 09:44:14 09:44:16 09:44:18 09:44:19 09:44:21 09:44:24 09:44:26 09:44:28

Q. Certainly, much easier to interpret it when you have a reference 09:44:28 09:44:30

genome, as opposed to you're doing de novo, correct? 09:44:32 09:44:36

MS. CIPRIANO: Objection to form. 09:44:36 09:44:36

A. Reference genome helps in the analysis of next generation sequence data. 09:44:36 09:44:36

MR. BILSKER: Alright. Why don't we take a break because we've been going about an hour. 09:44:40 09:44:40 09:44:42

A. Okay. 09:44:43

(Recess taken 9:44 to 9:55 a.m.) 09:44:44 09:51:47

Q. Dr. Bustamante, one of the things you talked about earlier this morning was "collapsed regions" of the genome, right, like repeats and collapsed regions of the genome? 09:55:23 09:55:24 09:55:26 09:55:30 09:55:33

A. That -- we mentioned -- I mentioned "collapsed regions" of the genome, yes. 09:55:35 09:55:37 09:55:39

Q. So the human genome by 2011 had been relatively well characterized, right? 09:55:40 09:55:42 09:55:44

A. There was a good -- I still 09:55:46

think called draft genome of the human genome. There were regions that were still not well mapped. 09:55:49 09:55:53 09:55:55

Q. In 2011, to the best of your knowledge, what percent of the genome was collapsed? 09:55:57 09:56:00 09:56:03

A. I mean, hard to know. I would say upwards of probably 85, 90 percent of the genome was accessible, especially using next generation sequencing. 09:56:06 09:56:08 09:56:12 09:56:17

Q. But what percent of the genome that was known at that time was collapsed and repeat? 09:56:21 09:56:23 09:56:28

MS. CIPRIANO: Objection. 09:56:29

A. Again, what's collapsed is -- we don't fully know, right. There are things that were regions that were unassembled. There were regions where you didn't know they were collapsed, right. So there were repeat mass regions. So it's, you know, on the order of ten -- again, it also depends on the sequencing technology that you're using. 09:56:30 09:56:32 09:56:34 09:56:36 09:56:39 09:56:42 09:56:46 09:56:51 09:56:52

So, if you're using Illumina 09:56:53

short-read sequencing versus ONT sequencing or PacBio sequencing, you might be able to sequence through some of the more complex regions with genome. 09:56:57 09:57:04 09:57:06 09:57:08

Q. If a person of ordinary skill in the art in 2012 didn't know how many regions of the genome were collapsed and repeat, they wouldn't have any expectation that a primer that they designed, specifically, for one target would potentially bind off target to a lot of other things, right? 09:57:09 09:57:11 09:57:14 09:57:16 09:57:19 09:57:22 09:57:25 09:57:29

A. You wouldn't know exactly how many they would bind to, but you would be aware of the concept that you may get off-target binding. 09:57:32 09:57:34 09:57:36 09:57:40

Q. You're aware of the concept that it's a theoretical possibility. 09:57:40 09:57:42

But why would you expect it to be relatively high, if you had no idea of what the level of collapsing of that part of the genome was? 09:57:43 09:57:45 09:57:47 09:57:50

A. Collapsing isn't the only way you would get off-target binding. 09:57:51 09:57:53

Q. We're just talking about off target to the fragment that you're trying to bind to in the first step of an extension reaction. 09:57:55 09:57:57 09:57:58 09:58:01

Why would you expect "a relatively high rate" of off target, if you have no idea what the level of collapse is in the genome of that region that you're targeting? 09:58:02 09:58:04 09:58:07 09:58:09 09:58:12

A. Could you repeat the question? 09:58:21

MR. BILSKER: Can you read it back for him, please. 09:58:23 09:58:23

(Whereupon, the question is read back as follows:

"Question: We're just talking about off target to the fragment that you're trying to bind to in the first step of an extension reaction.

Why would you expect 'a relatively high rate' of off target, if you have no idea what the level of collapse is in the genome of that region that you're targeting?") 09:58:46

A. Again, I would caveat by 09:58:46

saying it really depends on the region that you're targeting, but the fact that you would get off-target effects and more off-target effect with a single versus dual primers was well understood at the time. 09:58:48 09:58:50 09:58:53 09:58:58 09:59:01 09:59:03

Q. Again, not what we're talking about. 09:59:03 09:59:05

We're not talking about off-target effects right now. We're just talking about the single primer that you've designed for a single primer extension reaction. 09:59:05 09:59:07 09:59:09 09:59:13 09:59:15

If you don't know what the level of collapse is in that region of the genome that you're targeting, why would a POSA pre-2012 expect "relatively high rates" of off-target binding to that fragment? 09:59:15 09:59:17 09:59:20 09:59:23 09:59:27

A. They may be concerned about off-target effects precisely because they don't know how many time it has collapsed and especially if you're trying to target a region that is a complex region of the genome, off-target binding is a concern. 09:59:33 09:59:35 09:59:37 09:59:40 09:59:42 09:59:45

Q. Being "concerned" and expressing an opinion that there is going to be "a relatively high rate" of off target are two different things, right? 09:59:48 09:59:49 09:59:52 09:59:56

MS. CIPRIANO: Objection to form. 10:00:00 10:00:02

A. Could you simplify the question for me? 10:00:02 10:00:03

Q. Sure. I'll give you an example. I mean, walking in here there is scaffolding outside, right, in front of the building let's say. 10:00:04 10:00:05 10:00:07 10:00:10

A. That could be. I didn't see scaffolding coming in. But I'm happy to believe you that there was scaffolding outside. 10:00:11 10:00:14 10:00:15 10:00:17

Q. There is a big difference between being concerned that something may fall through the scaffolding and hit me, being concerned, and thinking there is "a relatively high rate" that that is going to happen, right? 10:00:17 10:00:21 10:00:21 10:00:24 10:00:25 10:00:27

Those are two totally different things, right? 10:00:28 10:00:30

A. I agree that "those are two totally different things." 10:00:31 10:00:33

I think in the matter before us, especially in the context of multiplexing, especially in the context of 2012 and the question of whether it was reasonable to hold an opinion that one would be suspicious that single primer could work, I think, it's reasonable that Dr. Brooks held the opinion that he held at the time. 10:00:34 10:00:36 10:00:38 10:00:44 10:00:46 10:00:50 10:00:54 10:00:56

Q. Well, again, being "suspicious" is totally different than expressing an affirmative statement that is you would expect "a relatively high rate" of off-target binding. 10:00:59 10:00:59 10:01:02 10:01:04 10:01:08

Being suspicious that it might happen is totally different than saying you would expect "a relatively high rate," correct? 10:01:11 10:01:13 10:01:14 10:01:17

MS. CIPRIANO: Objection, asked and answered. 10:01:17 10:01:18

A. I believe I've answered the question. 10:01:19 10:01:20

Q. Answer it again. 10:01:22

A. As I've stated before, I believe that in the context of single primer extension in multiple targeted regions. 10:01:23 10:01:25 10:01:30 10:01:34

It is reasonable to suppose, as Dr. Brooks did, that you may get a high degree of off-target binding at the time. It was disproven. I mean, at the end of the day, the supposition was disproven by the data. So it's a question of whether he could hold that opinion reasonably. I think it's a reasonable opinion for him to have held. 10:01:34 10:01:38 10:01:40 10:01:44 10:01:46 10:01:49 10:01:52 10:01:54 10:01:56

Q. So, to hold that opinion reasonably, actual scientific facts that you would have to rely on, one would be in a genome which has been mapped already, you would actually -- 10:01:56 10:01:59 10:02:02 10:02:04 10:02:06

A. Mostly mapped. 10:02:07

Q. You would have to see repeats or collapses in that region that you're targeting for you to be able to express the opinion that you would expect "a relatively high rate" of off target in 10:02:09 10:02:11 10:02:15 10:02:17 10:02:19

that first step of a single primer extension reaction, correct? 10:02:22 10:02:25

A. May or may not, depends on the region, depends on the condition. There are -- there are updates to the reference genomes where regions that were prior -- were previously collapsed are un-collapsed and you see that they were -- that the reason they were collapsed is because they thought to be one region. 10:02:27 10:02:29 10:02:32 10:02:36 10:02:37 10:02:38 10:02:41 10:02:42

Q. So there were regions that very well characterized pre-2012, correct? 10:02:45 10:02:47

A. There were regions that were well characterized before the human genome project. But, yes, before 2012, there were regions that were well characterized. 10:02:52 10:02:53 10:02:56 10:02:58 10:02:59

Q. So like the P53 genome, that's well characterized pre-2012, correct? 10:02:59 10:03:03

A. I -- yeah, although there can be multiple copies of P53. But let's -- we can choose -- a well characterized region. 10:03:04 10:03:07 10:03:10 10:03:13

Q. P53 is a cancer gene, right? 10:03:14

A. P53 is a cancer gene. 10:03:17

Q. It's a gene that people look at a lot, because it's responsible for many types of cancer, right? 10:03:19 10:03:21 10:03:23

A. That's accurate. 10:03:24

Q. Important gene, correct? 10:03:25

A. I would consider P53 an "important gene." 10:03:27 10:03:29

Q. Other ones like BRCA, BRCA 1, BRCA 2 that are linked to breast cancer, right? 10:03:29 10:03:32 10:03:35

A. They are. And there your duplications in BRCA 1 and BRCA 2 and there are duplications that are germline duplications and they're duplications in cancer. 10:03:35 10:03:36 10:03:38

THE STENOGRAPHER: Can you just go a little slower?

THE WITNESS: Sorry. I apologize.

THE STENOGRAPHER: You're a scientist. I'm just a Court Reporter.

THE WITNESS: I understand,

ma'am. I apologize.

THE STENOGRAPHER: That's okay; BRCA 1 and BRCA 2?

A. BRCA 1, BRCA 2 gene regions are important for cancer and they are also sometimes duplicated. 10:03:50 10:03:53 10:03:55

Q. BRAF, another important cancer gene that's well characterized pre-2012, correct? 10:03:58 10:04:01 10:04:03

A. BRAF is a well-characterized gene. It can also have duplications depending on whether you're talking germline or cancer somatic mutations. 10:04:04 10:04:05 10:04:07 10:04:10

Q. In fact, the BRCA gene -- pre-2012, Myriad Genetics was, actually, offering a clinical diagnostic based on sequencing, wasn't it? 10:04:13 10:04:15 10:04:19 10:04:21

A. It was a clinical diagnostic mostly focused on single nucleotide variants. The degree to which they were also able to detect duplications in that gene. It depends on perhaps other technologies. I don't know when they switched. It could have been 10:04:22 10:04:24 10:04:28 10:04:30 10:04:33 10:04:35 10:04:36

hybridization or... 10:04:37

Q. So you're not sure whether 10:04:38

pre-2012 Myriad was offering a product in 10:04:40

which -- a clinical product, diagnostic 10:04:44

product, in which they, actually, 10:04:46

sequenced the BRCA gene? 10:04:47

MS. CIPRIANO: Objection to 10:04:49

form. 10:04:50

A. That's not what I said. 10:04:50

I said, they were using a sequencing 10:04:51

product for single nucleotide variants. 10:04:53

There are also structural variants in 10:04:57

that gene and I'm not sure when they 10:04:59

switched technologies and whether they 10:05:04

were using just sequencing or using 10:05:07

sequencing and other technologies to 10:05:11

detect duplications. 10:05:12

Q. So the BRCA gene, the P53 and 10:05:14

the BRAF, were those well characterized 10:05:18

with respect to the level of collapse and 10:05:21

duplication? 10:05:25

A. In the reference genome. 10:05:27

But, again, if you're talking about a 10:05:29

patient sample, you might get multiple 10:05:31

binding that could be due to duplications in that sample. 10:05:35 10:05:38

Q. So it's theoretically possible you're saying? 10:05:38 10:05:40

A. It's generally theoretically possible. It might be the reason you might order a clinical test. 10:05:42 10:05:45 10:05:47

Q. Might actually do the test or create a library and sequence it to see if there are duplicates, right? 10:05:48 10:05:49 10:05:52

A. You -- yes, you would potentially sequence a panel of cancer genes. 10:05:54 10:05:57 10:05:59

Q. You're also aware, for example, of Affymetrix gene chips, right? 10:06:10 10:06:12

A. I am aware of Affymetrix gene chips. 10:06:16 10:06:18

Q. Back in the pre-2012 era, those gene chips had -- I'm just going to call them -- spots or probes on them, which in theory would capture fragments that were run over them that might be representative of mutations in a patient's sampling, correct? 10:06:18 10:06:21 10:06:26 10:06:28 10:06:33 10:06:36 10:06:40

A. They were designed to detect mostly single nucleotide polymorphisms, which are segregated variants in the population. 10:06:43 10:06:45 10:06:48 10:06:50

Q. And in detecting the single nucleotide polymorphisms for those regions, those regions in which they're detecting the SNPs, S.N.P. -- 10:06:51 10:06:56 10:06:57 10:06:59

A. Yes. 10:07:02

Q. -- would you say those regions were well characterized? 10:07:02 10:07:04

A. Affymetrix had multiple rounds of design for their arrays and often had to limit the array designed to well characterized gene regions. 10:07:08 10:07:12 10:07:17 10:07:19

Q. So regions that were used on Affymetrix' chips were, in your estimation, using the English language "well characterized," correct? 10:07:21 10:07:25 10:07:28 10:07:32

A. They had to limit themselves to the regions in the human genome for which their assays could yield reliable genotypes. 10:07:34 10:07:36 10:07:39 10:07:44

Q. The places where they limited 10:07:45

themselves or the regions they limited themselves to, were those regions that had collapsed or duplicate regions in the genome? 10:07:47 10:07:50 10:07:51 10:07:57

A. Sometimes they did. You could use the Affymetrix array to detect copy number variation. 10:07:57 10:07:59 10:08:01

Sometimes they trialed in variant probes precisely for that reason and sometimes you had situations where you had cross-talk among the probes. But, in general, it was a reliable assay for detecting SNP genotypes. 10:08:04 10:08:06 10:08:08 10:08:14 10:08:16 10:08:18

Q. Got it. 10:08:20

If we go back to the situation where we're designing primers, so pre-2012, are you familiar with a program called BLAST, B-L-A-S-T? 10:08:21 10:08:27 10:08:30 10:08:33

A. I've heard of "BLAST." 10:08:33

Q. I assume you've used it, correct? 10:08:35 10:08:37

A. I have used BLAST. I've even taught BLAST in one of my bioinformatics classes. 10:08:37 10:08:44 10:08:47

Q. And one of the ways BLAST could be used -- is BLAST used in primer design at all? 10:08:48 10:08:50 10:08:52

A. Could be used. 10:08:53

Q. How would it be used in primer design? 10:08:55 10:08:57

A. You might use BLAST to search the reference genome for the degree of homology of a given sequence to the rest of the genome. 10:08:58 10:09:04 10:09:09 10:09:13

Q. Got it. 10:09:14

So hybridization is one piece of DNA anneals or hybridizes -- anneals complementary to another piece of DNA based on certain conditions, correct? 10:09:15 10:09:21 10:09:25 10:09:27

A. I would agree with that. 10:09:30

Q. And based on the length of the primer and the annealling temperature, the polymerase you're using, whether you have other additives in there like magnesium or other things, you can actually make a prediction as to the conditions under which a primer might anneal to another sequence, correct? 10:09:31 10:09:33 10:09:40 10:09:45 10:09:46 10:09:49 10:09:51 10:09:54

A. In a hybridization array or in a PCR reaction? 10:09:58 10:09:59

Q. In a PCR reaction. 10:10:00

A. Yes, that's -- that is the goal of primer design. 10:10:03 10:10:05

Q. And, in 2012, if you used a program like Primer3 to design a primer to target a specific region that you're interested in, say, some gene that maybe is responsible for cancer, that's something that was frequently done by people of skill in the art pre-2012, correct? 10:10:10 10:10:12 10:10:15 10:10:17 10:10:21 10:10:25 10:10:27 10:10:30

A. And they would often design dual primers to target the gene region of interest, not just one primer. 10:10:30 10:10:32 10:10:34

Q. Whether it's dual primers or one primer, that is something that people did, correct? 10:10:35 10:10:37 10:10:38

A. And often in the context of dual primers. So that you could target the region you're most interested in and differentiate, for example, homology among similar genes. 10:10:39 10:10:41 10:10:43 10:10:45 10:10:47

Q. Right. 10:10:52

So let's just take the situation 10:10:52

where I've got a single primer. I've 10:10:54

created a single primer using a program 10:10:57

like Prime3 pre-2012 to target a specific 10:10:59

gene. 10:11:03

You got that in mind? 10:11:03

A. I'm following so far. 10:11:05

Q. So a computer program spits 10:11:07

out a primer, right? That's, essentially, 10:11:09

what it does? 10:11:11

It gives you a primer, which is an 10:11:12

oligonucleotide, with a number of 10:11:15

individual nucleotides, correct? 10:11:16

Or it's a polymer. It's not an 10:11:19

individual nucleotide, but a string of 10:11:20

nucleotides, right? 10:11:22

A. It would give you a sequence. 10:11:22

Q. You could take that sequence 10:11:24

and BLAST it against the known reference 10:11:26

genome, couldn't you? 10:11:29

A. You could. 10:11:30

Q. And what would you find if you 10:11:31

BLAST'ed it against the known reference 10:11:33

genome? 10:11:33

Could you actually come up with a prediction as to whether it's going to hybridize to parts of the genome other than what you're interested in? 10:11:37 10:11:38 10:11:41 10:11:43

MS. CIPRIANO: Objection to form. 10:11:45 10:11:46

A. Could you simplify the question for me? 10:11:46 10:11:48

Q. Sure. 10:11:49

What part don't you understand? 10:11:49

A. It was a compound question. 10:11:51

Q. So one of the things that you talked about was, well, you've got these collapsed regions of the genome and even if you design your primer, specifically, to target one region, say, of a gene, it's possible that there may be other parts of the genome that share homology and that it will anneal to that as well, right? 10:11:53 10:11:54 10:11:56 10:11:58 10:12:00 10:12:03 10:12:06 10:12:08 10:12:10

A. I'm not sure if that's what I said verbatim. But, in general, it is an encapsulation of the concept. 10:12:10 10:12:12 10:12:15

Q. So, to give yourself some level of security that that may not happen, you could take that primer that was designed, that single primer that was designed to anneal or hybridize, to one specific region and -- the terminology is called BLAST'ing it against the genome to see whether there's a prediction as to whether it's going to bind to any other part of the genome, correct? 10:12:17 10:12:20 10:12:22 10:12:24 10:12:26 10:12:30 10:12:33 10:12:36 10:12:38 10:12:41

A. So you would -- BLAST is not a binding algorithm. It looks for homology using the algorithm that sort of has a hash table representation of the genome. So, when you go through and you look for K-mers that are of a certain length and you find those K-mers, it gives you a sense of how many times it is represented in the genome. 10:12:42 10:12:43 10:12:47 10:12:57 10:12:58 10:13:00 10:13:04 10:13:07 10:13:09

Again, regions that are highly duplicated may themselves be collapsed, so they'll only come up once. So it doesn't necessarily get you away from that problem. But it is one of the ways 10:13:11 10:13:15 10:13:17 10:13:20 10:13:21

that you would attempt to improve your efficiency in primer design. 10:13:24 10:13:29

Q. So, actually, people designing primers -- people of ordinary skill in the art designing primers, in particular, even like a single primer would not only use a program like Primer3 but as a check like a competent scientist would also do other things, like search the genome by using a program like BLAST to see whether there are other regions of the genome which share homology where that primer that's been designed might also anneal to, right? 10:13:32 10:13:35 10:13:38 10:13:39 10:13:42 10:13:46 10:13:49 10:13:53 10:13:55 10:13:57 10:14:00 10:14:03

A. And I would say that is a simplification of the problem because you're often trying to optimize a multiplex reaction with many single primers that are all interacting and using a universal primer. At that point, BLAST alone cannot predict what will come out of that experiment. 10:14:03 10:14:06 10:14:09 10:14:13 10:14:16 10:14:18 10:14:23 10:14:26

Q. Not the question. 10:14:27

The question was, for the first step 10:14:28

of that extension reaction with a single primer extension, once the primer comes out of the program such as Primer3 pre-2012, you can take that sequence of the primer and compare it to a reference genome using a program like BLAST to make an approximation or a determination as to whether there is a likelihood that that primer, which has been designed, might anneal to other parts of the genome that you're not trying to target, right? 10:14:31 10:14:33 10:14:37 10:14:40 10:14:43 10:14:48 10:14:51 10:14:55 10:14:57 10:15:00 10:15:01

A. I -- I would agree that a step in optimizing primer design would be to use BLAST. At sometimes it will yield evidence that a primer binds to multiple locations in the genome and you may go back and redesign. It is evidence that primers, as designed, may yield -- may multiply blind. And if you use BLAST, you could potentially use it in a redesign. 10:15:05 10:15:12 10:15:15 10:15:21 10:15:23 10:15:25 10:15:29 10:15:32 10:15:35 10:15:37

Likewise, if you do an experiment with a primer and it comes back and you see that there are multiple binding and 10:15:37 10:15:39 10:15:41

off targets, you can then use BLAST to check whether this is a known region and that's the reason that you are getting multiple binding. 10:15:46 10:15:48 10:15:50 10:15:54

Likewise, there are times when BLAST may not be able to identify why a primer might bind to multiple regions including times when those regions are collapsed and unknown as collapsed in the reference genome. 10:15:54 10:15:57 10:16:06 10:16:08 10:16:11 10:16:15

Q. Right. 10:16:16

So, I mean, again, you're talking about theoretical possibilities when a collapse is not known. 10:16:16 10:16:18 10:16:21

But, I mean, if we're talking in percentages -- like, the level of collapse in the genome, we're not talking like 50 percent, are we? 10:16:22 10:16:25 10:16:29 10:16:31

A. I think, I had stated that, again, sitting here right now off the top of my head, my estimate is that about 85 percent of the genome was accessible to sequencing using Illumina at the time of the invention. It means 15 percent 10:16:32 10:16:34 10:16:38 10:16:43 10:16:45 10:16:46

wasn't. And there's all kinds of regions that we still are characterizing today using improved technology to improve the reference genome. 10:16:49 10:16:53 10:16:57 10:16:59

Q. But, for example, like the parts of the genome that were being accessed by an Affy chip, would you say that it's still 15 percent of those regions that were being accessed on an Affy chip were collapsed? 10:17:00 10:17:04 10:17:07 10:17:11 10:17:16 10:17:19

A. If we're going to speak about the MARA paper, can I have a copy of the MARA paper? 10:17:21 10:17:23 10:17:26

Q. I'm not speaking about the MARA paper. I'm asking you questions. 10:17:26 10:17:28

A. If it's specific to the MARA, we can talk -- in fact, MARA has the discussion about their conversion of SNPs and the efficiencies of conversion based on different metrics. 10:17:30 10:17:32 10:17:35 10:17:37 10:17:40

Q. Well, I asked you before whether the regions of the genome that the Affy chip was directed to were relatively well characterized and, I believe, that 10:17:41 10:17:43 10:17:46 10:17:51

you said, yes? 10:17:52

A. No, what I said was Affymetrix had to limit its array design to reasons of the genome that it could accurately probe and produce reproducible genotypes to and they went through multiple rounds of design. 10:17:53 10:17:57 10:17:58 10:18:00 10:18:04 10:18:06

Q. So given that they limited themselves to parts of the genome that they could reliably detect, is that an indication to you that the regions of the genome that they were accessing were relatively well characterized? 10:18:07 10:18:10 10:18:12 10:18:15 10:18:20 10:18:22

A. I would say that the regions of the genome that were genotyped through the Affymetrix array includes many regions that were well characterized and that the Affymetrix array also included additional probes for detecting copy number variation and other forms of variation that are amenable to investigation. 10:18:27 10:18:31 10:18:38 10:18:43 10:18:45 10:18:48 10:18:51 10:18:56

Q. So, the parts of the genome that were well characterized on the Affy chip, would you say that those regions 10:18:59 10:19:01 10:19:04

that were well characterized, they knew whether those regions were collapsed or not? 10:19:06 10:19:09 10:19:11

A. It depends on what version of the Affy array -- what Affy array are we talking about? 10:19:11 10:19:14 10:19:15

Q. Well, let's take the array that was actually being used in that Shapero paper, the MARA paper. 10:19:16 10:19:19 10:19:21

A. Could you give me a copy of the MARA paper so we can talk, specifically, about that array? 10:19:24 10:19:25 10:19:27

Q. Sure. 10:19:30

MR. BILSKER: Do you want a copy, Linnea? 10:19:39 10:19:40

MS. CIPRIANO: I have one. 10:19:40

(Deposition Exhibit QIAGEN 1006, Volume 32 Number 22 Nucleic Acid Research," was previously marked for identification.) 10:19:41 10:19:41 10:19:41

Q. So the MARA paper, the Shapero paper is exhibit QIAGEN 1006. 10:19:41 10:19:43

MR. BILSKER: I might have given you two copies there. 10:19:50 10:19:51

A. I'll give you one back. 10:19:52

MR. BILSKER: I'll give one 10:19:54
to the Court Reporter, who might 10:19:55
actually... 10:19:57

Q. So you asked for a copy of 10:20:04
the MARA paper and the question that was 10:20:06
standing was whether the regions of the 10:20:08
genome that the Affy chip that was being 10:20:11
used at the time of the MARA paper, 10:20:17
whether those regions were well 10:20:19
characterized? 10:20:20

A. It depends on which of the 10:20:21
arrays that we're talking about. They 10:20:22
used multiple arrays in this paper. 10:20:24

Q. Well, let's take any of them. 10:20:28

Were any of them well characterized, 10:20:34
the regions? 10:20:36

A. So, if we focus on the 10:20:39
commercially available Affymetrix gene 10:20:47
chip, say, the 100K array and I believe 10:20:52
that's one of the arrays that was used 10:20:57
here. They also used the 10-K array, if 10:20:59
I'm not mistaken. 10:21:03

In those arrays, you're often using 10:21:06

a restriction enzyme digest to identify regions of the genome that contain known polymorphisms and then actually you're often also using side selection. And so you are limiting yourself to a fraction of the genome that is well characterized both experimentally and computationally for markers that are within a certain distance of a restriction fragment or multiple restriction fragment sites. 10:21:10 10:21:19 10:21:24 10:21:27 10:21:30 10:21:31 10:21:35 10:21:39 10:21:41 10:21:45

(Stenographer clarification.) 10:21:59

A. Sites. 10:21:59

Q. So would you say -- so you're familiar with this paper, correct? You've read it? 10:22:05 10:22:08 10:22:09

A. I have read this paper. 10:22:10

Q. You've read it probably a few times, right? 10:22:11 10:22:13

A. I have probably read it more than once. 10:22:14 10:22:16

Q. And do you understand it? 10:22:16

A. I believe I have a good understanding of the paper. 10:22:18 10:22:20

Q. Are you familiar with how 10:22:23

they designed their primers? 10:22:24

A. In general or as -- are you 10:22:29

asking me about the MARA -- 10:22:34

Q. Yes. 10:22:36

A. -- technology? 10:22:37

I think, I have an understanding of 10:22:37

how MARA works. 10:22:39

Q. Do you know whether they used 10:22:42

a computer program to design their 10:22:44

primers? 10:22:46

A. We can look at the paper and 10:22:48

see if they mention a computer program. 10:22:50

Q. Well, I'll make it a little 10:22:51

bit quicker. 10:22:53

You can turn to page -- it's the 10:22:53

page that attorneys added on in the 10:22:57

bottom right corner rather then the 10:23:00

journal page number. 10:23:02

A. Okay. 10:23:03

Q. So, on Page 7 left-hand 10:23:03

column, "Materials and Methods," first 10:23:05

sentence. 10:23:07

A. (The witness reviews the 10:23:10

exhibit.) 10:23:13

Q. Do you see? 10:23:13

A. I see that. 10:23:16

Q. And so they used Primer3, which is a computer program, to design their single primer -- their target specific primer for their single primer extension reaction, right? 10:23:17 10:23:20 10:23:22 10:23:26 10:23:29

A. That they report that locus specific oligonucleotides were designed using Primer3. 10:23:31 10:23:33 10:23:35

Q. And not only did they use that, they also used the reference genome from July of 2003, the Bill 34, correct? 10:23:37 10:23:40 10:23:44

A. I see where it states that primers were designed using the July 2003 human reference sequence based on NCPI Bill 34. 10:23:50 10:23:52 10:23:55 10:23:57

Q. And you know -- do you know how long the three prime region of that primer -- of the primers they designed were? 10:23:59 10:24:01 10:24:03 10:24:06

A. It appears to state here that all oligos contain 23 basis of common sequence at the 5 prime end, the T3 10:24:10 10:24:13 10:24:17

promoter, followed by, approximately, 25 basis for locus specific sequence at the three prime end. 10:24:20 10:24:22 10:24:24

Q. And 25 basis at the three prime end, that's -- the chances of randomly hitting sequences when you have 25 basis of -- let me withdraw that. 10:24:25 10:24:27 10:24:33 10:24:36

Is 25 basis at the three prime end kind of a standard length for designing target specific primers? 10:24:38 10:24:41 10:24:43

A. It's in the range of where you would design a primer. 10:24:46 10:24:47

Q. So looking at that, looking at the -- just looking at the fact that they designed their primers using Primer3 mapped against the reference genome to areas that had already been targeted on an Affy chip that were well-characterized, would you say that a POSA in 2012 is going to think that those primers in the first step of an extension reaction are going to hit off target at "a relatively high rate"? 10:24:49 10:24:50 10:24:53 10:24:56 10:24:59 10:25:04 10:25:06 10:25:09 10:25:11 10:25:13 10:25:18

A. As we know from this paper, 10:25:18

the fact that they're using -- 10:25:21

Q. It's a yes or no. 10:25:23

MS. CIPRIANO: Objection, 10:25:30
form. 10:25:31

A. Could you restate the question 10:25:34
for me? 10:25:35

MR. BILSKER: Can you read it 10:25:36
back then please? 10:25:37

Q. I used to be able to remember 10:25:39
the questions in my younger days, but 10:25:40
it's a little harder now. 10:25:43

(Whereupon, the question is read back as follows:

"Question: So looking at that, looking at the -- just looking at the fact that they designed their primers using Primer3 mapped against the reference genome to areas that had already been targeted on an Affy chip that were well-characterized, would you say that a POSA in 2012 is going to think that those primers in the first step of an extension reaction are going to hit off target

at 'a relatively high rate'?")

A. They might. 10:26:17

Q. Not "they might." It's yes 10:26:19
or no. 10:26:21

Would you think -- would a POSA 10:26:21
say, I'm looking at this and I would 10:26:24
expect that those primers are going to 10:26:26
hit -- are going to anneal at a 10:26:28
relatively high off-target rate? 10:26:31

A. As I said, "they might." It 10:26:34
depends on -- and as we know from this 10:26:35
paper, in fact, there were off-target 10:26:38
effects. 10:26:40

Q. Yes or no, at a relatively 10:26:40
high off-target rate? 10:26:42

MS. CIPRIANO: Objection, 10:26:44
asked and answered. 10:26:44

A. I believe I've answered your 10:26:45
question. 10:26:46

Q. You have not. 10:26:46

So the question is a yes or no 10:26:47
question. You know, if you just say 10:26:49
there is no possible way in the world 10:26:52
that I can answer that yes or no, then 10:26:54

say it. But the question still stands. 10:26:55

Because Dr. Brooks made a 10:26:57

representation to the Patent Office under 10:27:01

oath that a person of ordinary skill in 10:27:04

the art would think that using single 10:27:06

primer extension, you would hit off 10:27:10

target at a relatively high rate. 10:27:13

And I'm asking you to step back -- 10:27:15

and this is, you know, a 2005 or 2004 10:27:17

paper. Let's say you're interpreting it 10:27:23

in 2004 up to 2011. 10:27:24

Would a person of ordinary skill in 10:27:27

the art think, based on the way the 10:27:31

primer was designed against portions of 10:27:33

the genome that Affy believed were well 10:27:36

characterized, that those primers are 10:27:40

going to anneal in the first step of an 10:27:42

extension reaction at a relatively high 10:27:46

off-target rate, yes or no? 10:27:50

MS. CIPRIANO: Same objection. 10:27:52

A. Because of the way Affymetrix' 10:28:00

technology -- 10:28:03

Q. Sorry. You got to answer it 10:28:03

yes or no and then you can go on to your 10:28:05

explanation. 10:28:07

MS. CIPRIANO: David, you 10:28:07
can't interrupt his answer. 10:28:08

MR. BILSKER: Yes, I can, if 10:28:09
he's going off script and he's 10:28:10
giving me a narrative. 10:28:12

In a trial, a judge would 10:28:13
say, answer the question and then 10:28:15
you can do your but or whatever 10:28:16
you want to do. But there needs 10:28:18
to be an answer to the question 10:28:19
of yes or no. 10:28:21

MS. CIPRIANO: He's giving you 10:28:21
an answer to the question. You have 10:28:23
to let him answer the question. 10:28:24

Q. Yes or no, that's what I'm 10:28:26
asking for. 10:28:27

MS. CIPRIANO: Same objection. 10:28:29

A. I've tried to answer the 10:28:39
question. Because the answer is it 10:28:40
depends and it's dependent on this 10:28:45
particular experiment. 10:28:47

Q. Dr. Brooks does not say, "it 10:28:48
depends," does he, in Paragraph 14 of his 10:28:49

declaration, which is Tecan Exhibit 2026. 10:28:52
He says -- yes or no, he says that -- he 10:28:56
says, I thought that the target specific 10:29:01
primers would bind to off-target sites at 10:29:03
a relatively high rate leading to 10:29:05
nonspecific enrichment nucleic acid 10:29:07
sequences that would flood the sequencing 10:29:10
system and confound sequence analysis. 10:29:14
He doesn't say, "it depends." 10:29:16
He says, this is what you would 10:29:18
expect. 10:29:20
So I'm asking you looking at the 10:29:20
primer design and the regions that they're 10:29:22
targeting, the way the primers were 10:29:24
designed in QIAGEN Exhibit 1006, which is 10:29:26
the Shapero MARA paper, would you say 10:29:29
that is what you would expect, that in 10:29:32
the first step of the extension reaction 10:29:34
these primers are going to bind at 10:29:36
relatively high off-target rates, yes or 10:29:38
no? 10:29:42
MS. CIPRIANO: Objection to 10:29:42
form. 10:29:43
A. Dr. Brooks wasn't talking 10:29:45

about this paper. 10:29:46

Q. Well, he was talking about 10:29:48
the Jones paper. 10:29:49

Jones which was a patent explaining 10:29:53
the same methodology, correct? 10:29:57

A. There's overlap between Jones 10:30:00
and the Shapero paper. 10:30:02

Q. Alright. Well, let's just 10:30:03
take it back. 10:30:05

Looking at Shapero, would you 10:30:06
expect, yes or no, based on the way the 10:30:07
primers were designed, as explained in 10:30:11
QIAGEN 1006, the Shapero MARA paper, that 10:30:15
the primers that are being used in the 10:30:19
single primer extension reaction in that 10:30:23
first step of extension are going to bind 10:30:26
at a relatively high-off-target rate, yes 10:30:28
or no? 10:30:32

A. They might. 10:30:32

Q. So, yes, you would expect it? 10:30:35

A. It is not unreasonable for 10:30:57
someone to "expect it." 10:30:59

Q. You, as a POSA pre-2012, 10:31:00
would you expect that those primers, 10:31:03

which are described in QIAGEN 1006, the Shapero MARA, would bind at a relatively high off-target rate to the fragment that they're targeting? 10:31:05 10:31:08 10:31:11 10:31:14

MS. CIPRIANO: Objection to form. 10:31:15 10:31:18

A. I would need time to look at the primers in order to form an opinion. But, in general, it is not unexpected that you will get some of them to be -- some of them to demonstrate off-target effects. 10:31:18 10:31:20 10:31:25 10:31:28 10:31:33 10:31:35

Q. Alright. So let's see if we can do some definitions. 10:31:35 10:31:38

What would you say is a relatively high off-target rate? 10:31:41 10:31:45

MS. CIPRIANO: Objection, asked and answered. 10:31:47 10:31:47

Q. A number. 10:31:47

What's your belief as to what a relatively high off-target rate is? 10:31:48 10:31:51

A. It depends on the experiment in question and the readout. Certainly, anything above 50 percent would be 10:31:55 10:31:57 10:32:06

considered a high off-target rate. At times even above 25 percent would be a high off-target effect. 10:32:08 10:32:12 10:32:14

Q. So it's 75 percent on target, 25 percent off target you could consider to be relatively high? 10:32:17 10:32:20 10:32:21

A. It could be relatively high, because -- again, because you're going to multiplex the reaction. In the case of MARA, as implemented in the arrays, it's not a big issue, because you have hybridization doing the work for you in detection. 10:32:22 10:32:24 10:32:26 10:32:30 10:32:32 10:32:34 10:32:37

If you have a 75 percent yield in any step in a reaction and you're multiplexing, if you're doing a thousand such reactions in SPET, then the overall yield across all of your targets will be miniscule. 10:32:37 10:32:40 10:32:42 10:32:44 10:32:50 10:32:53

So it really depends on whether you're trying to optimize a multiplex reaction or looking at this single toy example, which I don't believe is representative of the questions that the 10:32:54 10:32:55 10:32:57 10:33:02 10:33:04

technology is aiming to address. 10:33:06

Q. So you said you would have to study the primers more to make a determination as to -- sitting here today as an expert, whether you would expect a relatively high off-target rate for the primers. 10:33:18 10:33:20 10:33:24 10:33:27 10:33:29 10:33:31

And let's -- I'll limit it to the 250 plex. 10:33:32 10:33:34

You know what I'm talking about when I say, "250 plex"? 10:33:35 10:33:36

A. I do. I believe I understand "250 plex." 10:33:37 10:33:40

Q. So, in 250 plex, they're, actually, looking at 250 separate loci, right? 10:33:41 10:33:43 10:33:46

A. Yeah. 10:33:46

Q. So what specific -- you said you would, actually, have to study it more to make a determination as to whether you thought -- we'll limit it to the 250 plex -- as to whether the extension reaction itself, the primers binding in the extension reaction are binding at a 10:33:47 10:33:51 10:33:52 10:33:54 10:33:58 10:34:01 10:34:04

relatively high off-target rate; is that fair? 10:34:07 10:34:11

A. I think you're putting me in a difficult situation, because I now know the results of the experiment, you know. 10:34:11 10:34:13 10:34:15

So, you know, in retrospect, it's -- it is accurate -- it is accurate to say that for the 250 experiment, it worked well. When they scale out to higher numbers, it didn't work so well. So it really depends on the situation. 10:34:17 10:34:20 10:34:24 10:34:28 10:34:30 10:34:34

So, again, for a single locus, it's a, you know, potentially trivial problem. 10:34:35 10:34:37

For a thousand loci you're trying to multiplex, it's a combinatorial problem. 10:34:41 10:34:43

And so, I think, it really depends on, you know, the experiment you are trying to, ultimately, design to using the technology, which is multiplexing of many loci simultaneously with good balancing across the loci and to the question here whether NGS as a readout would be a reasonable way of doing that knowing what we know in 2011. 10:34:46 10:34:48 10:34:51 10:34:53 10:34:56 10:35:00 10:35:04 10:35:07 10:35:09

Q. Alright. So you said a lot of things in there. And I'm going to try to remember them and, like, talk about certain things, specifically. 10:35:12 10:35:14 10:35:16 10:35:18

So I believe that you said that a single locus is a relatively "trivial problem"? 10:35:19 10:35:24 10:35:27

A. Your setting it up as a "relatively trivial problem." 10:35:27 10:35:29

Q. Well, I think you said it was a relatively "trivial problem." 10:35:30 10:35:32

A. It could be a "relatively trivial problem." 10:35:34 10:35:35

Q. So, in the single primer extension situation using single primers, as described in the MARA Shapero 1006, you're saying using single prime extension as described there for a single locus is a relatively "trivial problem"? 10:35:36 10:35:38 10:35:41 10:35:45 10:35:45 10:35:48

A. No, I said it is -- it could potentially be for a single locus, but that's not the problem. The problem is you're designing for many loci at the same time. 10:35:50 10:35:52 10:35:54 10:35:56 10:35:58

Q. So what did you mean by it's a relatively -- it could be a relatively "trivial problem," designing single primer extension for a single loci? 10:35:58 10:36:00 10:36:03 10:36:05

A. I'm not sure that's exactly what I said. 10:36:06 10:36:08

Could you read back what I said around the -- 10:36:08 10:36:08

THE STENOGRAPHER: I have to fix it. You guys are flying. 10:36:08 10:36:14

A. Maybe we should slow down. 10:36:14

MR. BILSKER: Can you search for the word "trivial." It came up kind of in that long answer he gave a while ago.

(There is a discussion off the record.)

(Whereupon the partial answer is read back as follows:

"Answer: I think you're putting me in a difficult situation because I now know the results of the experiment, you know. So, you know, in retrospect, it's -- it

is accurate -- it is accurate to say that for the 250 experiment, it worked well.")

MR. BILSKER: Let's stop there.

Q. That's how it chronologically came out in your answer. 10:37:11 10:37:13

So you say for the 250 plex, "it worked well." 10:37:14 10:37:16

So there's a 250 plex experiment in Shapero, the MARA methodology, which is QIAGEN Exhibit 1006, right? 10:37:16 10:37:20 10:37:25

A. Yes. 10:37:28

Q. What did you mean by it worked relatively well? 10:37:29 10:37:31

A. Using MARA with the hybridization array, as a readout, worked well because of the design of the hybridization array with probes that are specific to each allel. You're able to mitigate the effects of off-target binding. 10:37:32 10:37:35 10:37:39 10:37:43 10:37:47 10:37:51 10:37:54

They cannot -- we actually cannot know from this experiment how much 10:37:55 10:37:58

off-target binding there was. But because they were only targeting 250 SNPs, all of which were already on the array, on an array that's already been optimized, they were able to get a reasonably high call rate, even if the concordance rate isn't as good for a typical microarray. 10:38:00 10:38:02 10:38:06 10:38:10 10:38:12 10:38:15 10:38:18

Q. Just interestingly, you say the concordance rate was not the same as it was for the typical array. 10:38:24 10:38:27 10:38:29

The concordance rate, are you using the discrimination score for that? 10:38:32 10:38:34

A. No, I'm using -- so concordance is the -- essentially, the replicability of the assay, as compared to a gold standard. In this case, they used -- the full array is the gold standard. 10:38:35 10:38:37 10:38:43 10:38:48 10:38:50 10:38:53

Oftentimes when you -- if you were to run the array twice, you'd get 99.5, 99.6 percent concordance. They found -- or, rather, .4 percent discordance. They found about fourfold higher discordance using the MARA method, even in the 10:38:53 10:38:56 10:38:59 10:39:04 10:39:09 10:39:12

simplest setup, which is their 250 primer plex. 10:39:14 10:39:18

Q. That's kind of a misleading statement; isn't it? 10:39:19 10:39:21

MS. CIPRIANO: Objection to form. 10:39:23 10:39:27

A. Could I rephrase -- could you explain why you think that is a misleading question? 10:39:28 10:39:30 10:39:32

Q. Well, would you agree with me if someone is being intentionally misleading -- 10:39:32 10:39:34 10:39:36

A. Well, I would -- 10:39:37

Q. Hold on. 10:39:37

Would you agree with me -- well, let's take it back. 10:39:38 10:39:39

In the academic world, there is a lot of news lately about academic misconduct and academic fraud in published papers, correct? 10:39:41 10:39:43 10:39:45 10:39:48

A. Sure. 10:39:52

Q. And would you agree that scientists who intentionally misrepresent things kind of are not to be believed? 10:39:53 10:39:55 10:39:58

A. I don't believe I'm misrepresenting. 10:40:01 10:40:03

Q. I'm not talking about you right now? 10:40:04 10:40:05

A. Okay. 10:40:06

Q. I'm saying, in general, would you agree with that? 10:40:06 10:40:07

A. I am uncomfortable with this line of question, in the sense that I'm not sure what you consider a "misrepresentation." 10:40:10 10:40:12 10:40:15 10:40:18

Q. I'm talking in generalities right now. 10:40:19 10:40:21

Would you agree with me that scientists who intentionally misrepresent in their papers really are not to be believed? 10:40:21 10:40:23 10:40:25 10:40:28

A. The scientists who in their papers misrepresent information are -- that's problematic. I realize that's problematic. 10:40:28 10:40:30 10:40:37 10:40:39

Q. And you said that discordance rate was fourfold higher using MARA than just using the prior methodology that 10:40:40 10:40:42 10:40:48

they used to create the libraries, correct? 10:40:52 10:40:54

A. About three to fourfold higher. 10:40:54 10:40:56

Q. Were they using the same thresholds in making that determination? 10:40:57 10:40:58

A. They're looking at concordance. 10:41:03 10:41:04

Q. Were they using the same thresholds in making the determination as to whether there was concordance? 10:41:04 10:41:06 10:41:08

A. In general, you measure -- 10:41:13

Q. I'm not talking about "in general." 10:41:16 10:41:17

A. You're not including the no calls. So, when you look at concordance, you're looking at the called genotypes and how they compare to a gold standard. 10:41:17 10:41:19 10:41:21 10:41:23

When you, typically, run microarrays, either concordance rate is in the 99.5 percent at the time of inventions under question and even at the time of the publication of this paper. 10:41:26 10:41:27 10:41:29 10:41:34 10:41:36

Q. Did you look in this paper as 10:41:37

to the thresholds they were using to determine whether something was called in the prior way that it was done and in the MARA methodology did you look at whether they were using the same thresholds to make those determinations? 10:41:39 10:41:41 10:41:46 10:41:49 10:41:51 10:41:55

A. They -- in general, when we report concordance -- 10:41:57 10:42:02

Q. I'm not talking about "in general." 10:42:02 10:42:04

A. Okay. 10:42:04

Q. I'm talking about in this paper, which you've read a number of times. 10:42:04 10:42:05 10:42:06

I mean, you are a biostatistician by training, right? 10:42:09 10:42:10

And you know mathematics, right? 10:42:12

Math is like pretty unequivocal, right? 10:42:14 10:42:17

Were they using the same thresholds to make the call? 10:42:20 10:42:22

A. So -- 10:42:28

Q. Yes or no? 10:42:29

MS. CIPRIANO: Objection to 10:42:29

form. 10:42:31

A. So, in fact, they were using a higher -- potentially a higher threshold, which would actually increase concordance. So they were using, I believe, a -- again, when we're talking about this paper and concordance, they were working to tune the threshold to maximize concordance. And at the concordance levels that they reach, the concordances are below the concordance that one, typically, sees when you run the whole genome sequencing -- with the whole gene sampling assay multiple times. 10:42:31 10:42:33 10:42:35 10:42:37 10:42:42 10:42:47 10:42:52 10:42:54 10:42:57 10:43:00 10:43:02 10:43:06 10:43:09

Q. So you're, actually, saying if you use a higher threshold to make a determination as to whether something is there or not -- so I got two situations. One -- 10:43:12 10:43:13 10:43:15 10:43:17 10:43:20

A. The no -- the no calls are not included in concordance. 10:43:20 10:43:21

Q. The situation where you have one threshold that's high and one threshold that's lower to make a 10:43:23 10:43:27 10:43:29

determination as to whether something is called, you're saying in a situation where you set your threshold higher you're actually going to get more calls than when you set the threshold lower? 10:43:31 10:43:34 10:43:35 10:43:37 10:43:41

A. Let me qualify that answer. 10:43:45

(The witness reviews the exhibit.) 10:43:54

So what they state here is that the discrimination score of a probe pair is defined as the ratio of the difference between the PM and MM over the sum of PM and MM where "PM" is the Perfect Match intensity and "MM" is the mismatch cell intensity, and thus service as a measure of detection of DNA target sequences. 10:43:55 10:47:03 10:47:07 10:47:09 10:47:14 10:47:23 10:47:29 10:47:32

Typically, if the discrimination score for a SNP from a particular sample is less than .08, the specificity of hybridization signal is considered weak. So they used that discrimination score and a cutoff of .08 to filter out the weak signals on the 250 and 750 plex MARA. 10:47:36 10:47:38 10:47:40 10:47:42 10:47:45 10:47:49 10:47:55 10:48:03

They used a .03 score that is, 10:48:03

typically, used, as they say -- that that is higher than the typical threshold of .03 used in WGS detection. 10:48:08 10:48:14 10:48:17

Q. It's higher by like more than 50 percent? 10:48:22 10:48:25

A. Yes. 10:48:27

Q. So you're using different -- they're using different thresholds. They're using a much higher threshold in MARA than they were using in the prior methodology that was used to prepare the library for the chip, correct? 10:48:27 10:48:29 10:48:31 10:48:33 10:48:36 10:48:37

A. They are using a higher threshold. We don't know whether they're making genotype calls on everything that passes through the DS threshold. 10:48:40 10:48:41 10:48:43 10:48:48

Q. Right. 10:48:53

So you, as a scientist, a person with math training, cannot say that based on the data that's presented here that MARA is not performing as well as the prior library preparation method given that the DS is more than twice as high in the MARA analysis as it was in the prior 10:48:53 10:48:56 10:48:58 10:49:01 10:49:04 10:49:07 10:49:12

analysis? 10:49:16

A. We need to look and see. And, 10:49:16
I believe, in the papers referenced, we 10:49:21
could see the concordance rate at a DS 10:49:28
threshold of .08 versus .03. 10:49:32

Q. Right. 10:49:36

A. Now -- 10:49:37

Q. But you sitting here and in 10:49:37
your Declaration that you submitted 10:49:40
saying that MARA did not perform as well 10:49:41
as the prior library preparation method, 10:49:44
you're actually comparing apples and 10:49:48
oranges given that the threshold used in 10:49:50
MARA is more than twice as high as it was 10:49:53
in the prior library preparation method, 10:49:56
correct? 10:49:58

A. The concordancy is to the -- 10:49:59
so I believe the rationale -- so they're 10:50:04
using concordancy to the prior genotype 10:50:09
calls as the gold standard, which is why 10:50:13
they set them at a high threshold value. 10:50:15
That is not to say that when you, 10:50:18
typically, run you use a .03 as the 10:50:20
typical threshold. 10:50:23

Q. Yeah, but you're dancing around it, the question. 10:50:25 10:50:27

A. I'm not. I'm not. 10:50:27

Q. You unequivocally stated in your Declaration that MARA library preparation method was not performing as well as the prior methodology that was used, even though they're using different thresholds and it's the DS score that's used -- SNPs are called using the DS score, right? 10:50:29 10:50:31 10:50:33 10:50:35 10:50:40 10:50:42 10:50:44 10:50:48

A. We -- so, in this particular paper, they're using a .03 threshold to generate a true set to compare against. 10:50:49 10:50:51 10:50:57

At a .08 threshold, when you run two microarrays, you may still have that high concordance rate. We should check to see what is in the typical -- the .03 may or may not be what is, typically, run for microarrays when you're doing the replicate experiment. 10:51:00 10:51:04 10:51:07 10:51:09 10:51:13 10:51:15 10:51:17

Q. So, basically, based on this paper, there is no support for the statement that you made in your 10:51:19 10:51:20 10:51:21

Declaration when you said MARA doesn't perform as well as the other and you made a big deal of it. You said it's like four times -- it's a factor of four. 10:51:22 10:51:25 10:51:27 10:51:29

I mean, it's nonsense, isn't it based on this paper? 10:51:31 10:51:33

MS. CIPRIANO: Objection to form. 10:51:34 10:51:34

A. I -- I stand by the statement that as reported here, the concordance rate in their own hand, using their thresholds is below the typical concordance rate that we get from microarrays when optimized. 10:51:35 10:51:37 10:51:40 10:51:43 10:51:45 10:51:47

Q. That's like saying you run the hundred meter dash in 15 seconds and the world record is, you know, 9 seconds and, therefore, those two things are comparable. Even though, I mean, you're probably more than 40 years old and people who are olympic athletes are in their 20s and 30s and train all the time that you're comparing apples and oranges. 10:51:48 10:51:55 10:52:06 10:52:09 10:52:11 10:52:13 10:52:15 10:52:19 10:52:23

One is using a threshold that is 10:52:24

more than twice as high as the other to make SNP calls, and you're saying, oh, I'm not a -- I'm putting blinders on to the fact that they're jumping over a higher hurtle. 10:52:26 10:52:27 10:52:30 10:52:33 10:52:35

A. That is -- 10:52:36

Q. But I'm going to say it's four times as bad. 10:52:37 10:52:39

A. I think -- I think you're mischaracterizing the statement in the sense that they chose these thresholds to optimize for their concordance rate using a .08 that the investigator chose. They report a concordance rate that is objectively four times higher in discordance than when one typically achieves with microarrays. That is a very accurate statement. 10:52:40 10:52:41 10:52:47 10:52:50 10:52:54 10:52:58 10:53:00 10:53:05 10:53:07 10:53:10

Different investigators may choose different thresholds in order to optimize where they make calls or don't make calls, optimized in their hands using their own filter. The highest rate they could get was a discordance rate, which 10:53:12 10:53:14 10:53:16 10:53:18 10:53:20 10:53:23

is four times higher than the typical discordance rate. 10:53:25 10:53:27

Q. Right. 10:53:28

Giving themselves the detriment of making their threshold more than two times higher than what is typically used? 10:53:28 10:53:30 10:53:32

A. Because they also wanted to have a high call rate. Because both call rate and concordance are important metrics of usability of the array. 10:53:35 10:53:36 10:53:39 10:53:42

Q. Alright. We'll let the Judges decide whether that's a reasonable statement that you made. 10:53:44 10:53:46 10:53:49

What actual evidence do you see in the Shapero paper, QIAGEN Exhibit 1006, that shows you on the 250 plex they're getting high off-target binding in the first step of the extension reaction? 10:53:50 10:53:54 10:53:58 10:54:02 10:54:08

MS. CIPRIANO: Objection, misstates the record. 10:54:10 10:54:11

Q. What actual evidence do you see in the paper? 10:54:11 10:54:13

A. I believe, I've actually written in my declaration one can't 10:54:14 10:54:15

conclude the degree of off-target effect from the way that this experiment was run and the technology that you're using to assay. 10:54:17 10:54:20 10:54:23 10:54:25

Q. So there is no -- so fair statement, there is no evidence in the paper itself that the single primer and the single primer extension reaction that's used in the 250 plex or the single primer -- the single primer's plural that are used in the single primer extension reactions, as reported in the MARA paper, there is no actual evidence that they are binding at a high off-target rate in that first step of the exemption reaction, correct? 10:54:25 10:54:28 10:54:30 10:54:36 10:54:37 10:54:40 10:54:42 10:54:44 10:54:47 10:54:49 10:54:54 10:54:55

A. Whether or not they are binding at a high target rate, you couldn't read it out because the hybridization assay is designed to detect particular SNPs. So the off-target effects are washed out in the readout from the experiment. 10:54:56 10:54:57 10:54:59 10:55:01 10:55:03 10:55:05 10:55:07

Q. Yeah. Let's see if you can 10:55:08

stick to my question, instead of creating your own question. 10:55:10 10:55:12

There is no actual evidence in the MARA paper itself, QIAGEN Exhibit 1006, that shows a person of ordinary skill in the art that the primer -- the single primers that are used in the single primer extension reactions in the 250 plex are binding at a relatively high off-target rate in that first step of the extension reaction, correct? 10:55:13 10:55:15 10:55:19 10:55:22 10:55:24 10:55:26 10:55:27 10:55:31 10:55:33

A. I don't believe that the MARA paper can be interpreted in terms of off-target effects because of the way the readout is done using the hybridization array. 10:55:34 10:55:36 10:55:39 10:55:40 10:55:42

Q. Right. So there is no actual evidence in the paper itself that the primers in the 250 plex are binding at a relatively high off-target rate, correct? 10:55:43 10:55:44 10:55:47 10:55:49

A. I don't think you can know from the results of the experiments reported in the paper because of the way the experiment is designed. 10:55:51 10:55:52 10:55:54 10:55:56

Q. Right. 10:55:58

A. If you had high off-target 10:55:59
effects, they're washed out through the 10:56:01
hybridization process. 10:56:02

Q. Right. 10:56:03

So I know you don't want to answer 10:56:04
the question for some reason, but I'm 10:56:05
going to ask it again. It's a yes or no 10:56:07
question. 10:56:09

There is no actual evidence 10:56:09
presented in the paper that would show a 10:56:12
POSA that the primers that are used in 10:56:14
the 250 plex reaction, as reported in 10:56:17
QIAGEN 1006, the Shapero reference, are 10:56:20
binding at a relatively high off-target 10:56:22
rate, correct? 10:56:25

MS. CIPRIANO: Objection, 10:56:26
asked and answered. 10:56:27

Q. Yes or no? 10:56:28

A. There is no evidence either 10:56:29
way. 10:56:30

Q. Now, one of the other things 10:56:33
that you talked about -- well, you know 10:56:35
what, we've been going for a while. Why 10:56:38

don't we take a break. 10:56:40

A. Okay. 10:56:41

(Recess taken 10:56 to 11:13 a.m.) 10:56:51 10:57:30

MR. BILSKER: Alright. Let's go back. 11:14:20 11:14:22

Q. Going back to QIAGEN Exhibit 1006, which is the Shapero MARA paper. 11:14:22 11:14:25

Point me to data in that paper which would tell a POSA that the primers in the 250 plex are targeting the fragments at a relatively high off-target rate. 11:14:27 11:14:30 11:14:33 11:14:37 11:14:40

A. I'd like to point to my Declaration where we discuss interpretation of this experiment. 11:14:41 11:14:43 11:14:47

Q. Well, you have your Declaration in front of you. You're free to look at it. 11:14:51 11:14:55 11:14:57

But I don't want to spend a half hour for you reading through your Declaration and chewing up all the time. And this is the main reference we've been talking about in the IPR. 11:14:58 11:15:00 11:15:01 11:15:03 11:15:05

I would think that you would be familiar with it. And I'm asking you the question. 11:15:07 11:15:08 11:15:12

What data in the MARA paper, Shapero 1006, shows a POSA pre-2012 that there's a relatively high off-target rate of binding of the primers in the 250 plex, if any exist at all? 11:15:13 11:15:16 11:15:23 11:15:26 11:15:31

A. (The witness reviews his declaration.) 11:15:36 11:15:58

So, as I've discussed in my declaration, particularly, as it refers to the experiments around Chromosome 21, there were issues with the conversion rate of markers. And there is a discussion by the authors around potential factors that they discount, including GC content and others and the so-called primer conversion rate. 11:15:58 11:16:01 11:16:07 11:16:16 11:16:18 11:16:28 11:16:31 11:16:36 11:16:46

Ultimately, they did not provide an explanation for the failed target generation, but one could suppose that part of the failed target generation could be due to off-target effects that 11:16:48 11:16:49 11:16:51 11:16:55 11:16:57

impact the reliability of the genotype calls. 11:17:04 11:17:06

Q. So maybe you didn't hear my question. 11:17:07 11:17:08

The question was based on the 250 plex, not the 1,000 or the 4300 plex. 11:17:08 11:17:10

So what data in the paper on the 250 plex would tell a POSA -- what data, if any, in the paper would tell a person of ordinary skill in the art reading the Shapero MARA paper, QIAGEN 1006, that the primers in the 250 plex are binding at a relatively high off-target rate in the first step of the enrichment reaction? 11:17:13 11:17:16 11:17:19 11:17:25 11:17:27 11:17:31 11:17:35 11:17:37

MS. CIPRIANO: Objection, form. 11:17:40 11:17:41

A. Could you simplify the question for me? 11:17:41 11:17:43

Q. No. It's about as simple as it could get. 11:17:43 11:17:46

What data, if any, in the paper itself, in the 250 plex experiment demonstrates to a person of ordinary skill in the art that the primers in the 11:17:46 11:17:50 11:17:55 11:17:59

250 plex reaction are binding to their target sequences in the first step of the extension reaction -- in the extension reaction at a relatively high off-target rate? 11:18:00 11:18:04 11:18:08 11:18:10 11:18:13

A. (The witness reviews the exhibit.) 11:18:14 11:18:14

As I have mentioned previously and mentioned in my Declaration, because of the way the experiment is designed and uses hybridization as a readout, the impact of off-target binding is mitigated and it is difficult to surmise the degree of off-target binding from that experiment. 11:18:20 11:18:21 11:18:24 11:18:27 11:18:31 11:18:35 11:18:38 11:18:40

Q. So, in other words, there's no data that you can, actually, point to in Exhibit 1006 that would tell a POSA pre-2012 that in the 250 plex reaction the primers are binding at a relatively high off-target rate, right? 11:18:42 11:18:43 11:18:46 11:18:52 11:18:57 11:19:00

A. The experiment was not designed to assess the off-target binding rate because the readout using genotyping 11:19:01 11:19:02 11:19:05

array makes it a highly accurate reaction for the on-target effects. 11:19:09 11:19:16

Q. Again, you keep avoiding the answer. It's a simple yes or no. 11:19:18 11:19:20

There's nothing that tells a POSA pre-2012 in the 250 plex reaction, hey, these primers are binding at a high off-target rate, right? 11:19:22 11:19:24 11:19:28 11:19:31

A. This experiment was not designed to detect the off-target effects. In fact, it was designed to mitigate any off-target effects by the use of the hybridization array. So it would be an extrapolation of the experiments to make conclusions around the off-target effects. 11:19:32 11:19:34 11:19:36 11:19:38 11:19:40 11:19:43 11:19:47 11:19:49

Q. So what in this article based on the 250 plex would tell a person of ordinary skill in the art, hey, this library preparation method, this single primer extension method used in the 250 plex reaction is producing such crappy data that I wouldn't even bother trying to use this methodology to create a 11:19:50 11:19:53 11:19:57 11:19:58 11:20:00 11:20:03 11:20:06 11:20:09

library to put on an Illumina sequencer? 11:20:11

MS. CIPRIANO: Objection to form. 11:20:14 11:20:18

A. Could you simplify the question for me? 11:20:18 11:20:20

Q. Again, what's unclear about it to you? 11:20:21 11:20:22

A. Could you simplify the question for me? Could you -- 11:20:23 11:20:25

Q. What information in QIAGEN 1006, the Shapero MARA reference, tells a person pre-2012 that the library preparation method described there for the 250 plex is going to produce so many off-target amplicons that it would not even be worthwhile to attempt to try to create a library using this methodology for enrichment to run on an Illumina sequencer at that time? 11:20:26 11:20:29 11:20:34 11:20:39 11:20:41 11:20:45 11:20:51 11:20:54 11:20:59 11:21:03

A. Because of the design of the experiment, a POSA would understand that the utility has been potentially proven around microarray use. 11:21:07 11:21:08 11:21:12 11:21:18

There is nothing to suggest at the 11:21:21

time of the publication or into the period of NGS that it would translate given potential concerns in this and other literature around the use of single primers. 11:21:24 11:21:29 11:21:31 11:21:35 11:21:38

Furthermore, none of the papers that go on to cite, much less implement MARA and the -- using NGS. 11:21:39 11:21:41 11:21:46

Q. Well, then we'd be talking about anticipation. We're, actually, talking about obviousness. 11:21:51 11:21:52 11:21:54

Can you point to anything in this paper that would tell a person of ordinary skill in the art pre-2012, hey, this enrichment method, run for the hills, you cannot use this enrichment method to prepare a library for NGS sequencing, such as an Illumina sequencer in pre-2012, because you're going to get such crappy results? 11:21:56 11:21:57 11:22:00 11:22:02 11:22:04 11:22:07 11:22:12 11:22:14 11:22:17

What data in here indicates that to a person of ordinary skill in the art? If there is no such data, just say it. 11:22:19 11:22:21 11:22:22

MS. CIPRIANO: Objection, 11:22:24

asked and answered. 11:22:25

A. As I have stated previously, 11:22:27
the design of this experiment would lead 11:22:29
a POSA to understand its utility in the 11:22:36
context of hybridization arrays. There 11:22:43
is nothing in the paper that suggests 11:22:44
that it would transfer well into NGS and 11:22:47
because of concerns around single primer 11:22:51
versus dual primer for multiplexed 11:22:55
amplicons and the fact that the array 11:23:01
itself did not work as well as the 11:23:03
standard array would not motivate a POSA, 11:23:05
in my opinion, to take this into NGS and, 11:23:08
again, the evidence in the literature is 11:23:13
that nobody took it into NGS. 11:23:15

Q. Well, somebody -- 11:23:17

A. In fact, the paper is not all 11:23:18
that's cited. 11:23:20

Q. If somebody took it into NGS, 11:23:22
there would be no case because there 11:23:23
would be no patent, right? 11:23:25

It would be -- somebody would have 11:23:26
used it. 11:23:28

So let's take that off the board, 11:23:28

because you're creating hypotheticals which are just nonsense, right. And I would still like you to answer the question. 11:23:30 11:23:31 11:23:33 11:23:35

What would tell a person of ordinary skill in the art pre-2012 there is -- the data in here is so bad and so unequivocal that you would not even attempt to try are to use this library preparation method to prepare a library for next generation sequencing such as on an Illumina sequencer? 11:23:35 11:23:38 11:23:39 11:23:44 11:23:46 11:23:49 11:23:51 11:23:54

MS. CIPRIANO: Objection to form asked and answered. 11:23:55 11:23:56

Q. I'm asking you to point to actual data in this paper. 11:23:57 11:23:58

A. Again, I read this paper by Affymetrix employees as a demonstration of how they can target a subset of SNPs that they already know well -- or work well and demonstrate that in their hands it doesn't work as well as the existing technology and one cannot conclude from the paper that off-target effects aren't 11:24:00 11:24:04 11:24:06 11:24:09 11:24:12 11:24:16 11:24:19 11:24:24

a source of part of the reason it doesn't work as well. 11:24:31 11:24:33

Q. You're really going to go back to it doesn't work as well, even though the threshold was two and a half times higher? You're really doing that, seriously? 11:24:38 11:24:39 11:24:42 11:24:44 11:24:48

A. In my opinion, this is a paper by Affymetrix employees demonstrating that they can get some of the SNPs on the array to be targeted. But the broad utility of this, particularly, in the NGS is not established by this paper. There's nothing in this paper that suggests it will transfer over into NGS. 11:24:52 11:24:54 11:24:57 11:25:00 11:25:04 11:25:07 11:25:09 11:25:10

Q. So 99.4 percent of the SNPs targeted by the locus specific primers across nine individuals had a discrimination score of greater than .08, which they called binding the SNPs, right? 11:25:12 11:25:18 11:25:20 11:25:22 11:25:24 11:25:29

A. We can turn to -- 11:25:30

Q. Page 10 under Table 1. 11:25:32

A. (The witness reviews the 11:25:40

exhibit.) 11:25:42

Can you repeat your question? 11:25:42

MR. BILSKER: Can you read it back for him, please. 11:25:58

I'll just restate it. 11:26:11

Q. Page 10 of Exhibit 1006 says that using MARA -- so we're in the left-hand column. "The results of MARA 250 primer plex are summarized in Table 1. A total of 99.4 percent of the SNPs targeted by locus specific primers across nine individuals had a mean DS of greater than .08." 11:26:12 11:26:17 11:26:23 11:26:26 11:26:29 11:26:33 11:26:36 11:26:39

Do you see that? 11:26:43

A. I do see that. 11:26:44

Q. So 99 percent -- 99.4 percent of the SNPs targeted were, in fact, represented when using MARA, correct? 11:26:45 11:26:50 11:26:54

A. That is accurate. These are high performing SNPs that they have chosen as a first experiment. 11:26:59 11:27:02 11:27:04

Q. Yeah. Even when they used a discrimination score that was two and a half times -- more than -- more than two 11:27:08 11:27:10 11:27:11

and a half times higher than the discrimination score used to call SNPs in the prior methodology? 11:27:17 11:27:19 11:27:22

A. If they had used a lower discrimination score, they would have called fewer SNPs, right? 11:27:23 11:27:25 11:27:27

Q. No. 11:27:31

A. Yes. 11:27:31

Q. Quite the opposite. 11:27:32

A. If the discrimination score -- 11:27:35

Q. You're confused by that. I'm not going to spend more time on it. 11:27:42 11:27:44

A. It depends on which way we're going with the threshold on the discrimination score. If they had chosen a higher threshold, they would have called fewer SNPs. 11:27:46 11:27:48 11:27:49 11:27:51 11:27:53

Q. Yeah. 11:27:54

A. Okay. 11:27:54

Q. Yeah. They chose a threshold that was two and a half times as high as the previous methodology, yet they still got 99.4 percent of the SNPs called. 11:27:58 11:27:58 11:28:01 11:28:03

So, again, I'm not going to belabor 11:28:06

this. You're confused by it. We'll just move on. 11:28:09 11:28:11

What level of amplification do you actually need to have something light up on the Affy chip? 11:28:11 11:28:14 11:28:16

A. You need the equivalent of at the time somewhere between 500 nanograms to a microgram of DNA. 11:28:18 11:28:22 11:28:25

Q. So, if, in fact, the MARA preparation method in the 250 plex was off target at a relatively high rate, would it actually produce enough DNA to see to light up on the chip? 11:28:27 11:28:31 11:28:34 11:28:39 11:28:43

A. It depends on how many cycles they did and whether they quantified -- it may or may not. 11:28:47 11:28:49 11:28:55

Q. Well, you've read the paper a bunch of times. Again, this is the main reference we're talking about. 11:28:56 11:28:58 11:29:00

Quantitatively if they were off target 50 percent of the time, would there have been enough DNA for 99.4 percent of the time for the chip to light up on the SNPs, as they were 11:29:01 11:29:05 11:29:06 11:29:08 11:29:11

supposed to? 11:29:13

A. What we know is that when 11:29:16
they underloaded the array, they didn't 11:29:17
get much data. 11:29:19

Q. And when did they "underload 11:29:21
the array"? 11:29:23

A. When they put in less than a 11:29:23
hundred nanograms of DNA or about a 11:29:25
hundred nanograms of DNA, as I recall. 11:29:29

Q. So, why even bother to do any 11:29:30
enrichment, why not just do universal 11:29:32
amplification? 11:29:32

You're going to get -- I mean, 11:29:35
you're saying the chip is doing all the 11:29:35
work, right? 11:29:37

The chip is doing all the work on 11:29:38
the discrimination, the hybridization 11:29:40
chip, right? 11:29:41

Why not just do amplification of 11:29:42
your sample, you'll produce the SNPs that 11:29:45
you want and the chips kind of -- it's 11:29:48
going to be the discriminating factor? 11:29:50

MS. CIPRIANO: Objection to 11:29:52
form. 11:29:57

A. In general, when you're doing whole genome amplification, it's problematic for the array. 11:29:57 11:29:59 11:30:02

Q. Why? 11:30:03

A. Because whole genome amplification, again, is a multiplex problem, it generates unbiassed -- it generates uneven amplification relative to the starting material. 11:30:03 11:30:05 11:30:08 11:30:11 11:30:16

Q. What level of enrichment do you actually need for the Affy chip to work properly? 11:30:18 11:30:20 11:30:23

A. You would need sufficient material for it to hybridize to sufficient probes to generate an intensity that could be read by the reader. 11:30:24 11:30:26 11:30:29 11:30:31

Q. And based on the data that's presented in MARA, you can certainly draw the conclusion that they were on target enough to produce enough DNA for the chip to light up correctly 99.4 percent of the time, correct? 11:30:32 11:30:34 11:30:37 11:30:39 11:30:42 11:30:46

A. And you must also realize that the off target wouldn't bind as 11:30:47 11:30:49

strongly as the on target and the majority of the array is off target, so that you're washing out any off target signal. 11:30:52 11:30:55 11:30:57 11:31:00

Q. So would you conclude that based on the fact that 99.4 percent of the SNPs on the chip using even a higher threshold than was used previously showed up, would you conclude -- would a POSA conclude pre-2012 that, at least, 50 percent of enrichment was -- there was, at least, 50 percent enrichment? 11:31:06 11:31:09 11:31:12 11:31:16 11:31:18 11:31:22 11:31:24 11:31:28

A. Again, I would say it's difficult to conclude enrichment and it's difficult to conclude the degree of off-target effects from the experiments because of the way the hybridization arrays are designed to work. 11:31:33 11:31:36 11:31:39 11:31:42 11:31:43 11:31:45

I would say that what we can conclude from the experiment is that in the hands of Affymetrix experts in this field well beyond POSA, they were able to get SNPs to work that had already worked very well across different arrays using 11:31:47 11:31:50 11:31:52 11:31:55 11:31:58 11:32:03

the MARA approach. 11:32:06

Q. Now, they weren't able to get it to work when they just used common primers to amplify the fragments, correct? 11:32:08 11:32:09 11:32:12

A. Because they underloaded the array. 11:32:16 11:32:17

Q. Well, they -- when they used the common primers, primers that were common to the adaptor sequences, only 6.6 percent of the SNPs showed up, right? 11:32:18 11:32:21 11:32:23 11:32:27

A. Because they underloaded the array. If they had loaded the same amount of DNA, they would have gotten hybridization to the rest of the array. 11:32:31 11:32:32 11:32:35 11:32:38

Q. Alright. So you're saying that the negative control that they designed going through peer review -- so you've gone through peer review, right? 11:32:40 11:32:42 11:32:44 11:32:47

A. I have gone through peer review. 11:32:49 11:32:50

Q. And people that review papers in peer review in academic publications -- and Nucleic Acids Research is actually a relatively prestigious journal, right? 11:32:50 11:32:53 11:32:55 11:32:57

A. (No response.) 11:32:57
Q. Right? 11:33:03
A. Yes. 11:33:03
Q. So you're saying the reviewers really screwed up, because they missed -- when the negative control was reported here as only producing 6.6 percent of the SNPs, they should have said, guys you need to put a caveat in here because it's really not a negative control because you underloaded the array, so this really -- your negative control didn't really prove anything, you really screwed up? 11:33:04 11:33:07 11:33:09 11:33:12 11:33:15 11:33:17 11:33:20 11:33:21 11:33:24 11:33:26
All the reviewers missed that, but only you, Carlos Bustamante, was able to figure that out, right? 11:33:27 11:33:30 11:33:32
MS. CIPRIANO: Objection, misstates the testimony. 11:33:33 11:33:33
A. That's not what I said. 11:33:34
What I said was given that they've underloaded the array, it is not surprising that they didn't get much binding. 11:33:37 11:33:39 11:33:42 11:33:45
Q. Well, but you're, basically, 11:33:46

saying their control is just garbage, it's not showing anything because it's an apples to oranges comparison, because they underloaded the array and all the reviewers and all these scientists at Affymetrix in trying to, actually, show that they were performing, like, better than the negative control missed it too, but you only, Dr. Carlos Bustamante, have figured that out? 11:33:48 11:33:50 11:33:52 11:33:54 11:33:56 11:34:00 11:34:02 11:34:05 11:34:07 11:34:11

MS. CIPRIANO: Same objections. 11:34:11 11:34:13

A. That's not what I said. 11:34:13

I said, it's not surprising that their negative control yielded what they expected, which is that if you don't load sufficient material in the array, that you're not going to get hybridization; certainly, not the discrimination score that they said. 11:34:15 11:34:17 11:34:19 11:34:21 11:34:23 11:34:25 11:34:28

Q. So they underloaded the array? 11:34:29

They performed 35 cycles of PCR for the negative control experiment and you think they underloaded it? 11:34:31 11:34:34 11:34:35

A. Given the -- they did not do a whole genome amplification, right. So, if -- having loaded what they loaded, it's not surprising that you're not getting sufficient material to bind. 11:34:42 11:34:48 11:34:53 11:34:55 11:34:57

Q. Well, they actually -- it, actually, was a little bit better because they size fragmented, right, to sizes that, actually, were somewhat enriched for what they were looking for already, added the adaptors on. 11:34:58 11:34:59 11:35:01 11:35:04 11:35:08 11:35:10

So they reduced the complexity of the genome by size fragmentation where they only got things that were in the size range that they thought were going to be representative of what they were going to be looking for and then amplified that over 35 cycles. 11:35:11 11:35:14 11:35:17 11:35:20 11:35:21 11:35:24 11:35:26

And your conclusion is their negative control is garage and it doesn't show anything, cause they underloaded the array? 11:35:29 11:35:30 11:35:32 11:35:35

A. As I'm -- as I've stated before, I believe, it is not possible to 11:35:37 11:35:40

conclude from the negative control given the starting material that they put in. 11:35:43 11:35:48

Q. So what you're, actually, saying is the negative control is garbage, it's not really functioning as a negative control? 11:35:52 11:35:54 11:35:55 11:35:58

It's not giving you any useful information? 11:35:58 11:36:01

MS. CIPRIANO: Objection, misstates the testimony. 11:36:01 11:36:02

A. That's not what I said. 11:36:03

I said that the arrays are designed for a certain amount of starting material. And given the starting material that they put in, it is not surprising that the majority of the markers without the locus specific primer did not hybridize. 11:36:04 11:36:09 11:36:12 11:36:15 11:36:17 11:36:21

Q. Oh. So the locus specific primer's, actually, doing some enrichment then? 11:36:27 11:36:30 11:36:33

A. I have -- I have stated before, you know, the MARA method in the hands of Affymetrix worked reasonably well. It didn't work nearly as well as 11:36:34 11:36:38 11:36:41 11:36:44

the standard whole genome of sampling assay. 11:36:46 11:36:49

But in their hands, it worked reasonably well and largely because of the high reproducibility of the Affymetrix' arrays and because the arrays were doing the bulk of the work on washing out the background signal. 11:36:50 11:36:52 11:36:55 11:36:59 11:37:01 11:37:02

Q. Is it your -- a POSA reading the MARA Shapero paper, QIAGEN 1006, would they conclude that the locus specific primers were enriching at all, for that locus, that they were targeting in the 250 plex? 11:37:04 11:37:09 11:37:12 11:37:14 11:37:17 11:37:19

A. I think they would conclude that the assay as -- 11:37:24 11:37:25

Q. Not the question, okay. 11:37:26

We have a limited amount of time and if you're just going to go on these questions that you're creating in your own head rather answering mine, we're not going to be able to finish and we're going to have to ask the Judges at the PTAB so for more time. So let's stick to 11:37:27 11:37:29 11:37:31 11:37:32 11:37:35 11:37:36 11:37:38

the question. 11:37:41

Would a POSA in 2012 reading the 11:37:42

MARA paper, QIAGEN Exhibit 1006, conclude 11:37:44

based on that data that the locus 11:37:47

specific primers were enriching for the 11:37:50

locus at all in the 250 plex reaction? 11:37:52

MS. CIPRIANO: Objection to 11:37:55

form. 11:38:04

Q. It's a yes or no. 11:38:04

A. When we use the term 11:38:07

"enrichment" throughout these discussions, 11:38:09

we are often referring to enrichment as 11:38:14

measured by next generation sequencing. 11:38:17

I would say that one would conclude 11:38:21

that the single primer extension approach, 11:38:24

as implemented in MARA and against a 11:38:26

hybridization array, demonstrated that 11:38:31

the approach could genotype known 11:38:34

markers, particularly, small number of 11:38:37

known markers and could potentially yield 11:38:39

useful results. 11:38:45

Q. Yeah. So really you're not 11:38:46

answering the question again and we might, 11:38:48

actually -- I mean, if we were in front 11:38:50

of a District Court Judge, we'd break and we'd have the Judge intervene, because you're not answering the question. 11:38:52 11:38:54 11:38:55

And I'm getting a little tired of you creating -- not answering the question and running around with something else. 11:38:57 11:38:59 11:39:01

So I'm going to ask you again. It's yes or no question. 11:39:03 11:39:05

Would a POSA in 2012 conclude based on the data in QIAGEN 1006 that the locus specific primers in the 250 plex reaction are enriching for the locus -- for the loci at all, yes or no? 11:39:05 11:39:08 11:39:12 11:39:16 11:39:20

MS. CIPRIANO: Objection to form. 11:39:23 11:39:24

A. I believe, I've answered the question. 11:39:28 11:39:30

Q. No, you have not. 11:39:30

It's yes or no. I want you to say yes or no. That's all I want to hear from you. 11:39:31 11:39:33 11:39:35

MS. CIPRIANO: David, you can't control how he answers. 11:39:35 11:39:36

MR. BILSKER: Yes, I can. 11:39:37

You can't -- you cannot have a witness refuse to answer the question. 11:39:38 11:39:39 11:39:40

Q. If you refuse to answer, just tell me, I refuse to answer. It is a yes or no question. It's simple. 11:39:41 11:39:42 11:39:45

Yes or no? 11:39:48

A. It depends on what you mean by "enrichment." 11:39:48 11:39:50

Q. Well, what do you mean by "enrichment"? 11:39:50 11:39:53

A. When we've discussed "enrichment," we've discussed enrichment in the context of next generation sequencing. 11:39:53 11:39:54 11:39:56 11:39:57

So, since there is no next generation sequencing here, it is -- you can't summarize. So I would say -- 11:39:58 11:39:59 11:40:02

Q. So what -- what level of enrichment is necessary to do sequencing on an Illumina sequencer of the things that you're looking for? 11:40:04 11:40:05 11:40:08 11:40:10

MS. CIPRIANO: Objection, foundation. 11:40:14 11:40:15

A. Could you couch that in a -- in terms of a specific experiment that you have in mind? 11:40:19 11:40:24 11:40:27

Q. Could I couch that -- well, you're making these -- you and your client are making these generalized statements. 11:40:29 11:40:31 11:40:33 11:40:36

What level of enrichment does the patent require that the library preparation methodology achieve? 11:40:36 11:40:38 11:40:40

A. There's no -- 11:40:44

MS. CIPRIANO: Objection to form. 11:40:44 11:40:44

A. There's no specific level of enrichment that's outlined. 11:40:45 11:40:47

Q. So you've, actually -- you're, actually, saying that the patent, actually, does not tell you a particular level of enrichment that's necessary for someone to sequence on a next generation instrument such as an Illumina sequencer, correct? 11:40:48 11:40:51 11:40:52 11:40:54 11:40:58 11:41:02 11:41:03

A. If we were to look at the claims, you -- we would see that 11:41:04 11:41:06

enrichment occurs through the amplification process that uses the universal adaptors. 11:41:07 11:41:09 11:41:12

Q. Again, not an answer to the question. 11:41:16 11:41:17

Is there a quantitative number level of enrichment that's required? 11:41:17 11:41:19

A. There is no threshold that I recall in the patent that speaks to this issue. 11:41:20 11:41:22 11:41:27

I believe that as outlined in the claimed invention, because of the specificity of the primers and the use of the universal primers for amplification, you are largely able to allocate the sequencing reads to the targets of interest. 11:41:27 11:41:30 11:41:34 11:41:37 11:41:42 11:41:50 11:41:53

Q. In an Illumina sequencer, even if 95 percent of the reads are things that you're not interested in, are not the material that you're interested in, you still can get useful data, correct? 11:41:55 11:41:58 11:42:00 11:42:02 11:42:04

A. It depends -- 11:42:08

MS. CIPRIANO: Objection to 11:42:08

form. 11:42:08

A. It depends on the biological question being answered -- being asked. 11:42:08 11:42:11

Q. Well, 95 percent of the reads that you're getting are not what you're looking for and only 5 percent are. 11:42:13 11:42:18 11:42:20

An Illumina sequencer will still function and you can still get useful date off of that, correct? 11:42:23 11:42:25 11:42:27

A. It depends on the biological question. 11:42:28 11:42:30

As I've stated before, in our work on ancient DNA, for example, you care so much about that precious sample, that you're willing to throw away a large amount of the data. 11:42:30 11:42:33 11:42:33 11:42:36 11:42:37

Q. So, for example, Neanderthal DNA is more important than DNA that's related to a cancer mutation that people are going to treat modern day; is that what you're saying? 11:42:38 11:42:40 11:42:42 11:42:45 11:42:47

A. That's not what I said. 11:42:48

I said it depends on the biological question and the motivation of the 11:42:49 11:42:52

investigator. 11:42:56

Q. I mean, you, in fact -- with 11:42:57
the ancient DNA, I mean, you, in fact, are 11:42:59
aware that when they created the first 11:43:02
draft of the Neanderthal genome, that up 11:43:04
to 95 percent of what they put on an 11:43:07
Illumina sequencer was stuff like microbe 11:43:10
DNA, other things that they didn't care 11:43:14
about at all, correct? 11:43:16

A. I -- I've mentioned this 11:43:19
multiple times into the deposition. It's 11:43:20
the specific applications in interest. 11:43:23

So, in that case, not a lot of 11:43:26
Neanderthals. You spend a lot of money 11:43:28
and time to generate the library. You 11:43:30
have sufficient funding. You are happy 11:43:32
to brut force the question at hand. 11:43:36

Q. In other words, even knowing 11:43:38
going in that 95 percent of what you might 11:43:41
put onto the Illumina sequencer was not 11:43:46
going to be what you wanted, researchers 11:43:48
did not run away from sequencing that on 11:43:53
an Illumina sequencer, correct? 11:43:55

A. As a first attempt at a 11:43:57

Neanderthal draft genome, that was the case. 11:44:00 11:44:02

They also spent a lot of time improving library prep to increase the yield on -- of the endogenous DNA. 11:44:03 11:44:05 11:44:07

Q. So I'm going to pass you what's been marked as QIAGEN Exhibit 1102. 11:44:13 11:44:15

(Deposition Exhibit QIAGEN 1102, article titled, "A Draft Sequence of the Neandertal Genome," was previously marked for identification.) 11:44:15 11:44:15 11:44:15 11:44:30

Q. So you're very familiar with this paper, right? 11:44:30 11:44:32

A. I am familiar with this paper. 11:44:32 11:44:34

Q. In fact, you cited it multiple times, correct? 11:44:34 11:44:35

A. I have cited it multiple times. 11:44:36 11:44:38

Q. And if we turn to Page 2 of Exhibit 1102, which I'm going to call "the Green paper," "The Draft Sequence of the Neandertal Genome." 11:44:38 11:44:40 11:44:43 11:44:46

So this paper was published in 2010, right? 11:44:48 11:44:53

A. It states here that it was published 7 May, 2010. 11:44:53 11:44:54

Q. And I assume given that it was published in 2010, people, actually, carried out the work well before that, right? 11:44:55 11:44:57 11:45:00 11:45:02

A. The work would have been carried out before the publication date. 11:45:04 11:45:05

Q. Probably, at least, a year or two before, correct? 11:45:07 11:45:10

A. Presumably. 11:45:11

Q. And in the -- on Page 2 of Exhibit 1102, in the section that -- the middle column where it says, "Enrichment of Neandertal DNA." 11:45:11 11:45:16 11:45:25 11:45:27

Do you see that? 11:45:28

A. I do. 11:45:28

Q. Ninety-five to ninety-nine percent "of the DNA sequence in libraries was derived from nonprimate organisms, which are presumably derived from microbes that colonize the bone after the 11:45:29 11:45:31 11:45:34 11:45:37 11:45:39

death of the Neandertals," right? 11:45:42

A. That's what it states. 11:45:44

Q. So 95 percent to 99 percent 11:45:45

of what they were actually going to 11:45:48

sequence was not even primate genome, it 11:45:49

was microbe genome, right? 11:45:54

A. That's what it states. 11:46:01

Q. And they then enriched that 90 11:46:01

-- you know, 1 to 5 percent of the stuff 11:46:06

they were looking for. 11:46:09

They then enriched it by enzymatic 11:46:11

methods, correct? 11:46:17

A. That's what it states. 11:46:18

Q. And the increase that they 11:46:19

got was only 4 to 6 percent, right? 11:46:21

A. I don't think that's correct. 11:46:24

It's four to sixfold. 11:46:26

Q. "Four to sixfold." 11:46:27

So 4 times 1 percent would be 11:46:28

4 percent and 6 times 5 percent would be 11:46:32

30 percent. 11:46:36

So what they, actually, ended up 11:46:36

putting on an Illumina sequencer was 11:46:39

either at the lowest 4 percent of what 11:46:40

they wanted and at the highest 30 percent of what they wanted, correct? 11:46:44 11:46:46

A. Presumably. We'd need to look at the sequencing libraries and what the actual yield was to get an accurate determination. 11:46:48 11:46:51 11:46:53 11:46:57

Q. But what this says is what they put on the -- what they put on the sequencer in their estimation was 4 to 6 fold increases, which would be between 4 percent and 30 percent, right? 11:46:57 11:46:59 11:47:02 11:47:05 11:47:08

A. Again, to answer to that accurately, I would need to look at the actual percentage of non -- of primate DNA, after they had done their enzymatic enrichment. 11:47:10 11:47:12 11:47:14 11:47:17 11:47:21

Q. So you don't think they looked at the sequencing data before they made this statement? 11:47:21 11:47:23 11:47:24

I mean, it's like -- 11:47:25

A. That's not what I said. 11:47:25

Q. -- what 25 authors. 11:47:26

So you think their estimation in the paper is, actually, not correct, even 11:47:27 11:47:28

after they themselves looked at the sequencing data? 11:47:30 11:47:32

A. Sir, that's not what I said. 11:47:33

I said, to get a more accurate -- that the information may well be in the paper, as to the fraction of the genome that is primate or nonbacterial after enrichment. I'm perfectly fine with that. 11:47:34 11:47:38 11:47:39 11:47:42 11:47:47

Q. So you don't really have a reason to question whether the people who published this paper were being -- were not being accurate when they said that they had a "four to sixfold increase" of something that started at between 1 and 5 percent, right? 11:47:51 11:47:53 11:47:55 11:48:00 11:48:02 11:48:06 11:48:08

MS. CIPRIANO: Objection to form. 11:48:09 11:48:11

A. I have every reason to believe what they wrote here is accurate. 11:48:12 11:48:15

Q. Right. 11:48:16

And you're not questioning my math? 11:48:16

Like, 4 times 1 percent is 4 percent and 6 times 5 percent is 30 percent, correct? 11:48:18 11:48:21 11:48:24

A. Those are accurate statements. 11:48:26
Whether some libraries maybe had 11:48:28
more than 30 percent, can't know without 11:48:30
looking at the actual data but, you 11:48:34
know... 11:48:35
Q. Right. And some might have 11:48:36
had less than 4 percent, right? 11:48:37
A. And some might have less -- 11:48:39
yes, absolutely. 11:48:42
Q. But these authors pre-2010 11:48:42
didn't run from the hills and say, ah, I 11:48:45
can't use why NGS, I have to use an 11:48:48
Illumina sequencer to sequence this, even 11:48:49
though some of the stuff I'm putting on 11:48:52
the machine might only be 4 percent of 11:48:53
what I want -- 96 percent is garbage and 11:48:56
4 percent is what I want? They didn't 11:49:00
run for the hills, did they? 11:49:01
A. As I've stated in my 11:49:02
testimony, there are some biological 11:49:04
questions that are so interesting that 11:49:06
you are absolutely willing to throw many 11:49:07
resources at the problem. This is the 11:49:10
team that won the Nobel Prize for this 11:49:13

work, right. So it was such a fascinating biological question that they were willing to spend years of time and effort to get and improve sequencing of Neanderthal genome. 11:49:15 11:49:18 11:49:19 11:49:24 11:49:26

I think that is very different than whether one would -- and, you know, use single primer extension targeting based on the available data to a POSA in 2011, 2012. It's not the same question. 11:49:27 11:49:28 11:49:36 11:49:39 11:49:44

Q. So, if we go back to Dr. Brooks declaration, which is Tecan 2026. 11:50:27 11:50:31

A. (The witness complies.) 11:50:36

Q. In Paragraph 14, where he says, Off targets -- "I thought that the target-specific primers would bind to off-target sites at a relatively high rate, leading to nonspecific enriched nucleic acid sequences," right? 11:50:42 11:50:46 11:50:51 11:50:53 11:50:57 11:51:00

We can agree that what they put on the sequencer for the Neanderthal genome, what they put on that sequencer -- there was a lot of nonspecific fragments that were put on that people didn't really 11:51:02 11:51:04 11:51:08 11:51:11 11:51:15

care about, correct? 11:51:17

A. That's different enough 11:51:19
target from a single primer extension 11:51:21
reaction. 11:51:23

Q. Well, 95 -- in some cases, 11:51:23
96 percent of what they put on the 11:51:29
sequencer was not what they were looking 11:51:31
for, correct? 11:51:33

A. That's different than -- I 11:51:34
believe you're confounding the word 11:51:37
"target." 11:51:39

When we're talking about target and 11:51:40
off target, we're talking about the 11:51:42
single primer reaction. 11:51:44

In this case, they made a library 11:51:46
of all the extracted DNA from the 11:51:48
material. So it's different than 11:51:53
targeted and off target. 11:51:55

Q. Yes. 11:51:56

But what went onto the sequencer -- 11:51:57
what Dr. Brooks is saying in the single 11:51:59
primer extension reaction, you're going 11:52:02
to get amplification of so many 11:52:04
off-target products, stuff that you're 11:52:07

not interested in, that you're not going to be able to sequence, it's going to confound the sequencing analysis? 11:52:10 11:52:12 11:52:14

That's what he actually says in the next sentence, right? 11:52:17 11:52:19

A. He doesn't say you can't sequence it. He says, it's going to confound the analysis. 11:52:20 11:52:21 11:52:23

Q. So it's just going to make it a little more difficult? 11:52:24 11:52:26

A. Depends on what "confound" means. 11:52:27 11:52:30

Q. Well, what does it mean to you? 11:52:31 11:52:32

You claim to be a person of ordinary skill in the art. 11:52:32 11:52:34

So what does that mean? 11:52:34

A. I would -- 11:52:34

Q. Or is it just nonsense? 11:52:35

A. It's not "nonsense." I never said it was "nonsense." 11:52:38 11:52:40

I think "confound" can mean complicate. And there are algorithmic solutions that can yield solutions or 11:52:42 11:52:44 11:52:47

bounds on solutions and sometimes "confound" can mean make uninterpretable. 11:52:51 11:52:52

Q. For example, in the fragments that are created in the SPE library in Shapero, we, actually, have reference genomes for those, don't we? 11:52:59 11:53:03 11:53:06 11:53:10

We have something to map it to, correct? 11:53:13 11:53:15

MS. CIPRIANO: Objection to form. 11:53:16 11:53:18

A. We're going back to Shapero? 11:53:18

Q. Yes. 11:53:20

A. Okay. Could you just ask your question again, please? 11:53:20 11:53:22

Q. So, in the 250 plex reaction in Shapero -- 11:53:23 11:53:25

A. Uh-huh. 11:53:26

Q. -- the fragments that are created using single primer extension, those fragments that are supposed to be created, hopefully, enriched -- 11:53:27 11:53:28 11:53:30 11:53:33

A. Uh-huh. 11:53:33

Q. -- for, we actually have a reference to map against, correct? 11:53:35 11:53:36

A. We do have a reference to map to and you have an expectation of what the reaction will do, because you can digitally look for the expected cut sites and the cut sites that are within a given distribution. Of course, there is variation in the cut sites. 11:53:38 11:53:39 11:53:46 11:53:49 11:53:53 11:53:55 11:53:57

But putting that aside, you have a starting expectation of where the SNPs that you're targeting and the genomic context in which they occur. 11:53:58 11:54:02 11:54:09 11:54:14

Q. So given that you have something to map against, does that make the sequencing analysis easier or harder, as compared to de novo sequencing, where you have nothing to map to? 11:54:15 11:54:16 11:54:18 11:54:21 11:54:25

A. I would have to say that the de novo problem is a harder problem. 11:54:27 11:54:29

Q. Okay. So, in the Neanderthal sequencing example, the -- I don't remember the number -- 1102, these people won the Nobel Prize I assume because there had not been a draft of the Neanderthal genome prior to their work, correct? 11:54:31 11:54:37 11:54:39 11:54:46 11:54:48 11:54:50

A. No. But they used the human genome as a scaffolding assembly. 11:54:54 11:54:56

Q. Would you say that the human genome was as good -- like, as accurate to map to as what the genome for the 250 plex, as represented in the MARA paper would -- which would have been more accurate to map to, the genome that was known for the SNPs in the MARA paper or the human genome compared to the Neanderthal genome? 11:54:58 11:55:00 11:55:02 11:55:07 11:55:11 11:55:13 11:55:14 11:55:17 11:55:19

A. I would say the human genome compared to the Neanderthal genome because it was a reference genome that was several years later. 11:55:20 11:55:22 11:55:23 11:55:26

Humans and Neanderthals are 98 percent identical. So you'd be able to map the reads. 11:55:31 11:55:33 11:55:35

Q. So you're saying using the human genome as a reference for the Neanderthal genome was, actually, easier than mapping the SNPs that had already been characterized in the MARA paper would be -- when doing -- 11:55:36 11:55:38 11:55:41 11:55:44 11:55:47 11:55:51

A. No. 11:55:51

Q. -- sequencing analysis on an NGS instrument? 11:55:53 11:55:54

A. What I said was that the reference genome would have been a better reference genome and mapping -- again, at the time they're using the Illumina sequencing with a certain read size. 11:55:54 11:55:56 11:55:59 11:56:01 11:56:06

When you're talking about mapping, in the context of Shapero, it would depend on what you're using to generate the sequencing read. 11:56:09 11:56:11 11:56:14 11:56:16

So, if you're, certainly, using NGS at the time, that would have been a nearly impossible problem. 11:56:17 11:56:19 11:56:22

Q. Well, there really -- I mean, NGS at the time in 2005. Let's go to 2010. 11:56:23 11:56:25 11:56:28

So, in 2010, using NGS to map to the Shapero reads -- 11:56:28 11:56:33

A. Using the same reference genome? 11:56:36 11:56:37

Q. Using the SNPs that had already been characterized by Shapero and 11:56:38 11:56:40

Affymetrix. 11:56:43

A. Are you using the same 11:56:44
reference genome, as Neanderthal, or are 11:56:46
you using the -- 11:56:48

Q. Why would I used the 11:56:49
Neanderthal reference genome? 11:56:51

A. No, no. I'm saying the same 11:56:52
version of the human genome that they're 11:56:54
mapping to, all things being equal. 11:56:55

Q. Either it could be the same 11:56:58
-- I mean, it could be what's been 11:57:00
deposited or Affymetrix had, actually, 11:57:02
published the sequences of those SNPs 11:57:07
that they were characterizing, right? 11:57:09

I mean, those were known and they 11:57:10
were mapped against -- 11:57:12

A. At the time -- based on the 11:57:13
mapping at the time of the human genome. 11:57:15
But you were using ABI 37/30 long reads 11:57:16
to characterize, right? Those are much 11:57:19
longer reads. 11:57:22

Q. And, actually, ABI reads -- I 11:57:24
mean, you've said that Sanger sequencing 11:57:26
is the "gold standard." 11:57:28

So, I mean, those are going to be pretty accurate, aren't they? 11:57:30 11:57:31

A. If they're -- if you're -- you've got 500 to 700 base pair reads. 11:57:33 11:57:34

(Stenographer clarification.) 11:57:37

A. 500 to 700 base pair reads. 11:57:37

Q. You do not dispute that by 2010 people could sequence on an Illumina instrument and even with as much as 95 percent of the reads not being things that they were interested in still get useful sequencing results, correct? 11:57:51 11:57:53 11:57:57 11:58:03 11:58:05 11:58:08

A. Depending on the biological question being asked. 11:58:09 11:58:11

Q. Yes, right? 11:58:12

A. Depending -- if -- if you're trying to sequence the Neanderthal genome and you're willing to throw away, you know, 95 percent of the reads and do 20 times as much sequencing, then you can, you know, obviously, generate a draft assembly of the human genome -- of the Neanderthal genome, as evidenced by the paper. 11:58:13 11:58:17 11:58:18 11:58:20 11:58:23 11:58:26 11:58:28 11:58:31 11:58:33

Q. And are you saying that in 2010 people would not be willing to, say, throw away 50 percent of their reads as garage on an NGS sequencer for something like SNP detection of cancer genes? 11:58:33 11:58:35 11:58:37 11:58:40 11:58:42

A. I think you -- that's a -- it depends on the context. If you're trying to implement he something clinically, 50 percent of the data being thrown away might not meet the threshold of reproducibility that a clinical lab director would require. 11:58:46 11:58:50 11:58:51 11:58:54 11:58:56 11:58:58 11:59:00

To my knowledge, there are no implementations of MARA at the time for clinical use. So, I think, it's an inappropriate comparison. 11:59:03 11:59:04 11:59:08 11:59:12

At the time the work that was being done was using dual primer amplicons or captured using other techniques. 11:59:13 11:59:15 11:59:20

Q. Do you know of a company called Natera? 11:59:24 11:59:25

A. I do know a company called Natera. 11:59:27 11:59:29

Q. So, back in 2010, when they 11:59:29

were doing their work to detect prenatal mutations or cancer mutations, are you saying they were not using single primer extension to enrich the libraries that they put on next generation sequencers? 11:59:31 11:59:35 11:59:38 11:59:40 11:59:43

A. I don't believe I talk about Natera in my declaration. Nor have I reviewed relevant information at that period of time. And I'm not prepared to discuss whether Natera might or might not have been doing at the time. 11:59:47 11:59:49 11:59:52 11:59:54 11:59:56 11:59:59

Q. Right. 12:00:01

So your equivocal statement that no one was doing it is, again -- 12:00:01 12:00:04

A. No, I said the MARA approach, as I understand it, was not being used clinically. 12:00:05 12:00:06 12:00:08

Q. So do you think the patent requires clinical use of MARA to enrich a library for next generation sequencing, or would a research use qualify as well? 12:00:09 12:00:11 12:00:15 12:00:18

A. The patent does not require clinical use. 12:00:21 12:00:23

Q. Okay. So all that discussion 12:00:23

about, it would not be -- it would not be acceptable in a clinical setting to throw away 50 percent of your reads for a clinical test really has nothing to do with the patent? 12:00:26 12:00:30 12:00:31 12:00:34 12:00:36

A. You're asking me about cancer genes and before you had asked me about its utility. So that's what I was answering. 12:00:37 12:00:38 12:00:41 12:00:43

Q. Right. 12:00:43

And before people developed clinical assays for things like detection of mutations in cancer, researchers actually performed the methodologies to develop the assays, right? 12:00:44 12:00:47 12:00:49 12:00:52 12:00:53

A. I would agree with -- 12:00:55

MS. CIPRIANO: Objection to form. 12:00:55 12:00:55

A. Would you state the question again, or could we have read back? 12:00:55 12:00:59

Q. Before someone develops a clinical test for something like detection of SNPs and cancer mutations where you said it would not be practical to throw 12:01:01 12:01:03 12:01:07 12:01:10

away 50 percent of the reads, before someone actually develops a clinical test, researchers, actually, do research on the assay to try to optimize it, correct? 12:01:12 12:01:14 12:01:16 12:01:20 12:01:23

A. I would agree with that statement. And what I said was it might not be acceptable to a clinical lab director, if I recall. 12:01:23 12:01:24 12:01:25 12:01:28

Q. But it would be acceptable for someone developing in the development stage of a clinical test to potentially throw away 50 percent of their reads? 12:01:29 12:01:31 12:01:34 12:01:36

A. Depending on the biological question, you may be willing to do additional sequencing as necessary to achieve the coverage that you seek for a biological question of interest. 12:01:38 12:01:40 12:01:43 12:01:44 12:01:47

MR. BILSKER: Now, I don't know what you want to do. I'm fine to keep going. I'm really not hungry. Your call. Leave it to you guys what you want to do. 12:01:51 12:01:53 12:01:55 12:01:57 12:02:00

THE STENOGRAPHER: You want to 12:02:03

go off the record? 12:02:04

MS. CIPRIANO: Yeah, let's go 12:02:05
off the record. 12:02:06

(There is a discussion off 12:02:08
the record.) 12:02:08

(Lunch recess taken 12:02 12:02:08
to 12:35 p.m.) 12:13:13

Q. Dr. Bustamante, from the time 12:36:10
when PCR started being used at high rates, 12:36:12
let's say, mid '80s, up to even present 12:36:17
day, short of actually sequencing, how do 12:36:21
people that are using PCR determine 12:36:27
whether they have obtained the amplicon 12:36:34
that they are trying to obtain using the 12:36:38
PCR primers? 12:36:42

A. So there are multiple ways to 12:36:49
do so. As you stated, sequencing would 12:36:51
be the gold standard. 12:36:53

You could also use probes to the 12:36:56
known sequence and seeing on a job whether 12:37:01
you're obtaining the fragment that you 12:37:09
think you're obtaining. And if you have 12:37:11
the known sequence and aren't sequencing, 12:37:15
you can also use features of that running 12:37:19

alongside the known sequence to see whether you're migrating, say, on a gel at the same location. 12:37:22 12:37:25 12:37:32

(Stenographer clarification.) 12:37:32

A. On a gel at the same location. 12:37:36

Q. I wasn't sure I understood what you said. 12:37:36 12:37:37

So I understood you said running it "on a gel," but you said you use probes also to run on a gel. 12:37:38 12:37:41 12:37:45

A. Well, I was saying you could -- for example, if you are looking to amplify a 300 base pair region and you're running a ladder, you can see whether you're getting a band at the location you expect. You can cut out that band. That's when you would, you know, potentially sequence. You could, obviously, also use, you know, an antibody that has the sequence that you're interested in to react and see whether you're binding at the location you expect so... 12:37:46 12:37:49 12:37:54 12:38:00 12:38:02 12:38:05 12:38:07 12:38:08 12:38:09 12:38:20 12:38:22 12:38:26 12:38:30

Q. Alright, I get it. 12:38:30

I thought I was understanding you saying, like, the running on the gel was linked to a probe. 12:38:31 12:38:33 12:38:35

But, actually, probing it is a separate issue? 12:38:37 12:38:39

A. It a separate approach. 12:38:40

Q. "A separate approach." 12:38:42

Alright. So running on a gel was a common way and it's still a common way today to make a determination as to whether your PCR reaction is giving you the amplicon you want? 12:38:43 12:38:45 12:38:48 12:38:51 12:38:54

A. At least, you know, to a first order. If you get a single band and it's the right size and only thing you're getting, then you would suppose that you've gotten the target of interest. 12:38:56 12:38:57 12:38:59 12:39:01 12:39:05

Of course, if your off target is the exact same size, then you might confound that. But, in general, your off target is different sizes and your on target -- than your on target, then you would get, you know, two bands on the gel versus one or multiple bands on the gel. 12:39:08 12:39:10 12:39:14 12:39:16 12:39:20 12:39:23 12:39:26

Q. And when you talk about off target -- so, like, in the single primer extension situation, if you talk about the single primer being off target, are you referring to miss priming, so it's landing somewhere on the fragment of interest in the wrong place and creating an amplicon from that? 12:39:32 12:39:38 12:39:40 12:39:43 12:39:47 12:39:50 12:39:53 12:39:57

A. There are multiple sources of off-target material. I would suggest that one of the primary off-target products would be another genomic region that shares homology with the target region of interest. So you're getting amplification of both of the regions, or if there is more than two regions, the plurality of regions that it could bind to. 12:40:03 12:40:07 12:40:13 12:40:17 12:40:21 12:40:23 12:40:27 12:40:31 12:40:34 12:40:39

(Stenographer clarification.) 12:40:39

A. It could bind to. 12:40:39

Q. Alright. So let's stop with that one. 12:40:39 12:40:41

Would you actually call that a miss priming event, if the primer is landing 12:40:41 12:40:43

on not only the thing that you knew about that it was supposed to land on, but another region which is, essentially, a collapse, as you've used it, which has the same homology and it's binding to that as well? 12:40:45 12:40:49 12:40:51 12:40:53 12:40:55 12:40:58

A. I didn't use -- 12:40:59

MS. CIPRIANO: Objection to form. 12:40:59 12:41:01

THE WITNESS: Sorry. 12:41:01

MS. CIPRIANO: Objection to form. 12:41:02 12:41:02

Keep going. 12:41:03

A. I didn't call it "miss priming." 12:41:03 12:41:05

You asked me about "miss priming." 12:41:06

Q. Yeah, but in your answer you referred to that. 12:41:08 12:41:09

So is -- 12:41:09

A. No. 12:41:09

Q. -- that a miss priming event, when the single primer in a single primer extension reaction binds or hybridizes to not only like what you think it's going 12:41:11 12:41:13 12:41:16 12:41:20

to bind to but also binds and primes a region, which shares homology with what you knew about, is that a miss prime? 12:41:22 12:41:28 12:41:30

A. Okay. So, in my answer, I meant to convey -- I'm sorry, if I wasn't clear -- that we can imagine the primer binding to the target of interest and a nucleotide fragment that contains the true target of interest, as well as additional fragments where the primer shares -- where the primer binds because the region shares homology with the target of interest. That would not be, as you're indicating, a miss priming. 12:41:33 12:41:36 12:41:39 12:41:44 12:41:51 12:41:53 12:41:55 12:41:59 12:42:02 12:42:05 12:42:08

Q. Okay. So that would not be a miss prime event? 12:42:10 12:42:13

A. As you're defining "miss priming" -- I believe you asked me about "miss priming" being in the same region of interest but not necessarily at the target of the supposed -- the hypothesized target of the primer. 12:42:14 12:42:16 12:42:18 12:42:21 12:42:24 12:42:27

Q. Would you call that an off-target event? 12:42:29 12:42:30

A. I would call that an "off-target event." 12:42:31 12:42:32

Q. And, again, going from a mapped genome and places where there's a large amount of homology shared, you said, approximately, 85 percent of the genome, that's not something that you worry about? 12:42:47 12:42:48 12:42:51 12:42:53 12:42:55

A. And that's -- I would -- again, what I meant to convey and to be specific is that at about the time of the invention, as I recall, if you're using Illumina paired end sequencing, say, using 75 base pair reads, you can uniquely map to reference genome about 85 percent of the time. 12:42:58 12:43:01 12:43:04 12:43:09 12:43:15 12:43:18 12:43:21 12:43:22

The longer the reads, paired end versus single end, you know, the uniqueness to which you can map. 12:43:28 12:43:30 12:43:34

Q. And would you also say that using a computer program to design your single primer and a single primer extension reaction when you have a map genome and then you can use BLAST to run the experiment digitally that, at least, 12:43:36 12:43:37 12:43:42 12:43:44 12:43:46 12:43:50

85 percent of the time you're going to not need to worry about an event where the single primer anneals to what you're looking at and is not annealling to some other region of homology that's close? 12:43:53 12:43:56 12:44:00 12:44:03 12:44:09

MS. CIPRIANO: Objection to form. 12:44:12 12:44:13

A. If you could simplify the question, I'd appreciate it. 12:44:14 12:44:16

Q. Again, tell me what you don't understand about it? 12:44:18 12:44:20

A. It was a rather long question. 12:44:21

Q. Yeah, well, sometimes when you need to get all the facts in, it can be long. 12:44:23 12:44:24 12:44:27

So what -- 12:44:27

A. Okay. 12:44:27

Q. -- don't you understand? 12:44:28

A. I'm just asking if you wouldn't mind restating the question. If not, we can... 12:44:28 12:44:30 12:44:32

Q. So we talked about primer design back at the time of MARA and later in 2010. 12:44:32 12:44:34 12:44:36

And people used commercial computer programs like Primer3 to design primers, right? 12:44:38 12:44:42 12:44:45

A. Yes. 12:44:46

Q. And they, also, had reference human genomes, right? 12:44:46 12:44:50

There was a reference human genome between 2005 and 2010, right? 12:44:52 12:44:54

A. Yes. 12:44:55

Q. So, after they designed their primers, they can actually BLAST it against reference genome and make determinations based on the stringency of their hybridization conditions in an extension reaction, what the likelihood of binding to places not only that they want but other places which might share homology, right? 12:44:56 12:44:57 12:45:01 12:45:04 12:45:08 12:45:10 12:45:12 12:45:15 12:45:17

A. I'd agree with that. 12:45:19

Q. And based on those facts, is there a quantitative number that -- would 85 percent be a likely estimation of the amount of times that it would bind only to what you want, as opposed to binding 12:45:20 12:45:23 12:45:26 12:45:30 12:45:32

to places in the genome which share similar homology? 12:45:35 12:45:38

A. I don't believe 85 percent would be a reasonable quantitative measure for the reason that first primers tend to be shorter than Illumina sequencing reads. With Illumina sequencing reads, you're using paired end mapping. So you're looking for -- 12:45:39 12:45:40 12:45:45 12:45:49 12:45:53 12:45:57 12:45:59

Q. Alright. Time out. We're not talking about Illumina right now. 12:45:59 12:46:01

We're talking about in the creation of the library. So it's not on the machine. 12:46:02 12:46:03 12:46:05

A. I understand. 12:46:05

My answer about the 85 percent of the genome that was accessible, as I indicated, is based on my understanding of the state of the art of Illumina sequencing at the time. It means that 15 percent was not accessible. 12:46:06 12:46:08 12:46:11 12:46:13 12:46:16 12:46:17

And you're asking me about whether the primers, which are much shorter and aren't paired end, it's just 30 base 12:46:19 12:46:22 12:46:25

pairs, are there -- are you able to reliably get 85 percent of the time unique mapping of primers onto the genome. 12:46:28 12:46:30 12:46:33 12:46:37

It depends on the region you're interested in. It may or may not be. 12:46:37 12:46:38

When Illumina first came out and had 36 base pair reads, it, certainly, wasn't 85 percent of the genome that you could uniquely map to. 12:46:41 12:46:44 12:46:47 12:46:49

So this question about uniquely mapping based on a reference genome and what the a priori expectation rely depends on the technology, depends on the question and depends on what regions you're trying to designing parameters to. 12:46:50 12:46:52 12:46:55 12:47:00 12:47:00 12:47:03

Q. Alright. So you're saying that the reference genomes that were -- first of all, they weren't created by Illumina sequencers necessarily. 12:47:03 12:47:04 12:47:08 12:47:10

They were created by the Human Genome Project and Sanger sequencing, which you've called the "gold standard," right? 12:47:12 12:47:13 12:47:14 12:47:17

So those reference genomes -- are you saying that the reference genomes really only access 85 percent of the genome to start with? 12:47:17 12:47:19 12:47:20 12:47:24

So you're not starting with a hundred percent that you're going to be comparing to but really only 85 percent? 12:47:26 12:47:27 12:47:29

A. And what I'm -- with the 85 percent number that I am alluding to is the unique mappability of the Illumina pair end reads. 12:47:31 12:47:32 12:47:35 12:47:41

Q. Alright. And what I'm talking about is I have a reference genome -- 12:47:42 12:47:43

A. Uh-huh. 12:47:45

Q. -- in let's say 2009, 2010. 12:47:46

Are you saying that the reference genomes that were available in 2009, 2010 are only going to identify 85 percent of the bases that exist in the genome? 12:47:49 12:47:50 12:47:53 12:47:58

A. That's not what I said. 12:48:00

Q. Alright. So that's not what you're saying. 12:48:01 12:48:02

So the reference genomes that were -- what percentage do you think of the 12:48:03 12:48:05

genome are represented by the reference genomes that were in existence in 2010? 12:48:06 12:48:10

A. If we're considering both heterochromatic and euchromatic, a -- it wasn't fully assembled and we still had unmapped regions. 12:48:13 12:48:16 12:48:26 12:48:29

I would say that in -- so that 85 percent number, just to go back for a moment, is to say that you could map uniquely to the reference genome 85 percent of the time. So that's using the reference genome as the hundred percent. 12:48:32 12:48:36 12:48:38 12:48:40 12:48:42 12:48:44 12:48:45

What fraction of the time could you design, you know, call it 25, 30 base pair primers and they would map uniquely to the human genome depends on the regions you're targeting. 12:48:46 12:48:48 12:48:52 12:48:55 12:48:58

Q. But you would be able to figure that out. 12:49:00 12:49:01

So, in 2010, if you designed a primer, let's say, with a 3 prime end that was 25 nucleotides, you would be able to use the sequence of that 25 12:49:02 12:49:04 12:49:08 12:49:08

nucleotide -- pre-prime end nucleotide primer and compare it to a reference genome that existed in 2010 and make a determination of the likelihood knowing your stringency conditions that it would bind not only to what you were trying to hybridize to but to other regions of the genome, right? 12:49:11 12:49:14 12:49:17 12:49:20 12:49:23 12:49:25 12:49:27 12:49:30

A. It depends on the 30 base pair fragment that you're designing. 12:49:30 12:49:32

You could, certainly, BLAST. And if you found more than one BLAST hit, you would know that it likely mapped to more than one location. What fraction of the time do you find two BLAST hits depends on what you're targeting. 12:49:37 12:49:39 12:49:41 12:49:43 12:49:47 12:49:49

Q. But, I mean -- well, depending on what you're targeting -- I'm not asking you how many times it's going to, actually, map, but you would get an answer? 12:49:50 12:49:52 12:49:53 12:49:55 12:49:56

A. And it, also, depends on whether you're talking about an exact match of the primer, if you're off by one 12:49:57 12:49:58 12:50:01

or two bases, you know. So you might get one top hit and a series of lower hits and you might still get priming off of those lower hits. 12:50:04 12:50:07 12:50:09 12:50:13

Q. Right. 12:50:14

But you would get some indication, hey, here's one like a hundred percent homologous region and here is a bunch of regions, which are -- here is one 95 percent homologous, here's another one that's 80 percent homologous, here's one that's 70 percent homologous. 12:50:14 12:50:17 12:50:20 12:50:23 12:50:26 12:50:28 12:50:29

Even if you had those four, you could then make a -- a person of ordinary skill in the art and one of the things they would do is then say, okay, let me use the analytical tools that we have available today with the likelihood that this thing is going to prime to bind and extend, right? 12:50:31 12:50:32 12:50:36 12:50:37 12:50:39 12:50:42 12:50:45 12:50:48

A. You, certainly, could. If the question was, if I had a set of genes that I'm interested in and I'm designing my single primer extension, those are the 12:50:50 12:50:52 12:50:54 12:50:58

genes I'm interested in. I'm going to run the reaction, because I need to prime in this area, how often am I going to tolerate off-target effects? 12:51:00 12:51:02 12:51:04 12:51:07

You know, you may get a lot of off-target effects, cause you're particularly interested in those genes. Hemoglobin, for example, you might be interested in the globins. 12:51:09 12:51:12 12:51:13 12:51:15 12:51:16

Q. You could make a determination or an estimation of what the likelihood that you're going to hybridize to something, quote, "off target," right? 12:51:18 12:51:19 12:51:21 12:51:23

A. You would get -- you could have an a priori estimate based on BLAST or other similarity searches of what other regions of the genome were similar. The degree to which that would lead to off-target effects would depend on all kinds of conditions, including how you ran your PCR and what your readout was. 12:51:25 12:51:27 12:51:31 12:51:34 12:51:38 12:51:40 12:51:42 12:51:42

Q. Got it. 12:51:44

So let's take that example that I just mentioned to you where I've got one 12:51:45 12:51:47

that's a hundred percent homology and three which are diminishing amounts of homology, right? 12:51:49 12:51:51 12:51:55

If I saw those four possibilities, I could also make an estimation of what the size of the amplicon might be, right, in the PCR reaction, right? 12:51:55 12:51:59 12:52:01 12:52:04

A. Not necessarily, because you're going to bind the universal primer to the fragment length and it's going to bind and prime the reaction or, you know, it will bind some fraction of the time and you'll either going to extend or you're not going to extend. 12:52:06 12:52:11 12:52:15 12:52:18 12:52:22 12:52:24 12:52:26

Q. But you could make an estimation, say, a lower end and an upper end of the size of the amplicons that you might get, right? 12:52:27 12:52:29 12:52:32 12:52:34

A. And that would, certainly, be best done with a dual primer design, cause then you'd know where the second primer is. 12:52:35 12:52:37 12:52:39 12:52:39

With a single primer design where you're fragmenting and have a universal 12:52:41 12:52:42

primer, you may not know where the other one ends. 12:52:44 12:52:46

Q. Except the other side even single primers is anchored by an adaptor, right? 12:52:46 12:52:49 12:52:50

A. It's a -- so you'll know they're going to be about the same length. 12:52:51 12:52:52

Q. In any event, you have established that a very common methodology for making a determination short of sequencing itself -- probably I'd venture to say the most common way people in labs, actually, do it, to see if using PCR they got the amplicon that they wanted is to run things on a gel against the ladder to see if the amplicons are the size that you would expect, right? 12:52:56 12:52:58 12:53:00 12:53:04 12:53:08 12:53:10 12:53:14 12:53:16 12:53:20 12:53:22

MS. CIPRIANO: Objection to form. 12:53:23 12:53:30

A. As I've stated, running a gel to assess whether you get the fragment length that you expect post-PCR is a standard tool. You might also get more than one locus that has the same length 12:53:30 12:53:34 12:53:38 12:53:42 12:53:48

off of an off target. 12:53:52

But, in general, you get one band 12:53:53
and you're running the ladder and the 12:53:55
product that you know is there, then 12:54:00
that's usually taken as good proof that 12:54:02
you're in the right ballpark. You have 12:54:06
to sequence to be sure, especially if 12:54:08
you're taking from one species to another 12:54:12
or something similar. 12:54:14

Q. You would have an added layer 12:54:15
of competence if before you did your PCR 12:54:19
you actually did a restriction digest 12:54:23
such that you were predicting certain 12:54:26
sizes of the fragments, right? 12:54:28

A. You could run those along 12:54:30
side as well. 12:54:31

Q. So, if you did a restriction 12:54:32
digest before you added your common 12:54:33
adaptor on, that would give you an added 12:54:36
level of confidence of what the size of 12:54:39
amplicons might be, even in that situation 12:54:42
where we had the diminishing level of 12:54:44
homology, right? 12:54:48

A. Using a restriction digest as 12:54:52

size selection creates what's known as a, you know, reduced representation so you're targeting a smaller fragment -- smaller fragment of the genome. 12:54:54 12:54:58 12:55:01 12:55:04

Q. Right. 12:55:05

And it gives you a higher level of confidence that you, actually, got the amplicons that you wanted, because you can make a better prediction as to what the amplicon sizes should be, even using a common primer that's targeting an adaptor when you run it on the gel, right? 12:55:06 12:55:08 12:55:09 12:55:10 12:55:13 12:55:16 12:55:20

A. Except in regions that are duplicated, because you'll also duplicate the cut sites. So you might still get the same cut sites, even in duplicated region. 12:55:23 12:55:26 12:55:28 12:55:30 12:55:32

Q. But in the duplicated region situation, that's not really a miss priming event, right? 12:55:34 12:55:36 12:55:38

A. Not what I -- I am talking about off-target effect -- off-target binding where the primer is binding to a homologous region. 12:55:40 12:55:43 12:55:45 12:55:49

Q. So let's turn back to QIAGEN 1006, which is the Shapero MARA paper. 12:55:51 12:55:55

A. Okay. 12:55:59

Q. Again, you're quite familiar with this, right? 12:56:03 12:56:04

A. I would say I'm familiar with the paper. 12:56:05 12:56:06

Q. You wouldn't say "quite familiar"? 12:56:07 12:56:09

A. I just said, I was familiar with the paper. 12:56:10 12:56:11

Q. So, if we go to Page 9 of the paper left-hand column under "MARA 250 plex." 12:56:24 12:56:26 12:56:38

A. Uh-huh. 12:56:38

Q. Do you see that? 12:56:39

So one of the things that the authors, these -- I think you characterized them as "experts" at Affymetrix. Actually, much higher level of skill than a person of ordinary skill. 12:56:40 12:56:42 12:56:43 12:56:47 12:56:50

Is that right? Is that how you referred to them? 12:56:53 12:56:55

A. I would consider them experts 12:56:55

in, certainly, microarray technology. 12:56:57

Q. Okay. So one of the things 12:57:00

that these "experts" in detecting SNPs 12:57:02

using microarrays did or one of the 12:57:06

things they said in this peer reviewed 12:57:09

paper was that -- if you go four lines up 12:57:12

from the left-hand column, "By 12:57:15

pre-selecting robust SNPs, that genotype 12:57:19

accurately by allel-specific 12:57:22

hybridization, we used genotype call 12:57:24

rates as a surrogate for the presence 12:57:28

(successful primer) or absence of [sic] 12:57:31

(unsuccessful primer) of MARA-generated 12:57:36

target DNA." 12:57:39

Do you see that? 12:57:41

A. I believe, you've added "of" 12:57:42

but, yes. 12:57:44

Q. Sorry. 12:57:45

So, when it says, "surrogate" -- 12:57:47

like, I know what a "surrogate" is in a 12:57:50

parenting situation. 12:57:52

But would the use of the word 12:57:53

"surrogate" mean that it's stand in for 12:57:56

making the determination as to whether 12:57:58

there -- and there's single primer extension reaction in the 250 plex was on target, they used the call rates as a surrogate for making that determination? 12:58:01 12:58:05 12:58:08 12:58:10

A. Whether it's on target -- so it would, at least, have on-target priming. It may also have off-target priming. It's not -- it's only speaking to the on-target priming. 12:58:12 12:58:15 12:58:18 12:58:21 12:58:23

Q. When it's on target, is that enrichment? 12:58:25 12:58:28

A. In the context of these patents, when we talk about "enrichment," we often are using NGS as a measure. So it is not "enrichment" in the sense used in the patents. 12:58:31 12:58:32 12:58:34 12:58:40 12:58:41

Q. Well, has it reduced the complexity of the sample that you're starting with in the creation of the library? 12:58:42 12:58:44 12:58:47 12:58:49

Does the library have more complexity or less complexity when they use a single primer extension in the MARA 250 plex? 12:58:49 12:58:51 12:58:56 12:58:58

MS. CIPRIANO: Objection, compound. 12:59:00 12:59:01

A. Could you split that question up for me, please? 12:59:01 12:59:02

Q. Well, sure. 12:59:03

They start with a whole genome, right? 12:59:04 12:59:06

That's their starting sample, right? 12:59:06 12:59:08

A. (No response.) 12:59:12

Q. Right? 12:59:12

A. They start with whole genomes -- they extract whole genome DNA. 12:59:13 12:59:18

Q. Right. 12:59:20

And in whole genome, what do you have 6 billion nucleotides about? 12:59:20 12:59:22

A. It depends on whether you're talking deployed or haploid. But, yes, you've got two copies of the 3 billion base pair genome. 12:59:26 12:59:28 12:59:29 12:59:32

Q. And at the end of the day using this MARA process, how many bases did they end up creating or having in the library they created? 12:59:34 12:59:36 12:59:44 12:59:48

A. I believe, they gave an estimate of this in their paper, if I recall. 12:59:51 12:59:53 12:59:57

Q. You can turn to Page 12, turning mark to Page 12 of Exhibit 1006 right-hand column right in the middle-ish. 13:00:00 13:00:04 13:00:06

I can read it to you, if you want. 13:00:16

A. Please go ahead. 13:00:21

Q. "This allows the range of annealling temperatures to be expanded using a 'touchdown' format," blah blah blah. 13:00:22 13:00:24 13:00:26 13:00:28

During the primary -- sorry. 13:00:34

"This allows the range of annealling temperatures to be expanded using a 'touchdown' format during the primary reaction, increasing the likelihood that any given primer will bind specifically to genomic DNA. The theoretical sequence complexity of target DNA generated by MARA is approximately equal to the average length of the amplification products multiplied by the level of primer multiplexing. In the 13:00:36 13:00:38 13:00:39 13:00:41 13:00:43 13:00:46 13:00:50 13:00:53 13:00:56 13:00:58 13:01:01

case of 4365" multiplex -- "4365-plex MARA, this is approximately 2 megabases. The high density genotyping arrays are capable of handling DNA targets that are approximately 300 megabases of sequence complexity?" 13:01:05 13:01:11 13:01:16 13:01:21 13:01:22 13:01:25

So do you see that? 13:01:26

A. I do. 13:01:28

Q. So, prior to MARA, the method that they used for generating the libraries reduced the complexity from genomic DNA, which is about 6 billion nucleotides down to 300 megabases, which is 300 times 10th to the 6, which is what, 300 million, right? 13:01:28 13:01:30 13:01:32 13:01:36 13:01:41 13:01:43 13:01:47

A. Yeah. Again, the 300 megabases here may be referring to the haploid genome size, but within, you know, within a factor of two. I believe they're probably saying from a 3 gigabase genome to a 3 meg -- 13:01:48 13:01:50 13:01:52 13:01:53 13:01:56

THE STENOGRAPHER: I'm sorry. I'm not familiar with the terminology.

THE WITNESS: No problem.

I apologize.

A. It is being reduced from, approximately, 3 gigabases to, approximately, 300 megabases to about a tenfold reduction. 13:02:04 13:02:06 13:02:10 13:02:15

Q. And the MARA -- so that's, actually -- you enriched your library in a sense, you reduced the complexity of your library, right? 13:02:17 13:02:19 13:02:23 13:02:26

A. Not of the library, of the target genome that is being queried. 13:02:27 13:02:31

Q. Okay. So, from your starting sample, which is genomic DNA, you've reduced the complexity and you've enriched for your target genome, right? 13:02:35 13:02:38 13:02:40 13:02:43

A. Another way of saying it is about 10 percent of the human genome is being queried, as part of the Affymetrix standard array. 13:02:44 13:02:46 13:02:48 13:02:54

Q. As opposed to 100 percent? 13:02:55

A. As opposed to 100 percent. 13:02:57

Q. And the MARA method reduces it by a factor of -- where did it go -- a 13:02:59 13:03:02

hundred, right, a little over a hundred, right? 13:03:09 13:03:11

A. Something on the order of that. 13:03:12 13:03:13

Q. So, from 300 million down to 2 million, right? 13:03:14 13:03:18

A. Yes. And it's not surprising because the -- I believe the 300 mega base array has got about a hundred thousand markers on it and here you're looking at about 4,000 markers. So it's on the order of what you'd expect. 13:03:21 13:03:23 13:03:26 13:03:28 13:03:31 13:03:34

Q. So, in the Shapero MARA paper, QIAGEN 1006, they present actual gels, do they not? 13:03:45 13:03:49 13:03:56

A. I believe there's a gel in the MARA paper. 13:03:57 13:03:58

Q. And if we look at Gel 1A, right, that's -- so you're there. 13:03:59 13:04:03

A. I believe it's labeled "Figure 2." 13:04:08 13:04:10

Q. Oh, I'm sorry; "Figure 2(A)." 13:04:11

So, in Figure 2(A), they run a ladder, right? 13:04:14 13:04:17

A. I see a ladder, what we would refer to as a ladder in the first lane with molecular weight. 13:04:22 13:04:26 13:04:28

Q. Right. 13:04:29

So in 2(A) up at the very top of it, there's something that's labeled -- right next to the letter (A) it says, "MW." And that ladder shows bands, which approximate the molecular weight or sizes -- 13:04:30 13:04:32 13:04:34 13:04:37 13:04:43 13:04:44

A. Uh-huh. 13:04:45

Q. -- right? 13:04:45

A. Yes. They've got base pairs to the left. So between a hundred and 750 base pairs are the bands in the lower half of the figure. 13:04:46 13:04:49 13:04:52 13:04:55

Q. And that is a very common way to present a gel? 13:04:55 13:04:57

You present a gel with, like -- it's usually on the far left-hand side. 13:04:58 13:05:00

You have your ladder, which indicates molecular weight sizes, correct? 13:05:02 13:05:04

A. I would agree with that statement. 13:05:08 13:05:09

Q. And when the Shapero folks submitted this paper for peer review and it got published, in that column below the figure they say that in each -- so I'm, actually, reading in the right hand column with the sentence that begins, "Representative secondary universal amplification products are shown in Figure 2A. Each of the nine genomic DNA samples used in MARA show a reproducible smear from 150 to 550 base pairs when the 250 locus-specific primers are present. This result is consistent with the expected size distribution" products -- "with the expected size distribution of products which ranges from 100 to 500 base pairs, with a mean size of 287 base pairs," right? 13:05:09 13:05:13 13:05:16 13:05:19 13:05:25 13:05:34 13:05:37 13:05:39 13:05:41 13:05:46 13:05:50 13:05:56 13:05:59 13:06:03 13:06:07 13:06:09 13:06:14 13:06:17

Do you see that? 13:06:19

A. I read that, where it says that in the paper. 13:06:19 13:06:21

Q. So the authors of the MARA paper said that based on their primer design and what they were supposed to be 13:06:22 13:06:24 13:06:26

targeting and the fact that they did restriction digests, their primers -- their single primer that was used -- single target-specific primer used in the single primer extension reaction of MARA should produce fragments between 10,500 base pairs, right? That's what they're representing here? 13:06:28 13:06:30 13:06:34 13:06:37 13:06:41 13:06:43 13:06:49 13:06:53

A. Ensemble distribution of fragments, not a single band, as I was indicating before. 13:06:53 13:06:56 13:06:58

So you have a smear of products. That smear of products has consisted across individuals and the smear of products may also contain off-target effects. 13:06:59 13:07:01 13:07:03 13:07:06 13:07:09

Q. But this is, actually, consistent in nine distinct samples with what they would have expected, right? 13:07:09 13:07:11 13:07:13

A. With and without off-target priming. 13:07:15 13:07:18

Q. Well, they actually did an analysis of what they should expect size-wise and this gel that they ran 13:07:19 13:07:23 13:07:26

shows that their PCR -- the PCR results that they got were, actually, consistent with the amplicon sizes that they would expect, which is also consistent with their primers priming on target, correct? 13:07:30 13:07:33 13:07:35 13:07:40 13:07:42

A. It's absolutely consistent with their primers priming on target and could also be consistent with primers priming off target and giving a size distribution in the same range of 150 to 550 base pairs, which would be expected, given the restriction digest that's being done. And if there were homology, you simply replicate those regions. 13:07:45 13:07:47 13:07:50 13:07:52 13:07:54 13:07:57 13:07:59 13:08:02 13:08:05

Q. So, even if you know the size of your restriction digest, you think the homologous regions are going to appear in the exact same region, in homologous regions in that -- let's just say you've created, you know, fragments that are between 100 or whatever it said, 100 and 600 base pairs long and your -- when you look at that, you see that the region that you're targeting is usually like 13:08:08 13:08:11 13:08:17 13:08:21 13:08:23 13:08:25 13:08:31 13:08:38 13:08:40 13:08:42

upstream of the three prime end by a hundred nucleotides, such that you're always going to get fragments that are about 500 base pairs long. 13:08:44 13:08:48 13:08:50 13:08:52

Are you saying the homologous regions are always going to be in the exactly the same -- 13:08:54 13:08:56 13:08:58

A. That's not what I said. 13:08:59

MS. CIPRIANO: Objection to form. 13:09:00 13:09:01

A. That's a long question, No. 1. 13:09:01

No. 2, what I said is what they're reporting here is a size distribution consistent with what they expected giving a wide range of product lengths between 150 to 500 base pairs consistent with on-target priming. 13:09:03 13:09:06 13:09:08 13:09:10 13:09:14 13:09:18

I'm happy to agree with the experts that this is strong evidence of on-target priming. If you had off-target priming, you couldn't rule that out by looking at the size distribution, because those off-target products could well be within this range that you're going to hybridize 13:09:19 13:09:23 13:09:26 13:09:28 13:09:31 13:09:32 13:09:36

against the array. 13:09:40

Q. Got it. 13:09:40

So earlier today, I guess, this morning you would talk about off-target effects, right? 13:09:41 13:09:45 13:09:49

And I always try to bring you back to let's just talk about the target-specific primer binding to or annealling to where it's supposed to anneal to, right? 13:09:49 13:09:52 13:09:55 13:09:59 13:10:02

A. Right. 13:10:02

Q. When you were referring to "off-target effects," I was assuming you were referring to more than just that; is that fair? 13:10:03 13:10:05 13:10:06 13:10:09

A. That is -- yeah, well, the priming of a homologous region is one example of an off-target effect. 13:10:09 13:10:14 13:10:17

Q. When you said, "off-target effects," were you also referring to, for example, primer dimers? 13:10:19 13:10:23 13:10:26

A. Primer dimers are another example of off-target effects. 13:10:27 13:10:30

Q. And a "primer dimer" is 13:10:32

something that people worry about, as they multiplex higher, right? 13:10:34 13:10:37

A. Prime dimers have a higher -- as you add more primers to a multiplexing reaction, you create combinatorial possibilities for a higher degree of primer dimerization. 13:10:39 13:10:46 13:10:48 13:10:53 13:10:56

Q. Right. 13:11:01

And the primer dimer hybridization could, actually, give you amplicons, which are not things that you want to see, right? 13:11:01 13:11:04 13:11:07 13:11:09

A. It can give you a plethora of artifacts. 13:11:09 13:11:12

Q. And, as you multiplex and you would compare the possibility of primer dimers in a two primer system, that -- two target specific primers where you use a forward and reverse target specific primer, as compared to a single primer extension, it's just simple math as to what the likelihood of the primer dimers is going to be, isn't it? 13:11:13 13:11:17 13:11:21 13:11:24 13:11:27 13:11:29 13:11:32 13:11:35 13:11:37

A. As I stated before, the more 13:11:39

primers you add to the reaction, you increase the probability -- the possibilities of prior dimerization. 13:11:40 13:11:44 13:11:46

Q. So, for example, just to elucidate that a little bit, if we were to take -- well, we'll just do it simply. 13:11:51 13:11:54 13:11:57

So, if we were looking at 1 loci and you were using two target-specific primers, one for the reverse, one for the forward, right, you actually have two different primers. 13:12:00 13:12:02 13:12:05 13:12:06 13:12:09

So, basically, it's one primer to one primer as your possibility for a primer dimer, correct? 13:12:11 13:12:13 13:12:15

A. I think that we can go through -- 13:12:18 13:12:23

Q. Let's just stick with my question, okay? 13:12:26 13:12:28

A. Okay. 13:12:29

Q. Keep it simple. 13:12:29

A. Sure. 13:12:30

Q. So forward and reverse primer, you, essentially, have primers of two different sequences. 13:12:31 13:12:31 13:12:31

You've got like a one primer to one primer chance of getting a primer dimer, right? 13:12:32 13:12:35 13:12:37

A. If you have only one primer, there is one way to get a primer dimer. 13:12:40 13:12:41

Q. Well, you have two primers. You have a forward primer and a reverse primer and -- 13:12:44 13:12:44 13:12:46

A. I thought you were asking me about the single primer first. I apologize. 13:12:46 13:12:47 13:12:49

Q. No, sorry. 13:12:49

We're talking about the two primer situation -- 13:12:49 13:12:51

A. Okay. 13:12:52

Q. -- right? 13:12:52

So you've got two. It's a -- one to one -- possibility, even when you have two primers, right? 13:12:53 13:12:54 13:12:56

Or when you have a distinct forward and a reverse, right? 13:12:57 13:12:59

A. If you have distinct forward and reverse, you can get primer dimers across those combinations. 13:13:02 13:13:05 13:13:10

Q. Okay. And, actually, in a single loci situation, the math is the same for a single primer extension situation. 13:13:11 13:13:13 13:13:15 13:13:19

So you've got one target-specific primer and you have a common primer, which usually binds to the adaptor. I mean, those are distinct, so the math is the same. 13:13:19 13:13:22 13:13:23 13:13:25 13:13:26

It's one primer to one primer, right? 13:13:27 13:13:29

A. In the example that -- with the single primer extension and the universal primer, you have some equivalence to the two primer scenario. 13:13:31 13:13:34 13:13:37 13:13:46

Q. Right. 13:13:48

The math is, essentially, the same, right; possibilities on the math side, right? 13:13:49 13:13:51 13:13:54

A. I believe that is the case. 13:13:57

Q. Alright. Now, when you go up to two, the math starts to change, right? 13:13:59 13:14:00

Because if I go up to two now, I've got on the two primer situation, right, 13:14:03 13:14:05

where we're using distinct forward and reverses? 13:14:09 13:14:12

So my forward primer now has the possibility -- in either of the 2 loci, my forward primer can potentially form primer dimers with two distinct primers on the reverse side, right? So it's one to two possibility, right? 13:14:12 13:14:16 13:14:19 13:14:22 13:14:27 13:14:31

A. I believe Shapero gave us a formula in their paper as to how the problem explodes with end primer pairs. 13:14:35 13:14:37 13:14:40

Q. Right. 13:14:44

So, in that one -- just to keep it simple again, right, in the two primer situation, it's -- for 2 loci, your forward primer has the possibility of hitting two distinct reverse primers, right? 13:14:44 13:14:46 13:14:49 13:14:53 13:14:55 13:14:58

So that's the math, right? 13:14:58

It's got two potential targets, right? 13:14:59 13:15:02

MS. CIPRIANO: Objection to form. 13:15:02 13:15:05

A. Again, we can -- 13:15:05

Q. Yes or no. I mean, we're keeping it mathematically simple. 13:15:06 13:15:08

A. I'm trying to keep up with your question, sir. 13:15:10 13:15:12

And, as I said, we can also easily turn to Shapero, who gives us a simple formula for how to estimate the number of -- how the number of primer pairs grow. 13:15:13 13:15:16 13:15:20 13:15:23

Q. So, actually, the single primer extension, as you multiplex, has a lot of advantages, because the math, just the pure math, are in its favor, as opposed -- with respect to creating primer dimers, right? 13:15:26 13:15:28 13:15:29 13:15:31 13:15:33 13:15:37

MS. CIPRIANO: Objection to form. 13:15:38 13:15:40

A. Could you simply restate the question for me, please? 13:15:44 13:15:46

Q. Sure. 13:15:47

In single primer extension, is the math more favorable to avoiding primer dimers in single primer extension or in what you call traditional PCR using two target-specific primers? 13:15:48 13:15:51 13:15:55 13:16:02 13:16:05

A. I believe Dr. Metzker called it a PCR in his deposition or -- in his deposition. 13:16:06 13:16:08 13:16:12

But we can call it traditional PCR, two primer PCR. 13:16:13 13:16:20

It is, certainly, the case that in two primer PCR, you have more combinations of primers and so more opportunity for primer dimers than with single primer extension. Whether you get there or not depends, again, on the multiplexing of the reaction and how things are designed. 13:16:22 13:16:29 13:16:31 13:16:34 13:16:36 13:16:38 13:16:41

The degree of off-target effects, though, depends on not just the primer dimers but the combination of the primer dimers and other off-target effects that could be contributing. 13:16:43 13:16:47 13:16:49 13:16:52 13:16:57

Q. Okay. In assessing the Shapero reference, QIAGEN 1006, did you -- let's keep it with the 250 plex. 13:16:58 13:17:01 13:17:06

Did you consider that primer dimers were adding to off-target effects? 13:17:08 13:17:12

A. Again, I think, in the Shapero reference, because hybridization requires 13:17:22 13:17:26

a high degree of similarity to the SNPs already on the array, the degree of primer dimers is hard to discern, because they're going to be washed out because they don't hybridize to the array. They're not read out. In next generation sequencing, they would, certainly, be read out. 13:17:31 13:17:35 13:17:42 13:17:45 13:17:48 13:17:49 13:17:50

Q. So, I mean, do you really think that you did an in-depth read with an in-depth understanding of the Shapero paper given that answer that you just gave me? 13:17:51 13:17:53 13:17:56 13:17:58 13:18:00

MS. CIPRIANO: Objection to form. 13:18:01 13:18:02

A. I'm not sure how to answer your question, sir. 13:18:05 13:18:07

Q. Did you just read this paper in a cursory fashion, or did you really dig in? 13:18:07 13:18:09 13:18:12

A. I spent a fair amount of time considering the paper. 13:18:13 13:18:15

Q. So you spent a fair amount of time. 13:18:17 13:18:19

So is Figure 2(A) in the library 13:18:19

preparation step prior to putting it on the array? 13:18:23 13:18:26

A. Figure 2A is before you've hybridized to the array. 13:18:28 13:18:34

Q. Got it. 13:18:35

So, prior to hybridizing to the array -- so the array has nothing to do with what's shown in Figure 2(A), right? 13:18:35 13:18:38 13:18:40

A. This is prior to putting it on the array. 13:18:45 13:18:47

Q. Got it. 13:18:47

And your testimony was that reading this article neither you nor a person of ordinary skill in the art would be able to discern whether the method that Shapero discloses and the data he discloses gives any indication of what level of primer dimers there are; is that right? 13:18:48 13:18:51 13:18:56 13:18:57 13:19:00 13:19:03 13:19:06

A. I said that the level of primer dimers wouldn't be relevant, because you're hybridizing to an array. 13:19:07 13:19:09 13:19:11

Q. Alright. So does the paper, actually, give you any data by which you can determine whether there are primer 13:19:13 13:19:14 13:19:17

dimers being formed in the 250 plex? 13:19:19

A. If you're asking me about the 13:19:26
gel and whether I would expect to see 13:19:27
primer dimers migrating further down -- is 13:19:29
that what you're asking me to opine on? 13:19:34

Q. If you want to rephrase the 13:19:36
question, I'll let you answer that one. 13:19:37

I might have to have followups, 13:19:39
since you're creating your own question. 13:19:41

A. Why don't you ask me the 13:19:42
question you would like me to answer. 13:19:44

Q. Which I did and then you 13:19:46
reformulated it -- 13:19:48

A. Okay. 13:19:49

Q. -- as you've been doing all 13:19:49
day. 13:19:51

Is there any data in the paper that 13:19:51
shows you that primer dimers are being 13:19:55
formed in the 250 plex reaction in the 13:19:58
Shapero paper, Exhibit 1006? 13:20:05

MS. CIPRIANO: Objection to 13:20:10
form. 13:20:17

A. If you'd like to me answer a 13:20:17
question of a specific figure or 13:20:24

interpretation of a figure, I'm happy to do that, or a specific date that are in the paper that I've reviewed, I'm happy to answer that question. 13:20:24 13:20:25 13:20:30 13:20:33

Q. Do you want me to answer the question for you? 13:20:33 13:20:35

I mean, I'm asking you a question and you're, like, not able to answer it. 13:20:37 13:20:37

It's a pretty simple question. 13:20:38

Is there any -- and, again, I asked you whether you did a cursory reading of this paper and you said, no, you studied it in-depth. And you're presented as someone who is expert in this field who has done a lot of work. 13:20:40 13:20:42 13:20:44 13:20:47 13:20:50 13:20:52

I mean, if you've, actually, read it in-depth and not just cursorily, can you point to any data in this paper, which shows in the 250 plex reaction, primer dimers are being formed? 13:20:53 13:20:55 13:20:59 13:21:01 13:21:04

MS. CIPRIANO: Objection, argumentive, asked and answered. 13:21:05 13:21:06

A. As I've tried to do throughout the day and answer your 13:21:12 13:21:15

questions to the best of my ability, in my read of the paper, the readout through hybridization is a key component relative to the issue of off-target binding and other potential artifacts. 13:21:17 13:21:19 13:21:25 13:21:31 13:21:36

To the specific question about primer dimers, one could look at the gel and one would have expected primer dimers to migrate faster. And so there would be -- if there was a high degree of primer dimerization, there would be a strong band near the bottom of the gel. It could have been runoff. I don't know exactly where they cut off. 13:21:38 13:21:40 13:21:43 13:21:45 13:21:48 13:21:53 13:21:56 13:21:58 13:22:00

But that would be one place one would find primer dimers, if there were a large amount of primer dimerization. 13:22:01 13:22:03 13:22:06

Q. So given, you know, the length of the primers that are being used in the 250 flex, what are the possible size ranges of primer dimers that could possibly occur in the 250 plex? 13:22:08 13:22:10 13:22:14 13:22:16 13:22:18

A. We can turn back to the beginning of the paper where they give us 13:22:21 13:22:22

the sizes. 13:22:24

So, I believe, we're looking at 23 plus 25, so 48 base pairs. That would be one primer. 13:22:42 13:22:47 13:22:52

Q. So, if primer dimers were formed between the primers, given the lengths that they have, what are the possible size ranges? 13:22:54 13:22:57 13:23:00 13:23:02

A. We would expect them to migrate at about a hundred base pairs, right. They're below a hundred base pairs. 13:23:03 13:23:05 13:23:07 13:23:08

Q. And in Figure 2(A), which is a gel of run of all the amplicons, do you see a shred of evidence that there are any primer dimers in this? 13:23:09 13:23:11 13:23:14 13:23:16

A. I do not -- 13:23:18

MS. CIPRIANO: Objection to form. 13:23:19 13:23:20

A. I do not see a band. As I said, I don't know where exactly they cut off. It could be it's runoff. I don't have reason to believe that. 13:23:20 13:23:22 13:23:24 13:23:30

But, again, I believe, the focus 13:23:31

here is on the demonstration of the size product range in the target that they're looking at. 13:23:34 13:23:38 13:23:40

There is also no hundred base pair band, specifically, there that lights up. So I don't know to what degree you would be able to see it here. 13:23:41 13:23:44 13:23:46 13:23:48

Q. Well, there's a hundred base pair marker in there, right? 13:23:50 13:23:52

A. And there's no band at a hundred base pairs. 13:23:52 13:23:53

Q. Well, there is a hundred base pair marker annotated in Figure 2(A), right? 13:23:53 13:23:56 13:23:59

A. And it's not very bright. So I don't know if they've run the gel off. There is no hundred base pair band that I see on the gel. 13:23:59 13:24:01 13:24:04 13:24:07

Q. So you think annotating a hundred base pairs was just a phantom thing that they just threw in there for fun? 13:24:11 13:24:13 13:24:15 13:24:18

A. No, they could have -- again, you're asking me about whether there is 13:24:18 13:24:19

evidence in the gel for primer dimers. I don't see evidence. But I also don't see a band right at a hundred base pair and I also believe in many ways it's not relevant because the hybridization does the work. 13:24:20 13:24:23 13:24:25 13:24:28 13:24:30 13:24:31

Q. Well, it's relevant to this case, if they're trying to say that primer dimers are causing a lack of enrichment and you're getting a bunch of stuff that you don't want in single primer extension under the MARA. So that is relevant to this case. 13:24:32 13:24:33 13:24:36 13:24:40 13:24:42 13:24:44 13:24:46

A. Most of what I've focused on are the off-target effects due to priming in homologous regions that I've discussed prior. 13:24:46 13:24:47 13:24:50 13:24:53

Q. So the, quote, "off target events by targeting in homologous regions," you don't call that miss priming, right? That's not a terminology you would use, right? 13:25:04 13:25:08 13:25:11 13:25:14 13:25:16

A. I would call it off target -- off-target amplification or extension. 13:25:19 13:25:27

Q. So, just out of curiosity, if there's this homologous region that you hadn't thought your primer was going to bind to and you did put it on an NGS machine, like, do you think that's -- those are reads that you would throw away that are uninteresting, or would it be interesting to know that they're homologous regions that hybridizing get extended by these primers that you've designed very specifically to anneal to very specific regions? 13:25:34 13:25:37 13:25:38 13:25:40 13:25:41 13:25:44 13:25:46 13:25:48 13:25:50 13:25:53 13:25:55 13:25:56

MS. CIPRIANO: Objection to form. 13:25:57 13:25:58

A. Could you simplify the question for me? 13:26:00 13:26:01

Q. Yeah. 13:26:01

I mean, would those be completely uninteresting reads where the primer -- the single primer binds to homologous regions or would they be interesting reads? 13:26:02 13:26:04 13:26:07 13:26:09 13:26:11

A. It depends on the biological question. 13:26:11 13:26:13

Q. Sometimes they would actually be interesting reads? 13:26:13 13:26:15

A. They might be. They might not be. 13:26:15 13:26:17

Q. The 250 plex that Shapero records, that's a lot more multiplex than anything that appears in the '012 or '108 patent; isn't it? 13:26:19 13:26:23 13:26:25 13:26:29

A. We can turn to the '012 and '108 patent and go through it in detail, if you would like to. 13:26:30 13:26:32 13:26:34

Q. I think you said, again, you spent 2 or 300 hours on this case. You reviewed the patents relatively recently. 13:26:35 13:26:37 13:26:40

What's the level of multiplex? 13:26:43

A. Can I please get a copy of the '102 patent, so we can discuss it in detail and I can make sure I can ground my question -- my answer to your question? 13:26:44 13:26:46 13:26:49 13:26:51 13:26:51

Q. So sitting here off the top of your head you have no idea what the level of multiplexing is? 13:26:51 13:26:53 13:26:54

A. I want to be careful in 13:26:55

answering of your question, sir, and accurate. 13:26:57 13:27:00

Q. You don't have to call me "sir." That sounds like I'm an old man. 13:27:00 13:27:01

(There is a discussion off the record.) 13:27:01 13:27:28

(Deposition Exhibit QIAGEN 1009, '108 patent, was previously marked for identification.) 13:27:28 13:27:28 13:27:28

MR. BILSKER: You want that, Linnea? 13:27:28 13:27:29

MS. CIPRIANO: No. 13:27:30

Q. We'll just use the Exhibit 1001. The specs are the same between that and the '108. 13:27:33 13:27:35 13:27:39

A. (The witness reviews the exhibit.) 13:28:20 13:28:20

Can I also get the '108 patent? 13:28:20

Q. It's exactly the same except for the claims. I think your Counsel can probably represent that. We can try to keep the paper down. 13:28:22 13:28:23 13:28:29 13:28:31

A. (The witness continues to review the exhibit.) 13:28:38 13:28:56

Q. But if you don't, maybe I'll give you a copy of it as well. I'm just telling you it's exactly the same. 13:28:56 13:28:59 13:29:01

MS. CIPRIANO: Is there something that you wanted to compare? 13:29:02 13:29:03 13:29:04

THE WITNESS: I was looking for one of the examples. 13:29:06 13:29:07

A. (The witness continues reviews the exhibit.) 13:29:14 13:29:14

MR. BILSKER: Here, Linnea, you can hand it to him. 13:29:18 13:29:19

THE WITNESS: Thank you. 13:29:21

Q. The examples are identical so... 13:29:23 13:29:25

A. Yeah, I'm refreshing my mind -- I'm refreshing my memory. 13:29:26 13:29:31

And would you mind repeating your question for me? 13:29:54 13:29:56

Q. Yeah. 13:29:56

What level of multiplexing did the inventors show in the '012 and '108 patent? 13:29:57 13:30:00 13:30:04

A. I believe that in one of the 13:30:14

examples, it's 16 primer extension products. 13:30:16 13:30:26

(Stenographer clarification.) 13:30:26

A. Sixteen primer extension products. 13:30:26 13:30:29

Q. Are you sure you read that right? 13:30:29 13:30:30

Is it locus 16S and 18 extension products maybe? 13:30:31 13:30:34

A. There's -- no, in the second example, I believe, it's 16 independent reactions. 13:30:35 13:30:37 13:30:39

(The witness reviews the exhibit.) 13:30:45

Q. So "16 independent reactions," right, that's not even multiplexing where you have a problem because you're doing each reaction individually, right? 13:30:53 13:30:55 13:30:56 13:30:58

A. (The witness reviews the exhibit.) 13:31:21 13:31:26

Q. You want to answer that question? 13:31:26 13:31:27

A. Give me a moment. 13:31:29

I believe that the 16 individual primer extension products are pooled. 13:31:50 13:31:52

Q. After the extension? 13:31:55
A. I believe that is accurate. 13:31:56
Q. So you don't really have to worry about all the problems that the inventors claimed existed in doing your extension reaction in the same -- in the same soup, right, your multiplex extension reactions in the same soup, when you do the extension reactions independently? 13:31:58 13:31:59 13:32:01 13:32:04 13:32:07 13:32:10 13:32:11 13:32:14
MS. CIPRIANO: Objection to form. 13:32:15 13:32:16
A. Give me a minute to ensure that all of the -- all of the examples are as you state. 13:32:26 13:32:28 13:32:36
Q. Well, I'll make it easy for you, alright. I mean, let's just stick with Example 2. 13:32:37 13:32:39 13:32:41
In Example 2, if you run all of your extension reactions in separate tubes, you're not concerned with a multiplexing problem that the patent purports to solve, which is you're going to get a lot of off-target events, you're 13:32:42 13:32:44 13:32:46 13:32:48 13:32:50 13:32:53

going to get primer dimers, when you start multiplexing at a high level? 13:32:56 13:32:59

I mean, doing each extension reaction in separate tubes kind of alleviates that problem, right? 13:33:01 13:33:03 13:33:05

A. I would agree with that statement. 13:33:08 13:33:09

Q. And that was already being done by people like RainDance. 13:33:09 13:33:10

I mean, that type of multiplexing was already done, right? 13:33:13 13:33:15

A. I'm -- the level of RainDance multiplexing is not something that I reviewed, as part of this Declaration per se. But if memory recalls, that that's on the order of about what could be accomplished. 13:33:19 13:33:30 13:33:33 13:33:37 13:33:41 13:33:45

Q. I mean, even the patent itself in Column 1 mentions doing PCR in emulsions, which is RainDance. 13:33:46 13:33:48 13:33:51

A. RainDance is an example of emulsion PCR. 13:33:53 13:33:56

Q. Okay. So let's go to Example 1, which is not solving a problem, which 13:33:57 13:33:59

doesn't actually exist in theory. 13:34:01

So Example 1, they're not running them in separate test tubes, but what's the level of multiplexing reported in Example 1? 13:34:04 13:34:06 13:34:09 13:34:11

I mean, I can help you, if you want, if you don't want to struggle seeing this for the first time. 13:34:13 13:34:15 13:34:17

You want me to help you? 13:34:19

A. Please give me a minute to refresh my memory on Example 1. 13:34:26 13:34:30

Q. So we don't waste a lot of time, I'm just going to direct you to Column 32, like between Liens 10 and 15. 13:34:37 13:34:39 13:34:41

A. There are 18 highly conserved sequence blocks -- 13:34:50 13:34:53

(Stenographer clarification.) 13:34:53

A. There are 18 highly conserved sequence blocks identified across the 16S genomic loci. 13:34:54 13:34:57 13:34:59

THE STENOGRAPHER: I cannot understand what you're saying. I'm sorry. 13:34:59 13:34:59 13:34:59

THE WITNESS: I apologize. 13:35:02

A. I believe the number is 18. 13:35:02
Q. Yeah. 13:35:05
MR. BILSKER: Yeah, and I can tell you what he said, if you want. 13:35:06
He said, I believe, there are 18 highly conserved loci blocks across, and then I don't remember what else. 13:35:08 13:35:09 13:35:13 13:35:15
A. 16S. 13:35:16
Q. Across 16S. 13:35:17
Alright. So that would be 18 plex, right? 13:35:19 13:35:23
A. That would be accurate. 13:35:23
Q. And what Shapero is, actually, reporting on is data related to a 250 plex, right? 13:35:25 13:35:28 13:35:32
A. That would be accurate. 13:35:33
Q. A lot more -- to use the same word again -- a lot more -- 250 plex is a lot more complex than an 18 plex, right? 13:35:34 13:35:37 13:35:40
A. The degree of complexity also depends on the differences in sequencing reads but, in general, 18 targets are easier to differentiate than 250 targets. 13:35:47 13:35:52 13:35:58 13:36:02

Q. Got it. 13:36:05

So one of the things that you did 13:36:06
in your Declaration was you identified a 13:36:17
multitude of papers or, like, many papers 13:36:20
that you said would teach a person of 13:36:23
ordinary skill in the art prior to 2012 13:36:28
that there's just no way that you would 13:36:30
ever want to use single primer extension 13:36:32
to create a library that would be 13:36:34
sequenced on a next generation or 13:36:38
massively parallel sequencing, right? 13:36:41

A. I believe, I discuss papers 13:36:44
that have cited MARA, as well as other 13:36:46
literature that teaches away from the use 13:36:49
of SPET for -- than detection with NGS. 13:36:51

Q. Because there's all these 13:36:57
problems that may arise, like, you get 13:36:58
off-target priming and extension with 13:37:03
only a single primer, right? 13:37:05

MS. CIPRIANO: Objection to 13:37:07
form. 13:37:09

A. Could you rephrase the 13:37:09
question? 13:37:10

Q. Sure. 13:37:10

You're saying a person of ordinary skill in the art reading all this literature that you cited would recognize that MARA is really not going to be any good because all these papers discuss all the problems that you're going to encounter, if you use a single primer extension reaction, right? 13:37:11 13:37:13 13:37:14 13:37:17 13:37:21 13:37:23 13:37:24 13:37:26

A. I believe I've documented in my Declaration a body of literature that speak to the potential problems with the MARA technology and why it would teach away from NGS -- 13:37:28 13:37:31 13:37:36 13:37:38 13:37:40

Q. Right. 13:37:41

A. -- combining with NGS. 13:37:42

Q. And, prior to 2012, it's your opinion that in order for a person of ordinary skill in the art to even think about using something like MARA, to create a library to be sequenced on a massively parallel sequencer, all the problems that these papers that you cited have identified would have to be solved before a person would even contemplate 13:37:43 13:37:49 13:37:53 13:37:54 13:37:57 13:38:00 13:38:03 13:38:06 13:38:08

using a library created, for example, in the 250 plex of Shapero on a massively parallel sequencing platform, right? 13:38:11 13:38:14 13:38:17

MS. CIPRIANO: Objection to form. 13:38:20 13:38:21

A. Could you simplify the question for me? 13:38:21 13:38:22

Q. There are a lot of problems that you believe you identified in all these papers that you cited saying single primer extension is no good for creating a library for massively parallel sequencing, right? 13:38:23 13:38:25 13:38:27 13:38:29 13:38:33 13:38:35

A. I've documented why there was concern in the literature that using a single primer versus a dual primer amplicon strategy would be problematic for high degree multiplexing. 13:38:36 13:38:38 13:38:40 13:38:45 13:38:47

Q. Because you couldn't ensure with one primer that you'd be on target a lot of times; is that right? 13:38:51 13:38:56 13:38:59

A. That's one problem that I've raised. 13:39:02 13:39:05

Q. So you would have to come up 13:39:05

with a methodology to create your primers in such a way that you would ensure that they're on target high amounts of times, such that you'd create a library, which is sufficiently enriched, to go on massively parallel sequencing platforms, right? 13:39:06 13:39:08 13:39:12 13:39:15 13:39:17 13:39:19 13:39:22

A. Depending on the degree of multiplexing and the degree of off-target binding. 13:39:22 13:39:24 13:39:27

Q. Now, in your Declaration, you did not contest that the enrichment steps described in the Shapero paper were any different from the enrichment steps that are disclosed in the '012 and -- in say the '012 patent, right? 13:39:27 13:39:33 13:39:37 13:39:41 13:39:44 13:39:48

Just the steps of extension -- well, fragmenting, ligating the adaptor, that's partially duplex, extending with a single primer and then amplifying using a primer, which is complementary to the adaptor sequence, and another primer, which is complementary to the tail of the target specific primer. 13:39:50 13:39:57 13:40:01 13:40:06 13:40:10 13:40:12 13:40:14 13:40:18

Those steps are exactly the same in Shapero's MARA, as they are described in the claims of the '012 patent, correct? 13:40:18 13:40:21 13:40:24

MS. CIPRIANO: Objection to form. 13:40:27 13:40:32

A. Could you restate your question for me? 13:40:32 13:40:33

Q. No, I can't. We're going to read it back because -- 13:40:34 13:40:36

A. That's fine. 13:40:36

Q. -- it was very specific, so listen. 13:40:37 13:40:38

(Whereupon, the question is read back as follows:

"Question: Now, in your Declaration, you did not contest that the enrichment steps described in the Shapero paper were any different from the enrichment steps that are disclosed in the '012 and -- in say the '012 patent, right?

Just the steps of extension -- well, fragmenting, ligating the adaptor, that's partially duplex,

extending with a single primer and then amplifying using a primer, which is complementary to the adaptor sequence, and another primer, which is complementary to the tail of the target specific primer.

Those steps are exactly the same in Shapero's MARA, as they are described in the claims of the '012 patent, correct?") 13:41:31

THE STENOGRAPHER: There was an objection to form. 13:41:31 13:41:33

A. So my interpretation is that the enrichment step occurs through 1D, which is the amplification step, using the universal primers. 13:41:35 13:41:37 13:41:43 13:41:46

Q. Yeah. 13:41:48

And the words describes in Shapero is exactly the way it's described in the claims, which is the amplification step uses a primer, which anneals to the complement of the adaptor sequence, which is created when you extend the single 13:41:49 13:41:51 13:41:53 13:41:56 13:41:59 13:42:01

primer, and a second prior, which anneals to the complement of the tail of the single primer, right? 13:42:04 13:42:07 13:42:10

A. I think the difference is in Shapero the microarray hybridization performs a great deal of the enrichment, as you're calling it, because you're only hybridizing highly homologous fragments that bind, specifically, to each of the two alleles. 13:42:12 13:42:16 13:42:24 13:42:25 13:42:29 13:42:36 13:42:39

Q. Alright. I'm going to stop you, because you're going completely off what the question was. 13:42:40 13:42:41 13:42:43

I'm not talking about the array. I'm talking about the enrichment steps, before you put it on the array, before you put it on the sequencing. 13:42:44 13:42:45 13:42:47 13:42:48

I'll make it easy. 13:42:50

There is nothing that in your Declaration -- and you can sit here and look at it -- where you challenge that any of the steps of the enrichment are missing in Shapero, correct? 13:42:51 13:42:53 13:42:55 13:42:56 13:42:58

A. Depends on whether we define 13:43:01

enrichment as including or not including the effect of the microarray. 13:43:03 13:43:11

Q. The only thing that you challenge is that there's not a motivation to combine Shapero with an actual -- 13:43:13 13:43:15 13:43:17

A. Sequencing. 13:43:21

Q. -- sequencing -- a multi-parallel sequencing platform, correct? 13:43:21 13:43:24 13:43:25

A. I have stated in my Declaration that there's no motivation to combine Shapero with a sequencing platform. 13:43:26 13:43:27 13:43:29 13:43:31

Q. Alright. So, if we consider the steps of enrichment to be 1A through 1E or, actually, 1A through 1D of the '012, you have not offered any opinion in your Declaration that Shapero does not disclose 1A to 1D, correct? 13:43:31 13:43:34 13:43:40 13:43:45 13:43:50 13:43:53

A. I would -- I would state that in my Declaration and in the -- 13:43:55 13:43:57

Q. Why can't you answer things yes or no when they're yes or no questions? 13:43:59 13:44:01 13:44:02

In your Declaration, which you have in front of you, have you offered a single opinion that Shapero does not disclose Elements 1A to 1D of the '012 patent; yes or no? 13:44:03 13:44:04 13:44:07 13:44:09 13:44:13

MS. CIPRIANO: Objection. Objection to form. 13:44:13 13:44:14

MR. BILSKER: No, I don't -- we don't need to waste time with him creating his own questions and going off and answering. It's a straightforward question. 13:44:14 13:44:16 13:44:19 13:44:20 13:44:22

A. As I've indicated and the patent states clearly, the enrichment step is through the amplification with the universal primers. 13:44:23 13:44:25 13:44:27 13:44:29

Q. Who cares. 13:44:31

Let's stick to the question, alright? 13:44:32 13:44:35

Is there anywhere in your Declaration, which you said you've now spent, at least, 200 hours on it -- did you write your Declaration? 13:44:36 13:44:39 13:44:41 13:44:43

A. Yes, I wrote my Declaration 13:44:45

in collaboration with the attorneys and, particularly, around the legal matter. 13:44:48 13:44:51

Q. During the breaks, have you discussed any of your answers to the questions that would come up? 13:44:52 13:44:53 13:44:55

A. Absolutely not. 13:44:56

Q. So, in that Declaration, which you claim that you've collaborated on and created, is there anywhere in there where you say Elements 1A, 1B, 1C, or 1D are not present in Shapero; yes or no? 13:44:57 13:44:58 13:45:01 13:45:03 13:45:08

A. Not as you're asking. 13:45:10

Q. Okay. See that was easy, right? 13:45:11 13:45:13

If you just answer the question, we'll get out of here a lot quicker. 13:45:14 13:45:15

And it's 1A to 1D in Shapero -- those elements, which you say Shapero -- there's all these problems and people would know there's a lot of off-target events and, therefore, because there's off-target events, they would not even contemplate using that library created by Steps 1A to 1D to place it on a 13:45:17 13:45:21 13:45:23 13:45:24 13:45:26 13:45:29 13:45:34 13:45:36

multi-parallel sequencing platform, right? 13:45:40
MS. CIPRIANO: Objection. 13:45:43
Q. Because there are all these 13:45:43
problems in all these articles that you 13:45:45
know have identified, right? 13:45:47
MS. CIPRIANO: Objection to 13:45:48
form. 13:45:49
A. And the fact that nobody 13:45:50
actually did it. 13:45:53
Q. Alright. So where in the 13:45:54
patent do you see any information on any 13:45:56
data, any new technologies that tells a 13:46:00
person of ordinary skill in the art how 13:46:04
to solve all these problems that you 13:46:07
claim existed in single primer extension, 13:46:08
in creating a library, which is enriched 13:46:12
for your target and does not have all 13:46:15
these off-target events? 13:46:17
Show me anywhere in the patent 13:46:18
where this patent describes how to solve 13:46:19
those problems that you claim to have 13:46:21
identified. 13:46:23
MS. CIPRIANO: Objection, 13:46:24
compound. 13:46:25

A. Could you break that question up for me? 13:46:28 13:46:29

Q. Where -- so you've identified all these problems with single primer extension that would lead a person of ordinary skill in the art reading Shapero not to use it on a multi-parallel sequencing platform. 13:46:30 13:46:32 13:46:34 13:46:36 13:46:37 13:46:40

And I am asking you where in the patent is there any data or new technology or new techniques that conveyed to a person of ordinary skill in the art that all these problems that you've identified have been solved by what's disclosed in the '012 patent? 13:46:41 13:46:44 13:46:47 13:46:51 13:46:53 13:46:55 13:46:58

MS. CIPRIANO: Same objection. 13:47:01

A. So, in practicing the '012 patent, because of the design of the system, as described in Steps 1 through D, the products that are made accessible for sequencing are enriched for the target sequencing of interest. 13:47:04 13:47:06 13:47:15 13:47:19 13:47:23 13:47:25

Q. It's the exact same steps as what Shapero discloses. 13:47:26 13:47:28

So what have they changed from what Shapero discloses to make the enrichment that occurs by following the exact same steps now performed well where Shapero wouldn't perform well? What difference? 13:47:30 13:47:31 13:47:33 13:47:35 13:47:39

MS. CIPRIANO: Objection to form. 13:47:42 13:47:42

A. As I've stated, in the embodiment of the patents, as evidenced by the NuGEN -- and I discuss in my Declaration around secondary considerations, the product worked. 13:47:46 13:47:50 13:47:57 13:48:01 13:48:02

Q. I don't care about that. I'm looking at the patent, as filed on the date of its filing. 13:48:06 13:48:08 13:48:10

What in there tells you -- for example, what in there tells you how to design primers in a single primer extension that are going to perform better than the primers that -- the way that Shapero designed them? 13:48:11 13:48:13 13:48:16 13:48:17 13:48:18 13:48:20

A. (The witness reviews the exhibit.) 13:48:25 13:48:28

MS. CIPRIANO: Objection to 13:48:28

form. 13:48:28

A. I cannot point to a specific place in the patent that describes an improvement in primers per se. 13:48:51 13:48:54 13:48:57

But, as I mentioned, when the readout of the product is considered, the technology was demonstrated to work. 13:48:59 13:49:05 13:49:09

Q. Where is the readout in the patent? 13:49:12 13:49:14

Do you see any sequencing data? 13:49:15

A. There is no sequencing data that I can point to in the patent. 13:49:15 13:49:16

Q. In fact, if you had good sequencing data at the time when you filed the patent, you would have put it in there, right? 13:49:17 13:49:19 13:49:20 13:49:22

MS. CIPRIANO: Objection, speculation. 13:49:22 13:49:23

A. I didn't write the patent. 13:49:24

Q. Yeah, but you're a person of ordinary skill in the art opining on it. 13:49:25 13:49:28

Do you see a shred of data anywhere that tells you're getting good on-target rates and that your reads are mostly of 13:49:28 13:49:30 13:49:33

what you want? 13:49:35

MS. CIPRIANO: Objection to form. 13:49:36 13:49:37

Q. And I can help you, if you want. There's nothing. But you can go and look yourself. 13:49:39 13:49:41 13:49:42

A. I do not see sequencing data. 13:49:45

Q. It's not funny. 13:49:48

Because you've got one company trying to exclude other companies from making stuff based on an enrichment method, which is identical to one that already existed, okay? 13:49:49 13:49:51 13:49:52 13:49:55 13:49:57

So I don't want to -- you chuckled, but this is not a laughing matter. 13:49:58 13:50:02

So I want you to point me to anything which shows -- is there a shred of data anywhere which would show that the library you create from these steps 1 to D perform high on-target rates? 13:50:03 13:50:05 13:50:07 13:50:10 13:50:13

MS. CIPRIANO: Objection, argumentive. 13:50:16 13:50:17

A. Sir, I did not chuckle. I was taking a sigh, as I took a breath, to 13:50:20 13:50:22

answer your question. 13:50:28

Q. That's why we have video most 13:50:31
of the time, because it wasn't a gu-tha 13:50:33
(phonetic). It wasn't a deep breath. It 13:50:35
was a chuckle but whatever. 13:50:36

A. Can you repeat your question? 13:50:44

Q. Yeah. 13:50:45

What data in the patent shows that 13:50:46
using Steps 1 to D produces a library, 13:50:49
which is highly enriched with a target? 13:50:52

A. There is no data per se. 13:50:58
There is a description of how to analyze 13:51:00
the data to estimate the enrichment. 13:51:04

Q. So it's prophetic, they didn't 13:51:07
even do it, did they? 13:51:10

A. Whether or not NuGEN had data 13:51:15
at the time, I can't speak to that, given 13:51:17
that I wasn't at the company. And I 13:51:21
don't know. I have what we have before 13:51:24
us to consider. 13:51:25

Q. Right. 13:51:26

As a scientist, when you're 13:51:27
publishing a paper -- or have you been on 13:51:28
any patents? 13:51:30

A. I have been on multiple patents. 13:51:30 13:51:31

Q. So, in your patents, if you're purporting to have developed something new and you have data supporting your claim that you have something new that works well, do you present the data? 13:51:32 13:51:33 13:51:36 13:51:38 13:51:40

A. I would often present the data. 13:51:43 13:51:44

Q. Cause, you know, in the scientific world, I mean, the data is the proof, right, not just someone saying, oh, it's going to work, right? 13:51:44 13:51:47 13:51:48 13:51:51

A. As I've mentioned, when we consider secondary considerations -- 13:51:53 13:51:56

Q. I'm not talking about that. 13:51:57

A. Sorry. 13:51:59

Q. Just stick to my question, right. 13:52:00 13:52:01

Data is the proof, right, that something is actually working, right? 13:52:02 13:52:04

MS. CIPRIANO: Objection to form. 13:52:06 13:52:07

A. There are multiple papers 13:52:07

that we can point to that make you -- 13:52:08

Q. In 2012, when this patent is filed, where is the data that shows that it's going to work? 13:52:11 13:52:13 13:52:16

A. There is no sequence data presented in this patent per se. 13:52:25 13:52:27

Q. So given that there are all these problems that you claim existed in the world that every person of ordinary skill in the art knows that would send them running for the hills, if you told them, use the MARA enrichment method in QIAGEN 1006 to create a library, which you're going to sequence on a massively parallel sequencer, given all those problems they say is going to send them running from the hills and they wouldn't even consider that, what makes them change their mind by reading this patent? 13:52:29 13:52:31 13:52:33 13:52:37 13:52:38 13:52:40 13:52:45 13:52:47 13:52:50 13:52:51 13:52:53 13:52:54 13:52:56

MS. CIPRIANO: Objection to form. 13:52:58 13:52:58

A. The design, as outlined in the embodiment of the claimed inventions, was demonstrated to work. 13:53:07 13:53:09 13:53:15

Q. Where is the data that shows it's working in 2012? 13:53:17 13:53:18

A. As -- 13:53:20

MS. CIPRIANO: Objection, relevance. 13:53:20 13:53:21

MR. BILSKER: There is no court in the world is there an objection in a deposition to "relevance," okay? 13:53:27 13:53:29 13:53:30 13:53:32

MS. CIPRIANO: In the Trial Practice Guide there is. 13:53:32 13:53:34

MR. BILSKER: And if you don't think that's relevant to obviousness, I think, you need to go back and to do analysis. 13:53:38 13:53:39 13:53:40 13:53:42

MS. CIPRIANO: We don't need to bicker. 13:53:44 13:53:46

MR. BILSKER: Well, if you're trying to coach the witness -- 13:53:47 13:53:48

MS. CIPRIANO: I'm not. 13:53:49

Q. Go ahead. 13:53:49

MS. CIPRIANO: Written description is not relevant to the invalidity in the PTAB proceeding. 13:53:50 13:53:51 13:53:52

It's not a -- 13:53:54

MR. BILSKER: We're talking 13:53:54

about obviousness. 13:53:55

MS. CIPRIANO: Okay. 13:53:56

A. I believe, I've answered your 13:53:59

question. 13:54:00

Q. No, you have not. 13:54:01

Given all the problems that you 13:54:02

claim exist in the world that steers a 13:54:03

person away from creating an enriched 13:54:06

library using the MARA method, which is 13:54:09

-- you've not offered any opinion that 13:54:11

the MARA method elements that follow 13:54:13

Steps 1 to D are any different than 13:54:16

what's claimed in the '012. There's 13:54:18

nothing in your Declaration that says 13:54:20

they're different on that. 13:54:22

What indicates to a person of 13:54:23

ordinary skill in the art reading this 13:54:26

'012 patent, which is Exhibit 1001, what 13:54:27

indicates to them that Steps 1 to D are 13:54:32

actually going to produce a library 13:54:35

enriched to a level at which you can 13:54:37

sequence on a massively parallel 13:54:39

platform? 13:54:41

A. It is my understanding that 13:54:45
you do not need to have a -- 13:54:49

Q. I'm not asking you for some 13:54:59
legal opinion. You're not a lawyer. 13:55:01

I'm just asking you, as a scientist, 13:55:02
what teaches a person of ordinary skill 13:55:04
in the art that Steps 1 to D are going to 13:55:07
work all of the sudden in 2012, but they 13:55:09
don't work when the exact same steps are 13:55:13
described in another paper? 13:55:15

A. I would respectfully put forth 13:55:17
that the MARA method, as implemented and 13:55:23
described, is targeted to a set of SNPs 13:55:30
for which you're doing the genotype 13:55:37
readout with the array. 13:55:40

In this case, you are designing a 13:55:42
system for multiplexing that makes use of 13:55:45
the single primer extension and with the 13:55:50
readout of sequencing can be evaluated in 13:55:54
terms of the success of on target versus 13:55:57
off target. 13:56:01

Q. Who cares? 13:56:01

In the Brooks Declaration, he said 13:56:02

you wouldn't even think of using a MARA-type method, because you're going to get so much off-target amplification? 13:56:04 13:56:06 13:56:08

A. We agree. 13:56:12

Q. The steps are exactly the same in MARA, as they are in the '012 patent, Exhibit 1001, Steps 1A to 1D. The enrichment steps are identical. 13:56:12 13:56:14 13:56:20 13:56:23

So why all the sudden are you not off target when you follow the steps in 1A to 1D? 13:56:26 13:56:28 13:56:30

Why are you not off target there, but you are off target when you follow MARA? 13:56:33 13:56:34 13:56:36

A. As I indicated, the degree to off target in MARA can't be assessed by the experiments, as described. They may or may not have off-target effects, okay. 13:56:37 13:56:40 13:56:46 13:56:49

Q. Well, there is no data in here to assess whether it's on target or off target either, right? 13:56:52 13:56:54 13:56:56

There's, actually, data in the MARA paper, which is consistent with it being on target. There's not a shred of data 13:56:57 13:56:59 13:57:01

in this patent. 13:57:03

So what would make somebody believe 13:57:04
that, again, given all the problems that 13:57:06
you describe exist in the world, that a 13:57:08
POSA would recognize all the problems 13:57:10
that exist with single primer extension 13:57:12
where they would just say, you're going 13:57:15
to get crappy results and not going to 13:57:17
get a good enriched library? 13:57:20

Why all the sudden did the exact 13:57:21
same steps in 2012 with not a shred of 13:57:23
data presented, why would it make a 13:57:27
person of ordinary skill in the art think 13:57:29
that a library created by what's claimed 13:57:30
here, those same steps is going to work? 13:57:33

A. The purpose of the patent is 13:57:35
not to prove that the method works. It's 13:57:38
to protect the idea and disclose the 13:57:40
invention and they then marshall evidence 13:57:45
as embodied both in the products and 13:57:49
additional scientific publications that 13:57:52
it did work. 13:57:55

MS. CIPRIANO: Can we take 13:57:55
a break? 13:57:56

MR. BILSKER: No, we cannot. I'm going to keep going for a few minutes and then take a break. 13:57:56 13:57:58 13:58:00

Q. You know one of the purposes of the patent is to enable a person of ordinary skill in the art to be able to practice the invention. 13:58:01 13:58:02 13:58:05 13:58:06

So, without having to do a bunch of experimentation, just to be able to read the patent and make it work. 13:58:07 13:58:10 13:58:12

So given all the problems that you identify in the world for making single primer extension work, what is described in the patent that, basically, now tells you that using single primer extension in steps, which are identical to Shapero's MARA, what is described in here that allows you, a POSA, to now believe, hey, here is a way to make it work? 13:58:13 13:58:15 13:58:18 13:58:20 13:58:22 13:58:25 13:58:29 13:58:31 13:58:35

MS. CIPRIANO: Objection, asked and answered. 13:58:36 13:58:37

A. As I believe I've answered already, the invention as disclosed in the patent gives you a step-by-step 13:58:42 13:58:45 13:58:48

instruction on how to prepare the libraries for enrichment via single primer extension into next generation sequencing and can be evaluated for success of on-target binding. 13:58:53 13:58:55 13:59:00 13:59:03 13:59:04

Q. But the preparation of the libraries is no different than the preparation of the libraries as described in Shapero, right? 13:59:06 13:59:07 13:59:09 13:59:10

Prior to putting it on the array, prior to putting it on the Illumina sequencer, those steps are identical. 13:59:11 13:59:14 13:59:16

A. I would -- I would say that the MARA method, as described, is one example of the broader SPET, as described in this patent. 13:59:18 13:59:21 13:59:26 13:59:30

Q. So, again, given all the problems that you think existed in the world prior to this patent coming around, like, a person of ordinary skill in the art reading the Shapero paper, even with the data presented, which is all consistent with being on target, what would a person of ordinary skill in the 13:59:39 13:59:40 13:59:42 13:59:44 13:59:46 13:59:49 13:59:50 13:59:53

art reading this patent change, as far as the enrichment steps, to make it, actually, work to get an enriched library that Shapero does not teach? 13:59:56 14:00:01 14:00:03 14:00:06

A. In the Shapero example, as we've discussed, you are targeting known SNPs and reading out through hybridization. 14:00:11 14:00:14 14:00:18 14:00:19

Here you are able to design targets not only for genotype but for sequencing and can read out using universal adaptors that are ligated for next generation sequencing. 14:00:21 14:00:27 14:00:29 14:00:34 14:00:37

Q. Again, the enrichment steps are identical between Shapero and what's described in the '012 patent. 14:00:37 14:00:38 14:00:41

So, again, what I'm saying is, if you keep saying -- producing all these articles, which you claim show that Shapero and the MARA method -- and I'm just going to use -- suck and are going to give you crappy libraries that are not enriched, they're going to have all this off-target stuff, what does the '012 14:00:43 14:00:45 14:00:47 14:00:51 14:00:54 14:00:56 14:00:59 14:01:01

patent teach you about not making it suck and, actually, produce libraries that are highly enriched? 14:01:03 14:01:06 14:01:09

MS. CIPRIANO: Objection to form. 14:01:10 14:01:11

A. As I've tried to answer throughout the last set of questions, is my opinion that the invention, as disclosed in the '012 patent, gives a step-by-step recipe for producing enriched sequencing libraries and then can validate the extent to which target enrichment has occurred. 14:01:11 14:01:14 14:01:21 14:01:24 14:01:28 14:01:34 14:01:37 14:01:41

And the design of the experiment and the results of the experiment ended up demonstrating once read out that the method worked. 14:01:42 14:01:48 14:01:51 14:01:55

Q. Maybe I missed it. 14:01:56

Show me the results of the experiment that show you it works in the '012 patent. 14:01:58 14:01:59 14:02:01

A. I didn't say that the results are in the '012 patent. 14:02:02 14:02:04

I said that there's literature and 14:02:05

I point to the literature in my Declaration of the products that NuGEN produced that demonstrate the success of the product. 14:02:07 14:02:10 14:02:15 14:02:18

Q. So why -- 14:02:18

MS. CIPRIANO: It's 2 -- 14:02:18

Q. Why would a person reading the '012 patent in 2012, when the thing was filed, why would they believe this works given that you've told me there is all this literature that tells you it's not going to work? 14:02:21 14:02:23 14:02:26 14:02:28 14:02:30 14:02:32

A. They don't need to believe it works. They can go head and try it themselves and see it works. 14:02:33 14:02:34 14:02:36

Q. So why wouldn't the person try it themselves when they look at Shapero in the, you know, five years post when massively parallel sequencing, actually, came about, why wouldn't they try it? 14:02:37 14:02:39 14:02:42 14:02:43 14:02:46

A. The evidence is it wasn't tried. It wasn't -- 14:02:48 14:02:48

Q. Why would they be steered away from trying it? 14:02:49 14:02:51

A. Because the concerns around the potential effects, until somebody wrote it down and tried it and demonstrated it. 14:02:52 14:02:53 14:02:55 14:02:57

Q. But there is no demonstration here, no demonstration that it works? 14:02:57 14:02:59

A. The demonstration comes after the patent was filed and the subsequent publication. 14:03:01 14:03:03 14:03:06

Q. I'm looking for the demonstration, as you read it in 2012, which is the legally relevant time period. 14:03:06 14:03:07 14:03:09 14:03:11

What's the demonstration that it's actually going to work? 14:03:11 14:03:13

MS. CIPRIANO: Objection, asked and answered. 14:03:14 14:03:14

A. It doesn't need to be demonstrated in the patent. 14:03:15 14:03:15

MR. BILSKER: Alright. We can take our break. 14:03:15 14:03:16

A. Thank you. 14:03:17

Q. And I'll just remind you that you're not allowed to talk to your 14:03:18 14:03:19

attorney about -- 14:03:21

A. I'm going on my call. 14:03:21

Q. Oh, sorry. 14:03:23

A. Thank you. 14:03:26

(Recess taken 2:03 to 2:35 p.m.) 14:03:26 14:13:05

Q. Dr. Bustamante, can you turn again to the Brooks Declaration, Tecan 2026? It's on Page 38 of 69. The attorneys stamp is in the right-hand corner, bottom right-hand corner. 14:35:31 14:35:34 14:35:39 14:35:44 14:35:46

Are you there? 14:35:50

A. Page 38 you said? 14:35:51

Q. Yeah. 14:35:52

A. Yes. 14:35:53

Q. So Paragraph 16 -- 14:35:53

A. Give me a moment to re-read this please. 14:35:56 14:35:59

Okay. 14:36:28

Q. So are you understanding Dr. Brooks to be saying that a library enriched by single primer extension, as described in say Steps 1A to D of the '012 patent, would only produce a library 14:36:29 14:36:32 14:36:35 14:36:39 14:36:42

that was enriched for your target at about 50 percent? 14:36:46 14:36:48

A. I read that he states, "using the claim methods, I expect it to serve about 50 percent of sequence of interest in" -- 14:36:50 14:36:52

THE STENOGRAPHER: I'm sorry. You're reading too fast and too low and I can't hear you.

THE WITNESS: I apologize.

THE STENOGRAPHER: You can read it again just read it a little louder. 14:37:03

A. "Using the claimed methods, I expected to observe about 50 percent of sequences of interest in the sequencing results." 14:37:03 14:37:05 14:37:08 14:37:09

Q. Yeah, I don't need you to parrot back exactly what it says. That's why I asked you the question a little different. 14:37:10 14:37:11 14:37:14 14:37:15

Are you understanding that to mean that the library is enriched following the enrichment method described such that 14:37:16 14:37:17 14:37:19

it produces a library that only has 50 percent of your target sequence and 50 percent of things that are not your target sequence? 14:37:22 14:37:26 14:37:28 14:37:30

A. I would understand that to mean that about 50 percent of the sequence would be sequences of interest. 14:37:31 14:37:33 14:37:35

Q. Okay. In the enriched library? 14:37:37 14:37:38

A. In the library that was sequenced, 50 percent of the sequence would be sequence of interest. 14:37:40 14:37:41 14:37:43

Q. Well, it couldn't be 50 percent of the sequence of interest, if your library was only enriched to 20 percent of your target sequencing and 80 percent was stuff that was not your target sequence, right? 14:37:45 14:37:47 14:37:49 14:37:52 14:37:54 14:37:56

MS. CIPRIANO: Objection to form. 14:37:57 14:37:59

A. Could you restate the question for me, please? 14:38:01 14:38:04

Q. Sure. 14:38:04

To have reads that are 50 percent 14:38:05

of what you want, your library has to, actually, include the percentage of the target in the library before you put it on the sequencer? 14:38:06 14:38:10 14:38:13 14:38:15

It has to be, at least, 50 percent of the target sequence, right? 14:38:16 14:38:18

A. It depends on -- assuming that we're classifying reads as to being either on target or off target and the reads are all the same length, then the 50 percent of the reads and the total readout of the experiment would be on target versus off target so... 14:38:22 14:38:29 14:38:31 14:38:33 14:38:36 14:38:39 14:38:45

Q. How does that relate to the level of enrichment in the library? 14:38:46 14:38:48

A. So I would -- I would -- so, when we think about on target versus off target, in general, say in exome sequencing, for example, you would define on target to be reads that map to where you have probes, where you have designed the target reaching. 14:38:49 14:38:53 14:38:58 14:39:04 14:39:06 14:39:10 14:39:13

There are sometime edge of facts and depending on how much the probes 14:39:16 14:39:19

overlap, the total amount of real estate is -- you know, the total target size relative to the total of what got sequenced and you have more reads on the on target versus the off target. 14:39:21 14:39:28 14:39:33 14:39:37 14:39:40

Q. I didn't understand how that answered the question. 14:39:42 14:39:44

But are you saying that the reads that come out of the sequencer that are, quote, on target, what you want, are, roughly, proportional to the level of enrichment of the on target in the library? 14:39:45 14:39:47 14:39:51 14:39:52 14:39:54 14:39:56

A. Yes, that does -- yes. So the usual way one quantifies enrichment is the ratio of reads that map to the target region versus reads that map to the off targets and often you have much higher depth of coverage from the on-target regions versus the off target. 14:39:58 14:40:02 14:40:07 14:40:10 14:40:13 14:40:16 14:40:17

Q. And before, actually, doing the sequencing, how would you have any idea what the percentage of reads that are on your on target versus off target, 14:40:20 14:40:22 14:40:25 14:40:26

if you don't know what the level of enrichment of the library is? 14:40:29 14:40:31

MS. CIPRIANO: Objection to form. 14:40:34 14:40:34

A. In order to estimate the level of enrichment, you would need to first define the target regions and then anything that's not in the target region would be off target and may have a much larger amount of real estate; so depending on whether you're counting reads or total amount of sequence. 14:40:36 14:40:38 14:40:42 14:40:45 14:40:49 14:40:55 14:40:57 14:40:59

Q. Yes. So the question is this. 14:41:02

I enrich a library. I haven't put it on my sequencer yet. I'm in 2011. And I say, you know what, I'm pretty sure that I've created a library, which enriched to 50 percent, right? 14:41:04 14:41:06 14:41:09 14:41:12 14:41:16

I've run it on a gel. I've got fragments that seem to be the right size. I've done other downstream experiments that seem consistent with I'm finding all my targets and I believe that it's at 50 percent. 14:41:21 14:41:24 14:41:26 14:41:28 14:41:30 14:41:32

Would you -- and I say I really think I should put this on an MPS system to get, you know, the full sequence reads. 14:41:32 14:41:36 14:41:39

Would you tell that person -- you, as a person of ordinary skill in the art -- don't bother if you've only enriched to 50 percent, you don't want to put it on a massively parallel sequencing platform? 14:41:41 14:41:44 14:41:45 14:41:48 14:41:51

A. It would depend on the experiment and whether you at 50 percent would have sufficient depth of coverage to, say, call variants in the regions of interest or to detect mutations. It all depends on how big the region of interest is relative to the background. 14:41:54 14:41:56 14:42:00 14:42:01 14:42:05 14:42:09 14:42:12

Q. It depends on how deep my sequencing depth is going to be; is that one of the things you said? 14:42:18 14:42:20 14:42:22

A. The interpretability of the experiment would depend on the depth of sequencing in the target region versus the off-target region. 14:42:24 14:42:29 14:42:30 14:42:33

Q. So let's say I was using 250 loci on a Illumina HiSeq in 2011, which I 14:42:34 14:42:36

believe had two lanes in it. I don't remember how many -- eight lanes. 14:42:42 14:42:45

So I'm only going to use one of those lanes, in one of the 250 plex. 14:42:50 14:42:52

I'm going to get a pretty deep read for that -- for those 250 targets, right? 14:42:55 14:42:57

A. I can't do the calculation right here right now, but I would imagine that if what you have is three megabases of target, which, I believe, is what we looked at in the paper and even less than 3 megabases of target or 2 megabases of target, then you probably get a fair amount of depth of coverage. 14:43:04 14:43:05 14:43:07 14:43:10 14:43:13 14:43:16 14:43:20 14:43:22

Q. And if I said to you, I believe that my on-target rate for enrichment in that my library creation in my 250 plex is 50 percent, would you steer me away from sequencing that on a platform, because I'm not going to get usable data, it's going to be confounded and I can't do a sequencing analysis? 14:43:24 14:43:26 14:43:30 14:43:32 14:43:35 14:43:38 14:43:40 14:43:43

MS. CIPRIANO: Objection to form. 14:43:45 14:43:45

THE WITNESS: Ma'am, would you mind re-reading the question for me. 14:43:53 14:43:54

(Whereupon, the question is read back as follows:

"Question: And if I said to you, I believe that my on-target rate for enrichment in that my library creation in my 250 plex is 50 percent, would you steer me away from sequencing that on a platform, because I'm not going to get usable data, it's going to be confounded and I can't do a sequencing analysis?")

THE STENOGRAPHER: And there was an objection. 14:44:19

A. There are multiple questions there. 14:44:19 14:44:22

If the question is, would I steer you away -- is that the question? 14:44:23 14:44:24

It depends on, you know, where you are in the process of developing your assay. It might well be worth generating some test data and seeing how well it 14:44:29 14:44:33 14:44:35 14:44:39

works. 14:44:41

And if you did that, we can then 14:44:42
figure out whether you needed more 14:44:48
sequencing or improving the target. 14:44:50

Q. Alright. Let's go back to 14:44:51
Paragraph 16 of the Brooks Declaration. 14:44:55

Why in 2012 with single primer 14:44:57
extension would you have expected only 14:45:01
50 percent of the reads to be target 14:45:03
sequenced that you were interested in? 14:45:07

A. I can only speculate as to 14:45:16
why Dr. Brooks expected 50 percent. 14:45:18

Q. Do you agree with him? 14:45:21

A. I'm not sure I would agree to 14:45:25
50 percent. 14:45:30

Q. So you haven't seen any -- I 14:45:30
mean, you've now reviewed a bunch of 14:45:35
papers, right? 14:45:37

What quantitative analytical data 14:45:38
have you seen that would indicate to you 14:45:41
that an enrichment method using single 14:45:45
primer extension, such as described in 14:45:49
Shapero, QIAGEN 1006, would only provide 14:45:52
about 50 percent of reads, which are what 14:45:58

you want? 14:46:01

A. We can look at some of the 14:46:03
papers that I cite that make use of the 14:46:05
NuGEN technology. 14:46:07

Q. You said you would not 14:46:09
necessarily agree with him. 14:46:10

So what are you aware of that would 14:46:11
indicate -- like, he doesn't provide any 14:46:13
reference. He doesn't cite to any 14:46:15
material. He just -- this number of 14:46:17
50 percent comes out of the air. 14:46:19

What are you aware of that would 14:46:21
lead you to believe that the Shapero 14:46:23
method would only give you 50 percent of 14:46:26
reads that you want? 14:46:29

A. I didn't state that I would 14:46:34
put the number at 50 percent. What I'm 14:46:36
saying is that it's not unreasonable for 14:46:38
him to hypothesize about 50 percent and 14:46:42
then to be pleasantly surprised when it's 14:46:45
closer to 90 percent. 14:46:48

Q. You said you might necessarily 14:46:49
put it at 50 percent. 14:46:51

Well, what would you have put it at 14:46:53

2012? 14:46:57

A. That's a post hoc question. 14:46:57
Now that I know the answer, I can't -- 14:46:58
it's hard to put myself back there and 14:47:00
guesstimate. So maybe it might be more, 14:47:02
it might be less than 50 percent. 14:47:07

Q. So is there a number in 2011 14:47:09
level of reads that you get that are on 14:47:15
target that are -- that you would do and 14:47:20
that you would not do in a massively 14:47:26
parallel system? 14:47:29

A. It really depends on the 14:47:30
biological question. So I would say that 14:47:32
for some problems -- and if you're going 14:47:37
to get plenty of depth of coverage, you 14:47:42
can tolerate 50 percent of target. For 14:47:46
others, 50 percent off target might not 14:47:48
be sufficient to draw good conclusions 14:47:51
until -- you'd have to do more sequencing 14:47:55
in order to understand how well it's 14:47:58
working. 14:48:00

Q. So, again, you've worked at a 14:48:01
university where I assume you didn't have 14:48:03
your own say Illumina sequencer in your 14:48:05

lab, did you? 14:48:08

A. I did. 14:48:08

Q. Did you ever use the core facility? 14:48:09 14:48:10

A. I've used core facilities in the past. But I've also done a lot of sequencing in our own lab. 14:48:14 14:48:16 14:48:19

Q. So, when you use a core facility, for example -- I mean, a lot of people use core facility, because they don't want to spend what, a million dollars for the instrument and reagent costs, right? 14:48:21 14:48:22 14:48:24 14:48:26 14:48:28 14:48:30

At universities, a lot of people use the core facility, right? 14:48:32 14:48:33

A. Lot of places people use core facilities. 14:48:34 14:48:36

Q. And in a core facility, when you don't use the entire capacity of the chip, right, if you submit a sample -- let's say, there's only a couple of things that you're interested in sequencing, couple of loci. 14:48:36 14:48:38 14:48:40 14:48:43 14:48:45 14:48:49

The core facility, I think, we 14:48:50

already established will frequently wait until they get samples from many people to utilize the entire capacity of the flow cell, right? 14:48:52 14:48:55 14:48:58 14:49:02

A. Yes. 14:49:03

Q. Does the core facility, generally, ask you, hey, do you want to pay for the entire cost of running -- doing this run, even though you're not going to use the entire capacity, or do you want me to wait until we fill it up with other people's samples? Do they ask? 14:49:04 14:49:05 14:49:07 14:49:11 14:49:13 14:49:15 14:49:17 14:49:20

A. You can sometimes -- yeah, you can choose to run on the whole flow cell or wait until you have others that -- or run a spare lane, if others aren't running a full flow cell. 14:49:20 14:49:24 14:49:27 14:49:30 14:49:32

Q. And when you run on a spare lane or, you know, half a lane or whatever and I assume you barcode -- let's say it's one lane. 14:49:34 14:49:36 14:49:38 14:49:41

So HiSeq in 2011 -- 14:49:42

A. Sure. 14:49:42

Q. -- was eight lanes. So let's say you run on one of the lanes. 14:49:44 14:49:46

Does the core facility charge you for the entire cost of the run, or do they prorate it? 14:49:48 14:49:49 14:49:52

Like, if you use one out of eight lanes, are you charged one-eighth the cost? 14:49:53 14:49:55 14:49:58

A. Not exactly one-eighth, but you don't have to pay for the whole flow cell. 14:49:58 14:50:00 14:50:03

Q. So, generally, proportional to the amount of the flow cell that you used? 14:50:03 14:50:05 14:50:06

A. That would be a pretty reasonable estimate. 14:50:07 14:50:08

Q. So, to use the entire capacity of, say, an Illumina sequencer in 2011, say, the HiSeq was 11 lanes, what was the cost of that? 14:50:09 14:50:11 14:50:14 14:50:18

A. I would have to go back and look at it. I don't have a number off the top of my head. 14:50:22 14:50:24 14:50:28

Q. Alright. But, basically, I 14:50:28

think you said the level of enrichment at which you would be steered away from running a library on a massively parallel sequencer in 2011 is somewhat dependent on how much you're willing to spend and how important your running is; is that right? 14:50:35 14:50:41 14:50:43 14:50:46 14:50:49 14:50:51 14:50:54

A. I think you would weigh the cost relative to accuracy and whether NGS could yield the accuracy discounting for off-target effects vis-à-vis other technologies you could use, for example, run an array instead. 14:50:54 14:51:00 14:51:07 14:51:13 14:51:15 14:51:18

Q. But, certainly, if your enrichment method only produced a library that was 50 percent enriched for your target, as a scientific matter, that's not an indication that you're not going to get usable data on, say, something like an Illumina sequencer, right? 14:51:20 14:51:22 14:51:25 14:51:29 14:51:32 14:51:33 14:51:36

A. As I've stated, it really depends on the biological question, the size of the target, the necessary depth of coverage. You may need to run multiple 14:51:38 14:51:40 14:51:42 14:51:43

lanes in order to get usable data. 14:51:46

Q. What if I had a library and I had -- I created an enriched library and let's say it was a 10 plex and I could demonstrate through some means in the creation of that library that I had enriched to 90 percent, okay, you got that in mind? Enriched from my 10 loci, each one owns to 90 percent. 14:51:59 14:52:03 14:52:07 14:52:10 14:52:14 14:52:17 14:52:20 14:52:24

A. Okay. 14:52:26

Q. Would a person of ordinary skill in the art, do you believe, be steered away from using that enriched library to sequence on a massively parallel sequencer? 14:52:27 14:52:30 14:52:30 14:52:33 14:52:36

A. Again, it depends on -- it depends on the relative cost to other approaches, because if you only need 10 loci, you might choose something else as opposed to overkill with NGS, right. So it all depends. 14:52:37 14:52:40 14:52:43 14:52:46 14:52:48 14:52:51

Q. So, for example, the hybridization methods -- hybridize capture that was commonly used, let's say 14:52:53 14:52:57 14:53:01

-- I guess, it's still used today, but let's say 2011 and before. 14:53:04 14:53:05

What was the level of enrichment that was common using hybrid capture to create the library before it was put on say an Illumina sequencer? 14:53:07 14:53:09 14:53:14 14:53:16

A. It varied. 14:53:16

Q. So what did it "vary" between? 14:53:17

A. It varied between even generations of the same array. So let's say you're thinking about an exome array, early exome capture versus optimized exome capture. In the early days, exome capture had a lot of off-target effects. By the time it was highly standardized, you're getting 75, 80 percent, 90 percent of the reads being on target. 14:53:20 14:53:25 14:53:29 14:53:32 14:53:40 14:53:43 14:53:46 14:53:48 14:53:52

Q. Have you seen in the literature prior to say 2010 people creating libraries where -- that are run on massively parallel platforms where the reads -- the number of reads that were on target were hovering around 50 percent? 14:53:57 14:53:58 14:54:03 14:54:07 14:54:11 14:54:15

A. It depends on the definition 14:54:19

of off target and on target for that experiment. 14:54:21 14:54:23

Q. Well, out of the reads that were obtained, 50 percent are what they were looking for and 50 percent were things that they were not interested in. 14:54:23 14:54:25 14:54:28 14:54:31

A. Depends on whether they were using enrichment or not, what kind of enrichment. 14:54:33 14:54:34 14:54:36

Q. Yeah, I'm talking about people who enrich libraries that were then put on massively parallel sequencing platforms. 14:54:37 14:54:38 14:54:40 14:54:44

Have you seen sequencing data where the people report that only 50 percent of the sequencing reads were related to things that they were actually trying to target? 14:54:45 14:54:46 14:54:48 14:54:51 14:54:53

A. It -- it -- there are lots of -- you know, there are thousands of papers that use NGS. Thousands of potential targets that folks would be enriching for. I'm sure that there's -- in the literature folks that have sequenced have gotten 14:54:54 14:54:58 14:55:00 14:55:04 14:55:06 14:55:09

on-target rates less than 50 percent and, as we've talked about, ancient DNA oftentimes even with enrichment you don't reach 50 percent. 14:55:11 14:55:13 14:55:16 14:55:19

Q. So like, for example, a rare mutation -- if you had a rare cancer mutation that occurred, let's say, .01 percent of the time, would you say that would be a situation where you would want to spend a lot of time and potentially money to sequence that, even if you couldn't enrich it that well? 14:55:21 14:55:23 14:55:28 14:55:30 14:55:35 14:55:36 14:55:38 14:55:40

MS. CIPRIANO: Objection to form. 14:55:41 14:55:44

Q. Or because it's so infrequent at .01 percent, you don't care about those people that have that rare mutation, you don't care about treating them or finding treatments for them? 14:55:44 14:55:46 14:55:49 14:55:52 14:55:55

MS. CIPRIANO: Objection. 14:55:55

A. So, in the context of detecting mutations, somatic mutations in cancer, the reads that -- we need to distinguish between the frequency of the 14:55:58 14:56:03 14:56:08 14:56:12

mutant base and clones that carry that within the population of tumor cells. And so all of those reads whether they carry or don't carry the mutation that are mapping to the gene of interest would actually be on target. They would not be off target, because it's a low frequency variant. I don't think that's a good example. 14:56:16 14:56:22 14:56:27 14:56:30 14:56:33 14:56:35 14:56:37 14:56:39 14:56:41

Q. Well, if you're trying to detect a very low frequency or very rare cancer mutation 2010 and before and you have access to a massively parallel system, are you going to use the massively parallel sequencing system, as opposed to some other way of detecting that rare mutation? 14:56:44 14:56:45 14:56:48 14:56:54 14:56:56 14:57:01 14:57:03 14:57:06

A. You would, actually, want very high depth of coverage. So you would want a lot of on-target reads. 14:57:06 14:57:07 14:57:09

Q. Well, is it a yes or no? 14:57:11

Would you use the massively parallel sequencing system, as opposed to something else? 14:57:13 14:57:14 14:57:17

A. I would use the massively parallel sequence, if I had large on-target reads, because I need a lot of depth of coverage to detect .1 percent mutation. I'd need a 1000X coverage. 14:57:17 14:57:18 14:57:21 14:57:23 14:57:26

Q. So what's a large amount of on-target reads? 14:57:28 14:57:30

A. As I said, you need about a 1000X coverage to accurately detect .1 percent mutation. 14:57:31 14:57:32 14:57:34

Q. So that would mean that if I used a target-specific primer and I did enrichment and I did multiple cycles of PCR, I might create enough to, actually, give me a strong signal in a massively parallel sequencing read? 14:57:35 14:57:37 14:57:39 14:57:42 14:57:45 14:57:49

A. You would need -- the real question is how many reads do you have and how many mapped to the target that you're interested in. 14:57:50 14:57:52 14:57:54 14:57:56

Q. So you think for a rare mutation, I need a thousand -- a depth of coverage of a thousand to detect -- to get a reasonable or reliable sequencing? 14:57:56 14:57:58 14:58:04 14:58:07

A. For the .1 percent that you described, right, you'd need, you know -- you would want very high coverage, at least, 1000X because many -- most of the reads won't carry the mutation. They would still be on-target reads, but they won't carry the mutation. 14:58:09 14:58:11 14:58:15 14:58:17 14:58:21 14:58:23 14:58:25

Q. But you would, actually, get a 1000X, if you ran, say, even four lanes on an Illumina sequencer, right? 14:58:26 14:58:28 14:58:30

A. It depends on how many other genes you're multiplexing at the same time. I mean, we would have to talk about the specific panel and the hypothetical mutation and how much of the real estate is allocated to the gene of interest. But you would sequence to high coverage. I don't think that's in dispute. 14:58:31 14:58:33 14:58:34 14:58:36 14:58:39 14:58:41 14:58:43 14:58:45

Q. So let's take a look at QIAGEN 1025, which is an article written by Dr. Metzker. 14:58:48 14:58:50 14:58:53

(Deposition Exhibit QIAGEN 1025, article authored by Metzker titled, "Sequencing technologies

- the next generation," was previously marked for identification.)

Q. That you say Dr. Metzker teaches a way from using single primer extension or multiplex PCR to create an enriched library. 14:58:57 14:58:59 14:59:06 14:59:09

Do you remember drawing that conclusion? 14:59:20 14:59:21

A. I remember discussing that in my report. 14:59:23 14:59:25

Q. And you relied on Page 41 of Dr. Metzker's Exhibit 1025, which is Page 11, left-hand column in the section entitled, "Genome enrichment." 14:59:31 14:59:36 14:59:40 14:59:43

A. Give me a moment here to please turn to the relevant sections. I want to be accurate in answering your questions, sir. 14:59:49 14:59:51 14:59:56 14:59:58

Can you repeat where you would like me to look in the Metzker paper? 15:00:26 15:00:28

Q. Do you recall that you said in your Declaration that you said Dr. Metzker taught away from using PCR target 15:00:30 15:00:31 15:00:33

enrichment methods to create an enriched library, which you would sequence on an NGS platform? 15:00:37 15:00:40 15:00:42

A. I speak about Dr. Metzker's paper at multiple places in my Declaration. 15:00:43 15:00:45 15:00:48

Q. So do you remember making that statement? 15:00:48 15:00:50

A. There are different places where I speak about the paper and I would like to turn to that, so I can accurately answer your question. 15:00:52 15:00:54 15:00:55 15:00:59

Q. Go ahead. 15:00:59

A. (The witness reviews the exhibit.) 15:01:51 15:01:51

I am looking at Page 41 of Dr. Metzker's publication. 15:02:05 15:02:08

Q. Good for you. 15:02:11

I want you to answer the question. 15:02:14

A. Could you repeat the question for me, please? 15:02:16 15:02:19

Q. Yeah. I thought you were going to your Declaration to see how you had discussed it. 15:02:20 15:02:21 15:02:23

The question was, did you point to Page 41 as Dr. Metzker teaching away from using PCR to enrich libraries that would be sequenced on an NGS platform? 15:02:24 15:02:26 15:02:29 15:02:32

A. I reference Page 41 of Dr. Metzker's paper in my report. 15:02:35 15:02:38

Q. Yeah. 15:02:39

And can you answer the question? 15:02:40

A. I quote from Dr. Metzker's paper and we have the entirety of the paper in front of us. 15:02:42 15:02:44 15:02:48

Q. Is there -- I'll even read it to you. "The concept of targeting specific regions of the genome is well established, with PCR being the most widely used methodology, albeit on a small scale. PCR coupled with Sanger sequencing is suitably matched for analyzing a handful of candidate genes, but coupling PCR with high-throughput NGS platforms for targeting strategies is not practical, as sample preparation would require handing tens of thousands of primers individually or in large multiplex 15:02:49 15:02:54 15:02:57 15:02:59 15:03:01 15:03:04 15:03:08 15:03:09 15:03:12 15:03:16 15:03:19 15:03:22 15:03:25

groups to meet the needs of a single instrument run." 15:03:28 15:03:32

Do you think that that sentence or those sentences that I just read by Dr. Metzker is conveying that one would not enrich using PCR to create a library that is run on an NGS platform? 15:03:32 15:03:34 15:03:37 15:03:40 15:03:43

A. I think Dr. Metzker is clearly speaking to the complexity of trying to do the multiplex targeting using PCR in that quote. 15:03:47 15:03:50 15:03:54 15:03:57

Q. Right. 15:03:59

And there is a caveat in there, which is multiplexing to the level where you're going to use the entire capacity of the NGS platform, right? Do you see that? 15:04:00 15:04:03 15:04:05 15:04:08 15:04:15

A. Are you referring to "large multiplex group to meet the needs of a single instrument run"? 15:04:15 15:04:17 15:04:18

Q. Yeah, yeah. 15:04:19

That's what he's talking about, right? 15:04:24 15:04:26

MS. CIPRIANO: Objection to 15:04:27

form.

Q. He's talking about multiplexing where you're using "tens of thousands of primers," right?

A. Agreed.

Q. The patent doesn't require "tens of thousands of primers" on individual loci, does it?

A. He's also saying that a -- further above that with a small number of primers, targeting specific regions of the genome is probably straddlers (phonetic). The PCR being the most wildly used, "albeit on a small scale."

Q. Yeah.

What's "small scale," like 16, 17 loci?

A. Perhaps under five would be a small scale.

Q. What level of multiplexing is required by the claims of the '012 patent?

A. There is no level of multiplexing, specifically, required.

Q. In fact, the claims of the

'012 and '108 patent don't require multiplexing at all, do they? 15:05:19 15:05:22

A. There is -- none of the limitations, specifically, require multiplexing. 15:05:30 15:05:34 15:05:36

Q. Right. 15:05:37

So let's take a look at 1001, QIAGEN 1001, the '012 patent. 15:05:38 15:05:43

A. Okay. 15:05:52

Q. So if you look at Step B in Claim 1, which is in Column 35. 15:05:52 15:05:56

A. Uh-huh. 15:05:59

Q. "Annealling one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragment ligated to the partial duplex adaptor." 15:05:59 15:06:02 15:06:03 15:06:05 15:06:08

Do you see that? 15:06:11

A. I do see that. 15:06:11

Q. So the oligonucleotides there, the word "oligonucleotide" is what they're using to refer to "primers," correct? 15:06:12 15:06:15 15:06:17

A. I would agree with that. 15:06:19

Q. And annealling one primer is 15:06:20

not a multiplex reaction, correct? 15:06:23

A. No, but annealling more than 15:06:28
one is multiplexing. 15:06:31

Q. Right. 15:06:33

But the claims, actually, cover 15:06:34
non-multiplexing because it covers one, 15:06:36
but it also covers more, right? 15:06:38

A. We are not -- I am not 15:06:40
disputing that. 15:06:42

Q. Alright. And, in fact, if 15:06:42
you go to Step C it says, "extending the 15:06:44
one or more extension products or 15:06:48
extending the one or more oligonucleotides 15:06:53
annealed to the nucleic acid sequence" -- 15:06:57
so that's yet another indication in the 15:06:58
claim -- that multiplexing is, actually, 15:07:00
not required, right? 15:07:01

A. (No response.) 15:07:01

Q. Right? 15:07:07

A. I'm -- I am not disputing that 15:07:07
multiplexing is required. 15:07:10

Q. And then in Step D, it 15:07:11
actually says, "amplifying the one or 15:07:13
more oligonucleotide extension products." 15:07:15

So it, actually, is talking about amplifying just one extension product that's covered by the claim, right? 15:07:19 15:07:20 15:07:23

A. The one would refer to one, but it's one or more. 15:07:27 15:07:30

Q. Yeah. 15:07:31

A. So... 15:07:32

Q. And, actually, the Step F where it refers to "sequencing," "sequencing the enriched nucleic acid sequence," which could be just a single sequence, right? 15:07:32 15:07:38 15:07:41 15:07:43 15:07:46

It's covered by the claim? 15:07:47

A. Could be. 15:07:49

Q. Right. 15:07:50

So the claim covers sequencing just a single sequence that was enriched, right? 15:07:51 15:07:53 15:07:55

A. The claim -- the claims as written would cover one or more. 15:07:57 15:08:02

Q. Okay. So one is a single, right? 15:08:04 15:08:06

So the claims cover when you have just have one sequence that you'd be 15:08:06 15:08:08

sequencing, right? 15:08:10

A. I think we're in agreement. 15:08:10

It covers once or more. 15:08:12

Q. You're not saying that the 15:08:14

inventors were covering things that no 15:08:15

one would ever do that are completely 15:08:17

useless and no one would ever do that, 15:08:17

right, sequencing a single sequence on a 15:08:20

massively parallel platform? 15:08:21

A. I believe the way the claim 15:08:31

is written is to cover one or more. So 15:08:33

it's clearly thinking of the multiplex 15:08:36

scenario as part of the covered invention. 15:08:42

Q. Right. 15:08:45

But it's not requiring multiplex to 15:08:45

be practiced in the invention, right? 15:08:48

A. It is not requiring 15:08:49

multiplexing. Although, I think, it is 15:08:50

understood that it is quite useful in the 15:08:54

context of multiplexing. 15:08:56

Q. Even though the example, the 15:08:57

prophetic example, with no data that was 15:09:01

ever done was simply a 17 plex, right? 15:09:04

Or is it -- 15:09:04

A. It's either 17 or 18, on the order of. 15:09:07 15:09:10

Q. Right. 15:09:10

And, actually, the literature even tells you -- the literature even tells you that with traditional PCR two primers, you know, distinct forward and reverse target-specific primers, a lot of times you don't even run into problems multiplexing until you get above a couple dozen, right? 15:09:11 15:09:12 15:09:15 15:09:19 15:09:21 15:09:24 15:09:27 15:09:30

A. It depends on the level of -- the specifics of the multiplexing reaction. 15:09:32 15:09:37 15:09:41

Q. Right. 15:09:41

But the literature tells you a lot of times you don't even run into problems with multiplexing using distinct forward and reverse primers until you get into multiple dozens of loci, right? 15:09:42 15:09:43 15:09:46 15:09:49 15:09:51

MS. CIPRIANO: Objection to form. 15:09:54 15:09:56

A. In my experience, once you get above, say, a dozen loci you're 15:09:58 15:10:00

saying, you're opening yourself up to problems with multiplexing. 15:10:05 15:10:07

Q. So let's go back in the '012 patent. 15:10:08 15:10:15

So the '012 patent describes, essentially, two different things, right? 15:10:25 15:10:27

Its enrichment of libraries, that's -- we'll call that the upstream application, and then there are downstream applications, what you do with that enriched library, right? 15:10:29 15:10:32 15:10:35 15:10:36 15:10:38

A. I would say it's covering a -- as described in the preamble -- a method for sequencing an enrichment nucleic acid sequence of interest. 15:10:43 15:10:46 15:10:48 15:10:49

Q. Yeah, but I'm not talking about the claims. I'm just talking about the specification, right. 15:10:50 15:10:51 15:10:52

So you know what the specification is? 15:10:54 15:10:55

It's the whole part that, like, comes before the very end where it describes parts of the invention. 15:10:57 15:10:58 15:11:01

A. The description of the 15:11:04

invention -- 15:11:05

Q. Yeah. 15:11:05

A. -- uh-huh. 15:11:06

Q. So, in the description of what these people think they invented, part of it is just a method for creating an enriched library, right? 15:11:07 15:11:10 15:11:13 15:11:16

A. It's a detailed description of the elements of the invention. 15:11:19 15:11:21

Q. And one of those being the way to create an enriched library, which you can then put on just multiple distinct platforms to do something with, right? 15:11:22 15:11:24 15:11:26 15:11:30 15:11:32

A. I'm not sure I put it exactly like that, but we can, you know, continue with additional questions, if you -- if you have. 15:11:41 15:11:43 15:11:48 15:11:51

Q. Well, so, again, do you feel like you've read this patent carefully? 15:11:51 15:11:54

A. I have absolutely read this patent "carefully." I could speak about it. I've got -- you know, my Declaration points to it and discusses it in detail. 15:11:55 15:11:57 15:11:59 15:12:02

Q. Okay. Well, let's take a look at Column 15 -- 15:12:07 15:12:08

A. Okay. 15:12:10

Q. -- Line 6. 15:12:11

A. Okay. 15:12:14

Q. In one embodiment (which is not stated of the invention), nucleic acid can be double stranded. Enrichment of nucleic acid sequences of interest can be achieved by using the methods described herein for target enrichment." 15:12:15 15:12:20 15:12:24 15:12:27 15:12:29 15:12:32

It doesn't say you have to sequence. 15:12:35 15:12:36

It just says, in one of the embodiments, the methods described here can be used for target enrichment, right? 15:12:37 15:12:38 15:12:40

A. That's what it states. 15:12:44

Q. If you go down a little bit further, Line 51, "Overall the target enrichment methods as described above can be used to generate a composition comprising a library of nucleic acid inserts enriched for any target sequence of interest from a non-enriched library 15:12:45 15:12:48 15:12:54 15:12:57 15:12:59 15:13:02 15:13:05

comprised of nucleic acid inserts with an adaptor ligated to one or more both ends." 15:13:08 15:13:11

Do you see that? 15:13:14

A. I do. 15:13:14

Q. And that doesn't mention sequencing, right? 15:13:15 15:13:16

A. Not yet. 15:13:17

Q. And if we keep going at that same column, Column 15/Line 57, "A schematic of a preferred embodiment of the methods described herein for enriching for target sequences of interest is illustrated in Figure 1." 15:13:33 15:13:37 15:13:41 15:13:44 15:13:47 15:13:49

So, if you go to Figure 1, right, which is towards the front, do you see anything about sequencing? 15:13:52 15:13:54 15:13:56

A. Let me turn to Figure 1. 15:13:57

Q. It's on sheet 1 of 4. 15:13:59

A. I am aware of that. Thank you. 15:14:01 15:14:01

I see Figure 1. 15:14:21

Q. You see anything in there about sequencing? 15:14:22 15:14:24

A. At the end of the process 15:14:24

described in Figure 1, you have the creation of libraries with adaptors ligated ready for sequencing. 15:14:29 15:14:33 15:14:40

Q. It doesn't say "sequence," right? 15:14:42 15:14:44

It just -- this is library creation. It doesn't, actually, say "sequence," right? 15:14:45 15:14:46 15:14:47

A. It does not say "sequence" on the figure. 15:14:48 15:14:49

Q. Got it. 15:14:50

If we go to -- go to Column 26/Line 64. 15:14:51 15:15:07

A. Give me a minute. 15:15:09

Okay. 15:15:13

Q. I'll read for you. "The methods, compositions and kits described herein can be useful to generate amplification-ready products for downstream applications, such as massively parallel sequencing (i.e. next generation sequencing methods, generation of libraries with enriched population of sequence regions of interest or 15:15:13 15:15:16 15:15:19 15:15:22 15:15:26 15:15:31 15:15:35 15:15:39 15:15:42

hybridization platforms." 15:15:45

Do you see that? 15:15:47

A. I do. 15:15:47

Q. So the patent is telling you the methods that are described in this patent for enriching for a library, one of the downstream applications can be sequencing, right? 15:15:48 15:15:51 15:15:53 15:15:57 15:15:59

A. One of the applications can, certainly, be sequencing. 15:16:02 15:16:04

Q. And another can be a hybridization platform, right? 15:16:05 15:16:06

A. That is what is described here. Although the claims and the limitations clearly state sequencing. 15:16:11 15:16:15 15:16:20

Q. Right. 15:16:22

But the library creation, once you've created the library, the patent is telling you, hey, you've got this library that you've enriched by this method that we've described, you can use that library and put it either on a sequencing platform or you can use a hybridization, you can put that same library on a 15:16:23 15:16:25 15:16:27 15:16:29 15:16:31 15:16:34 15:16:36 15:16:38

hybridization platform, right? 15:16:40

A. That's what it states at the 15:16:42
top of Page 27. 15:16:43

Q. Right. 15:16:44

And a hybridization -- one of the 15:16:45
hybridization platforms would be an Affy 15:16:46
chip, right? 15:16:49

A. One of the hybridization 15:16:50
platforms might be an Affy chip. However 15:16:51
-- 15:16:55

Q. Well, let's see what the 15:16:55
claimed inventors, actually, said. I 15:16:57
mean, let's see how specific they were. 15:16:59

Again, you feel like you read this 15:17:02
patent in detail? 15:17:04

A. You're -- I'm sorry. You cut 15:17:06
me off, as I was trying to answer. But 15:17:09
go ahead. 15:17:11

Q. So, in Column 28, it 15:17:15
identifies "downstream applications," 15:17:18
right? 15:17:20

A. Uh-huh. 15:17:20

Q. And at Line 7 it says, "An 15:17:21
important aspect of the invention is that 15:17:26

the methods and compositions disclosed herein can be efficiently and cost effectively utilized for downstream analysis." 15:17:28 15:17:30 15:17:33 15:17:36

So there's the creation of the library, the enriched library, and then there's "downstream application for which it's used, such as next generation sequencing or hybridization platforms with minimal loss of biological material of interest." 15:17:37 15:17:39 15:17:43 15:17:46 15:17:49 15:17:50 15:17:52

Do you see that? 15:17:54

A. I do. 15:17:54

Q. The methods of the present invention can also be used in the analysis of genetic information of selective genomic regions of interest (e.g., analysis of SNPs" -- S-N-P-small s -- "or other disease markers) as well as genomic regions, which may interact with the selective region of interest." 15:17:56 15:17:58 15:17:59 15:18:02 15:18:04 15:18:10 15:18:14 15:18:16

Do you see that? 15:18:18

A. I do. 15:18:19

Q. And then it goes on. 15:18:19

There is a subheading that says, "Sequencing," and there's a number of types of sequencers identified there. There's Illumina sequencers. There's Solid from Applied Biosystems. 15:18:23 15:18:25 15:18:28 15:18:31 15:18:34

Do you see those? 15:18:37

A. I do. 15:18:38

Q. And then we go on. And there's -- in Column 29, it's also semiconductor sequencing, Ion Torrent. 15:18:40 15:18:44 15:18:46

Do you see that? 15:18:50

A. At the top? 15:18:51

Q. Line 15. 15:18:52

Do you see that? 15:18:56

A. I do. 15:18:56

Q. Alright. And then at Line 41, "The methods of the present invention can be used in the analysis of genetic information of selective genomic regions of interest, as well as genomic regions, which may interact with a selective region of interest." 15:18:57 15:18:59 15:19:03 15:19:05 15:19:08 15:19:11 15:19:13

So the methods of this invention, the library enrichment, it says, 15:19:16 15:19:19

"Amplification methods as disclosed herein can be used in the devices, kits and methods known in the art for genetic analysis, such as but not limited to," and then there's a bunch of list of patents. 15:19:21 15:19:23 15:19:28 15:19:31 15:19:33 15:19:34

And after the list of patents, it says, "In some cases amplification methods of the present invention can be used to amplify target nucleic acid of interest for DNA hybridization studies to determine the presence or absence of polymorphism." 15:19:36 15:19:38 15:19:40 15:19:43 15:19:45 15:19:47 15:19:50

Do you see that? 15:19:50

A. I do. 15:19:51

Q. And do you know -- I'm sure because you read this patent in detail -- that the patents that are mentioned there refer to Affy chips, right? 15:19:51 15:19:53 15:19:56 15:19:59

A. We can draw -- we can pull up those patents. 15:20:03 15:20:05

Q. I mean -- well, did you not look at them before today? 15:20:06 15:20:07

MS. CIPRIANO: Objection to 15:20:09

form. 15:20:10

A. I said, we can pull up the patents. 15:20:10 15:20:12

Q. That's not the question. 15:20:12

The question is, did you look up those patents to see that they were referring to Affy chips? 15:20:13 15:20:14 15:20:16

A. I believe they're referenced here so we can look up the papers and confirm that. 15:20:17 15:20:19 15:20:21

Q. Again, just see if you can stick with the question. 15:20:22 15:20:24

Did you look at those papers before sitting here today to identify whether those patents were referring to Affy chips for the hybridization studies? 15:20:25 15:20:27 15:20:29 15:20:32

A. I believe some of them may refer to the Affy chips, I'm not sure if they refer to additional -- 15:20:33 15:20:35 15:20:37

Q. Well, the purported inventors of this enrichment method are telling you once you create a library enriched by the steps that they identify for enrichment, those libraries can be used to genotype 15:20:38 15:20:40 15:20:43 15:20:46 15:20:48

either on an Affy hybridization chip or by sequencing on an MPS platform, right? 15:20:52 15:20:55

A. I believe it says such as but not limited to. So, I think, they're pointing to those patents as examples of the kind of hybridization arrays that one may use are including others. 15:20:58 15:21:01 15:21:03 15:21:05 15:21:07

Q. Right. So they're telling you that enriched libraries that are enriched by the methods described in this patent can be used in among other ways, not just limited to these ways, but can be used to sequence on an MPS platform, right? 15:21:08 15:21:10 15:21:13 15:21:15 15:21:19 15:21:22

A. Yes. 15:21:25

Q. And those same libraries can also be used to genotype on hybridization arrays such as Affy chips, right? 15:21:28 15:21:29 15:21:33

A. I don't believe that's in dispute. 15:21:39 15:21:40

Q. Okay. So let's take a look -- well, actually, let's go back to the Dr. Metzker paper, Exhibit 1025. 15:21:40 15:21:48 15:21:50

A. Okay. 15:21:54

Q. So, in that same column we 15:21:57

were looking at, the "Genome enrichment" column. 15:21:59 15:22:01

A. Give me a minute to turn back to that. 15:22:01 15:22:04

I'm on the column that you're referring to. 15:22:09 15:22:11

Q. So, when Dr. Metzker in that section that we had read just previously where he's talking about "tens of thousands of primers" and giant "multiplex groups," it's just not thousands, it's "tens of thousands," right, of primers? 15:22:12 15:22:17 15:22:19 15:22:21 15:22:24 15:22:27

That's, like, way beyond what the claims require, right? 15:22:30 15:22:33

MS. CIPRIANO: Objection to form. 15:22:34 15:22:36

A. As I think we've indicated, the claims do not require a level of multiplex -- specific level of multiplexing. 15:22:40 15:22:42 15:22:45 15:22:47

Q. So this identification where Dr. Metzker is saying, hey, if you're going to use "tens of thousands" -- if you're going to use the entire capacity 15:22:48 15:22:49 15:22:51 15:22:54

of an NGS machine where you would be looking at like "tens of thousands" of loci, that may not be that easy to do. 15:22:56 15:23:00 15:23:04

But that's not teaching away from using PCR and amplicon-based enrichment for situations where you're not worried about utilizing the entire capacity of an NGS platform or where you're not concerned about multiplexing levels of "tens of thousands"? 15:23:07 15:23:09 15:23:14 15:23:17 15:23:21 15:23:23 15:23:25

He's not teaching away from, say, like, what's in the patent, just the 17 plex at most? 15:23:26 15:23:28 15:23:31

MS. CIPRIANO: Objection to form. 15:23:34 15:23:38

A. Would you restate the question? 15:23:38 15:23:39

Q. Is Dr. Metzker in that paragraph where he's talking about "tens of thousands of primers," is he teaching away from multiplexing at small levels, which are required in the patent? 15:23:39 15:23:41 15:23:43 15:23:46 15:23:49

A. He has said and, as we've indicated above, "coupling PCR with 15:23:51 15:23:54

high-throughput NGS platforms for targeting strategies is not practical." 15:23:56 15:24:02

Q. Well, it was "not practical" in what way? 15:24:05 15:24:06

If you're trying to use the entire capacity of the instrument in a multiplex reaction, which would require "tens of thousands," but there's no need to use the entire capacity of an NGS system, as you admitted multiple times today, that people split up the capacity in a core facility, right? 15:24:08 15:24:10 15:24:13 15:24:15 15:24:17 15:24:20 15:24:22 15:24:25

MS. CIPRIANO: Objection to form. 15:24:25 15:24:26

A. And I would also indicate and draw your attention to Dr. Metzker here is really talking about using the dual primer PCR strategy. 15:24:26 15:24:29 15:24:31 15:24:35

Q. Then why did you bother citing it for teaching away from using amplicon-based enrichment, as described in the patent and SPE? 15:24:38 15:24:41 15:24:43 15:24:46

A. Because, as we've discussed, the dual primer PCR strategy is more 15:24:47 15:24:49

selective than single primer. So, even when -- 15:24:54 15:24:58

Q. Not in multiplex reactions it's not. 15:24:58 15:25:00

A. In terms of specificity, it is. It also generates off target -- it also generates additional artifacts due to the primer binding. But, in terms of the targeting, the target of interest, it's going to do a better job of selecting -- 15:25:01 15:25:03 15:25:06 15:25:09 15:25:10 15:25:12 15:25:15

Q. Alright. So what evidence do you have in the literature that targeting in a multiplex of, say, two dozen you get better on-target rates with two target-specific primers than with single primer extension? 15:25:15 15:25:16 15:25:17 15:25:20 15:25:23 15:25:25

What evidence do you have in the literature, prior to 2012, do you have to support that claim? 15:25:26 15:25:27 15:25:30

A. The evidence that we have for the single primer extension is the work on MARA. And at the time as Dr. Metzker is indicating here, the use of PCR is 15:25:31 15:25:36 15:25:38 15:25:43

really the dual primer PCR strategy, the amplicon sequencing, traditional amplicon sequencing. 15:25:45 15:25:49 15:25:52

Q. So, yeah, I don't see how you citing this supports any notion that you would be steered away from using single primer extension that Dr. Metzker is teaching those of skilled in the art run away from single primer extension to create enriched amplicon libraries, because it's not going to work. 15:25:53 15:25:55 15:25:57 15:26:00 15:26:03 15:26:05 15:26:07 15:26:09

That's not what he's saying, is it? 15:26:12

MS. CIPRIANO: Objection to form, argumentive. 15:26:14 15:26:15

A. My read here is as plain as what's written here. PCR by which he's -- he means dual prior PCR, but it doesn't say single primer extension PCR or similar single primer extension. And coupled with Sanger sequencing, we know works, for a small -- for a handful of candidates. 15:26:17 15:26:22 15:26:26 15:26:29 15:26:31 15:26:34 15:26:36 15:26:40

Q. Okay. 15:26:40

A. So it's quite obvious, in my 15:26:41

opinion. 15:26:43

Q. "Quite obvious" that he's talking about something that's not relevant to the claims in the patent, right? 15:26:43 15:26:45 15:26:46 15:26:47

A. I wouldn't agree with that statement. 15:26:48 15:26:49

Q. Let's go further down in that column to where it says, "Custom-designed oligo [sic] microarrays." 15:26:50 15:26:52 15:26:55

Do you see that? 15:26:57

A. I do. 15:26:57

Q. So, in this column, Dr. Metzker -- or in this paragraph that starts with that word, "custom-designed," he's, actually, referring to two groups where he says, "the BCM-HGSC" -- and the reference is Reference 68 -- "and the Cold Spring Harbor Laboratory" -- reference 69 -- groups reported capture efficiencies of 65 to 77 percent," and in parens, "Roche/454 platform." 15:27:15 15:27:19 15:27:21 15:27:26 15:27:29 15:27:34 15:27:36 15:27:39 15:27:43 15:27:50

Do you see that? 15:27:52

A. I do. 15:27:52

Q. So "Roche 454" is a massively parallel sequencing platform, correct? 15:27:52 15:27:57

A. It is. 15:27:58

Q. And what he's saying is the enrichment methods that people reported for creating a library that they then ran on a Roche 454 platform was somewhere between 65 and 77 percent, right? 15:27:59 15:28:02 15:28:07 15:28:10 15:28:14

A. That's what I would interpret. 15:28:17

Q. Which is, actually, closer to the 50 percent that Dr. Brooks said he would have expected in the 90 percent, which he said he got, right? 15:28:19 15:28:21 15:28:25 15:28:27

MS. CIPRIANO: Objection to form. 15:28:30 15:28:30

A. Are you asking me if 65 is closer to 50 percent than to 90? 15:28:34 15:28:35

Q. I am. 15:28:38

Because you had problems with the threshold at .8 where you said that's actually even a lower read. So I want to make sure we're consistent with the math here. 15:28:40 15:28:42 15:28:44 15:28:47 15:28:48

A. It was .08 and we were 15:28:48

discussing the directionally of where the threshold is discriminating. 15:28:50 15:28:53

Q. And you were, basically, saying with a higher threshold, that's like saying a person is going to clear a bar that's at 6 feet more times than they're going to clear a bar that's at 8 feet, right? 15:28:55 15:28:56 15:28:58 15:29:00 15:29:03 15:29:05

But, again, we don't need to belabor that. 15:29:06 15:29:07

A. Please don't mischaracterize what I was trying to explain. 15:29:08 15:29:10

Q. Well, what you explained in multiple different ways. They were completely inconsistent with each other. But, again, the transcript is pretty clear on it. 15:29:11 15:29:13 15:29:14 15:29:16 15:29:18

But this BCM -- this group that sequenced on the Roche sequencer, their library was only enriched to 65 or 77 percent, yet they did it, right? 15:29:19 15:29:22 15:29:23 15:29:26

MS. CIPRIANO: Objection to form, argumentive. 15:29:28 15:29:29

A. It states in the paper 15:29:31

that -- I believe "BCM" stands for Baylor College of Medicine reported capture efficiencies of 65 to 77 percent on the Roche 454 platform and, I believe, they're talking about exome capture. 15:29:33 15:29:37 15:29:38 15:29:40 15:29:43

Q. Right. 15:29:44

And you have no reason to believe that Dr. Metzker got that wrong given that he was part of the human genome product and he was at Baylor College of Medicine, right? 15:29:45 15:29:47 15:29:48 15:29:50 15:29:53

A. He doesn't -- whether that's relevant or not -- I mean, it's a publication that he cited to. So I have no reason to believe that he transcribed it inaccurately. 15:29:54 15:29:56 15:29:57 15:29:59 15:30:01

Q. Did you go back and read those publications that he cited there? 15:30:02 15:30:04

A. I may be familiar with those publications. 15:30:07 15:30:09

Let's turn to them now. 15:30:10

I know the Baylor College of Medicine group. 15:30:17 15:30:19

So those are two often cited papers 15:30:32

for capture efficiencies. 15:30:34

Q. So these people sequenced on a massively parallel platform, as reported in the literature, even though there was only 65 -- at the low end 65 percent of on target, right? 15:30:37 15:30:40 15:30:42 15:30:44 15:30:47

A. Yes. 15:30:53

Q. Okay. And then if we go down, the sentence continues. And I'll just -- it continues after the last paren. So "(Roche/454 platform) and 53% (Illumina/Solexa platform), respectively, with targeted exons being covered by at least one NGS read." 15:30:53 15:30:56 15:31:00 15:31:03 15:31:09 15:31:12 15:31:15

Do you see that? 15:31:17

A. I do. 15:31:17

Q. So, when somebody enriched for an Illumina platform, they, actually, reported data, even useful data, even though the percent of on-target reads was 53 percent, right? 15:31:18 15:31:23 15:31:26 15:31:30 15:31:35

A. With, one single read, right. 15:31:39

Whether you can draw any inference from a single NGS read is an open 15:31:40 15:31:42

question. I think it's a demonstration that you can get array capture to work and get an initial readout from NGS. I think you wouldn't necessarily use the data generated beyond saying we were able to get capture to work and do NGS. 15:31:43 15:31:45 15:31:48 15:31:52 15:31:54 15:31:57

Q. But -- 15:32:02

A. It's a single read. 15:32:04

Q. -- scholarly articles -- so, I mean, that was published in -- we can look and look at where it was published. 15:32:06 15:32:08 15:32:10

A. This was the early days of hybrid capture. 15:32:12 15:32:16

Q. So that was published in, I believe, Nature Genetics, right, which is -- I mean, Nature by itself, Nature and Science are kind of considered at the top of the heap, right, as prestige and scientific journals, right? 15:32:17 15:32:21 15:32:25 15:32:27 15:32:28 15:32:31

A. I would agree with that. I have several Nature and Science paper. 15:32:33 15:32:34

Q. And Nature Genetics is close to the top of the pyramid as well, in the specific field of genetics, right? 15:32:36 15:32:38 15:32:40

A. Absolutely. 15:32:42

Q. So you're not saying that 15:32:43
Nature Genetics published the paper with 15:32:45
results that really don't mean anything, 15:32:48
right? 15:32:50

A. No, that's not what I said. 15:32:50
I said, as you read here very clearly, 15:32:52
53 percent on capture with targeted exons 15:32:55
being covered, at least, one NGS read. 15:33:00
This is very early on in the development 15:33:02
of exome sequence. So this is really the 15:33:04
demonstration that you can get the capture 15:33:08
piece to work and readout with NGS. 15:33:10

MR. BILSKER: Give me just a 15:33:20
second. 15:33:21

(There is a discussion off 15:33:23
the record.) 15:33:57

(Recess taken 3:34 to 3:47 15:33:57
p.m.) 15:47:46

MR. BILSKER: It's a wide 15:47:46
table. 15:47:47

MS. CIPRIANO: It is. 15:47:47

MR. BILSKER: I don't want 15:47:48
to throw but... 15:47:48

Q. We're back on the record. 15:47:50
Dr. Bustamante. So we were looking at 15:47:52
Dr. Metzker's paper, QIAGEN Exhibit 1025. 15:47:54
And, in particular, Page 11 where he 15:47:59
references a number of studies from other 15:48:01
groups. 15:48:04
And one of the groups that he 15:48:06
references is Hodges, which is reference 15:48:09
69. 15:48:13
(Deposition Exhibit QIAGEN 1115, article authored by Hodges, et al., titled, "Genome-wide in situ exon capture for selective resequencing," was previously marked for identification.)
Q. And now I've passed you 15:48:13
Exhibit 1115, which is the Hodges paper. 15:48:16
Have you read this paper before? 15:48:19
A. I read this paper in the past. 15:48:20
Q. So you are familiar with it, 15:48:22
right? 15:48:24
A. I've read this paper in 15:48:24
multiple settings. 15:48:26
Q. Right. And they -- this is 15:48:26

the paper where the level of enrichment or the level of yields is somewhere in the 50 percent range up to 85 percent, right? 15:48:32 15:48:34 15:48:38 15:48:42

A. I can confirm for you, if you give me a minute to cross-reference but... 15:48:45 15:48:47 15:48:51

Q. I don't need you to confirm it. 15:48:51 15:48:53

A. Okay. 15:48:53

Q. But you are familiar with this paper? 15:48:53 15:48:55

A. As I said, I've read this paper multiple times. I did not read it in the last week in preparation, but I'm familiar with the paper and happy to go through. 15:48:55 15:48:57 15:49:00 15:49:02 15:49:05

Q. And, I mean, again, this is from Nature Genetics, which is a prestigious journal, right? 15:49:05 15:49:07 15:49:10

A. Yes. It's from Nature Genetics. 15:49:12 15:49:15

Q. It's not your experience that Nature Genetics publishes articles that 15:49:15 15:49:16

don't have a high scientific significance, right? 15:49:21 15:49:24

A. That is not usually their publication strategy. 15:49:26 15:49:28

Q. Let's take a look at another article. 15:49:34 15:49:43

(Deposition Exhibit Tecan 2029, Nature Biotechnology article titled, "Fixing the front end," was previously marked for identification.) 15:49:43 15:49:43 15:49:43 15:49:43 15:49:47

MR. BILSKER: I feel like I should turn this into a paper airplane. 15:49:47 15:49:48 15:49:51

Q. So Tecan Exhibit 2029, this is, actually, a paper that you yourself cited, right? 15:49:54 15:49:58 15:50:00

A. I believe, I cited this paper. We can double-check. I don't remember exactly all the citations, but I've also read this paper in the past. 15:50:02 15:50:04 15:50:07 15:50:10

Q. And this is a paper that Dr. Metzker cited as well, right? 15:50:11 15:50:12

A. I'm happy to double-check the 15:50:16

references. 15:50:18

Q. You can look at Reference 76 in the Metzker paper. 15:50:18 15:50:19

A. Okay. We can confirm that. 15:50:21

Reference 77 is not this paper. 15:50:39

Q. I didn't say 77. I said, 76. 15:50:42

A. I'm sorry, I heard 77. My apologies. 15:50:45 15:50:48

Seventy-six is this paper. 15:50:52

Q. And Nature Biotechnologies is another publication in the "Nature" family, correct? 15:50:53 15:50:55 15:50:59

A. Nature Biotechnology is one of the journals of the Macmillan Nature family. 15:51:00 15:51:03 15:51:07

Q. Again, relatively high on the acceptance scale of scientific prestige, right? 15:51:08 15:51:13 15:51:16

A. Well, this is not a peer reviewed paper, but it is a "News Feature," a sort of news and views, as it were. 15:51:16 15:51:18 15:51:19 15:51:22

Q. So you cited this as potentially supportive of your claim that 15:51:26 15:51:27

no one would ever look to something like single primer extension and Shapero to create a library used on an NGS platform because -- 15:51:31 15:51:34 15:51:36 15:51:41

A. If you could point me to the exact question you want me to answer relative to what I wrote, I'm happy to turn to that. 15:51:48 15:51:49 15:51:51 15:51:53

Q. Why did you cite this paper? 15:51:53

A. If you can point me -- 15:51:55

Q. I can't. 15:51:58

A. Okay. Then I will need to look for it, because I want to make sure I answer your question accurately. 15:51:59 15:52:00 15:52:02

Q. Well, I can represent that you guys cited it because it's a Tecan exhibit. So I'm not going to waste time finding the exact place you listed it. 15:52:04 15:52:05 15:52:09 15:52:11

But this paper is from 2008, right? 15:52:13

A. This paper is from 2008. 15:52:19

Q. And it actually says on the first page of the paper that sequencing an entire exome like for -- 15:52:21 15:52:23 15:52:26

A. Can you please point me to 15:52:29

where? 15:52:31

Q. Top right-hand column. 15:52:31

A. Top right-hand column; yes. 15:52:33

Q. So it's, actually, saying that the cost of sequencing an exome is rapidly approaching $5,000, right? 15:52:34 15:52:36 15:52:41

I mean, it actually says it's imminent in 2008, right? 15:52:50 15:52:52

A. That's what it states in this news and views. 15:52:54 15:52:56

Q. Right. That's an entire exome, right? 15:52:57 15:52:59

A. That would be an entire -- again, I need to qualify this. But based on what it states here it says, a thousand gene -- dollar genome was probably, at least, five years away, but the $5,000 exome using new capture methods is imminent. 15:53:00 15:53:03 15:53:11 15:53:13 15:53:14 15:53:15 15:53:18

Q. So, if you turn to Page 3, attorney stamped Page 3, but it's 1103 of the article, right-hand column. 15:53:20 15:53:24 15:53:27

A. Yes. 15:53:29

Q. So, on the right-hand column, 15:53:31

first full paragraph, he's actually saying, "So is solution-phase better than solid?" 15:53:33 15:53:36 15:53:38

"Solid" you understand him to be talking about Solid 454? 15:53:39 15:53:43

A. No. 15:53:46

Q. Alright. Just solid array hybridization? 15:53:47 15:53:51

A. That's what he's talking about. 15:53:51 15:53:52

Q. So he goes on to answer the question, "Not necessarily. Given the low cost of sequencing, tight specificity may not be that important. As sequencing prices drop, 'if half of your reads map someplace else, or aren't directly mappable to your region of interest, maybe you don't care -- you just throw them away, says Z-W-I-C-K," which is a name comma, "who adds the microarray probes might even help coverage by capturing targeted sequence that are much longer than the probe themselves." 15:53:53 15:53:55 15:53:58 15:54:02 15:54:06 15:54:09 15:54:12 15:54:14 15:54:17 15:54:23 15:54:25 15:54:26 15:54:28

So he's actually taking quotes from 15:54:31

people in the field and some of these people in the field are saying, you know what, given the cost of sequencing coming down rapidly, it really doesn't even matter, like, if 50 percent of the stuff that you sequence is not what you want, you just throw the stuff away, it's not a big deal, right? 15:54:34 15:54:36 15:54:37 15:54:40 15:54:42 15:54:45 15:54:47 15:54:49

A. Again, he's -- we have to qualify this by saying that this in the context of whole exome sequencing, the beginnings of these technologies and relative to the depth of coverage that's achieved. 15:54:50 15:54:53 15:54:57 15:55:01 15:55:04 15:55:06

So, if you achieve sufficient depth of coverage, you might be able to draw inferences, even if 50 percent of the reads don't map to the exome. 15:55:06 15:55:09 15:55:12 15:55:14

Q. And he's talking about reads on massively parallel sequencers, right? 15:55:19 15:55:22

A. That's the way you would sequence an exome. 15:55:27 15:55:29

Q. So he's saying even on a massively parallel sequencer, he's saying 15:55:29 15:55:32

in 2008, the cost of sequencing is coming down so much and so rapidly, that in a little while you won't even care? 15:55:33 15:55:37 15:55:41

People may not even care if 50 percent of the stuff -- the sequencing reads they get are not relevant to them, right? 15:55:43 15:55:45 15:55:47 15:55:50

A. To some investigators $5,000 for an exome at that time might not be expensive, but too many investigators it was quite expensive. It was well outside the reach of the science they were doing. 15:55:51 15:55:53 15:55:55 15:55:57 15:56:00

So, I think, you're talking about leading edge labs that are trying to promote the technology at the frontier and they are saying, as is often in the case in genomics, we're almost there, it's looking great, the technology works well. 15:56:03 15:56:04 15:56:07 15:56:09 15:56:11 15:56:13 15:56:14

This is not a surprising article and it's, again, appearing as a "News Feature." This isn't a peer reviewed scientific publication. This is an editorial. 15:56:15 15:56:16 15:56:18 15:56:22 15:56:23

Q. Well, it's 5,000 in an exome for 2008. On that first page, he's actually saying a thousand dollar genome is coming. 15:56:24 15:56:26 15:56:28 15:56:30

A. And it was not reached within the timeline. So this is, you know -- this is consistent with, you know, predictions that may or may not come true. 15:56:32 15:56:34 15:56:37 15:56:38

Q. Well, a genome is 6 billion bases. We know that what Shapero was, actually, looking at was many orders of magnitude less than that, which is what -- it was 2 million bases. 15:56:41 15:56:44 15:56:47 15:56:50 15:56:54

So the cost of sequencing an entire genome, which is 6 billion bases, is, certainly, going to be higher than sequencing 2 million bases that you've chopped your library down to through enrichment, right? 15:56:58 15:57:00 15:57:03 15:57:06 15:57:08 15:57:10

A. Depending on the cost of the enrichment technology. 15:57:11 15:57:12

Q. Well, and the prices that they're quoting here -- so, if you're not sequencing, if you're not using the entire 15:57:13 15:57:17 15:57:20

capacity of the sequencing instrument, it's got to even be less, because you're going to share -- potentially you can share those costs with other people, right? 15:57:22 15:57:24 15:57:26 15:57:27 15:57:29

A. So -- yes. But let's also realize that the sequencing costs aren't the only part of the cost. You might spend six months of post-doc time analyzing the data, if it's an indecipherable experiment. 15:57:29 15:57:34 15:57:36 15:57:38 15:57:41 15:57:42

Q. Do you know what a "Q score" is in sequencing? 15:59:07 15:59:09

A. If by "Q score," we mean a base quality score. 15:59:11 15:59:17

Q. Yeah. 15:59:17

A. I do know a "base quality score." 15:59:18 15:59:20

Q. Is a base quality score of 20 considered good? 15:59:20 15:59:23

A. I would say a base quality score of 20 is considered often a minimum threshold for whether you'd accept the base call. 15:59:24 15:59:26 15:59:28 15:59:32

Q. Would you -- an error rate in sequencing below .1 percent, that's a Q score of 30 or over, isn't it? 15:59:34 15:59:39 15:59:43

A. That would be -- yes, so the definition of a Q score would be -- so one in a thousand would be ten to the third. So it would be a Q score of 30. 15:59:47 15:59:50 15:59:57 16:00:00

Q. And if an NGS platform such as Illumina had a Q score of 30 in 2011, you wouldn't say that their error rate is really that, would you? 16:00:07 16:00:08 16:00:16 16:00:18

A. The quality score is not uniform across the sequencing read or the technology. So some bases have Q scores of 20. Some bases have Q scores above 20. 16:00:20 16:00:23 16:00:28 16:00:31

Q. So, if you had a Q score of above 20, say 30, would you say that's an acceptable level of raw error rate? 16:00:34 16:00:37 16:00:40

A. It depends on the depth of coverage. So, even if you have a -- if you have a single read with a Q score of 30, you might trust that data. You would want multiple reads to support a variant, as well as the allelic balance, if you're 16:00:44 16:00:46 16:00:50 16:00:52 16:00:55 16:01:00

trying to make a call as to whether it's heterozygous or not. 16:01:04 16:01:06

So it's one component that often goes into genotyping algorithm and other forms of interpreting next generation sequence data. 16:01:08 16:01:11 16:01:13 16:01:16

(Deposition Exhibit QIAGEN 1101, Nucleic Acid Research article titled, "An improved PCR method for walking in uncloned genomic DNA," was previously marked for identification.) 16:02:01

Q. It's two copies there. 16:02:01

So I've, actually, handed you Tecan Exhibit 1101. In the petition that was submitted, this same reference, I believe, was Exhibit 1044. This is just a better copy where you can see the gels. 16:02:20 16:02:23 16:02:26 16:02:30 16:02:33

But you're familiar with the Siebert reference, right? 16:02:35 16:02:38

A. I am familiar with the Siebert reference. 16:02:39 16:02:41

Q. And I assume you were familiar with it at the time it came out, as it was 16:02:41 16:02:43

a pretty significant methodology for genome for walking in unknown regions, correct? 16:02:46 16:02:49 16:02:51

A. Well, the paper came out in 1995. I was still in college when it came out. I'm not sure I read it at the time it came out, but I've read it before, including as part of the preparation for this proceeding. 16:02:52 16:02:54 16:02:56 16:02:58 16:03:01 16:03:04

Q. Do you disagree with the conclusions that are drawn in this paper? 16:03:05 16:03:07

A. Which "conclusion" in particular? 16:03:09 16:03:10

Q. Any of them. 16:03:10

A. We could walk through the conclusions you'd like me to opine on. 16:03:12 16:03:14

Q. Well, let's do it again. 16:03:16

Nucleic Acid Research, is that a relatively prestigious journal? 16:03:18 16:03:19

A. Nucleic Acid Research is considered a good journal. 16:03:21 16:03:23

Q. Is it peer reviewed? 16:03:23

A. Peer reviewed papers appear in Nucleic Acid Research. There might 16:03:26 16:03:28

also be other publications. 16:03:31

This is assumed to be a peer 16:03:32

reviewed publication. 16:03:35

Q. So, on Page 2 of this 16:03:39

document, which is 1088 of the actual 16:03:40

paper. So "1088" in the upper left-hand 16:03:43

column. "Page 2" on the bottom right-hand 16:03:48

column. 16:03:52

You see that there is a paragraph 16:03:52

-- three paragraphs up from the 16:03:54

"Acknowledgements," "We have found that 16:03:56

the high specificity of the method 16:03:58

described is primarily due to the 16:04:01

suppression effect of the adaptor/adaptor 16:04:04

primer combination, although in some 16:04:06

cases additionally [having] an amine 16:04:09

group on the lower strand of the adaptor 16:04:11

(vectorette blocking) yielded better 16:04:13

results." 16:04:16

Do you see that? 16:04:16

A. I do. 16:04:17

Q. Now, the methodology that 16:04:18

Siebert describes is a single primer 16:04:21

extension methodology, correct? 16:04:23

A. It is a single primer extension methodology for genome walking. 16:04:28

Q. Right. 16:04:30

So there is a single target-specific primer used on one end and on the other there is a ligation of an adaptor, right? 16:04:31 16:04:34 16:04:36

A. Yes. 16:04:41

Q. And the adaptor is then targeted to -- with a common primer to amplify the extension product, correct? 16:04:41 16:04:43 16:04:49

A. I believe that's correct. 16:04:53

Q. And do you disagree with Siebert's conclusion, which the editors of Nucleic Acid Research allowed to be published, which says that the method and the data that is supplied here shows that the methodology had high specificity in enriching or walking? 16:04:56 16:04:57 16:05:01 16:05:05 16:05:08 16:05:11 16:05:16

A. Remember, this is a paper that has to do with genome walking where you're trying to extend into an unknown region from a known region. It's an exploratory technique and there's really one product that is being generated versus, as we've 16:05:18 16:05:21 16:05:23 16:05:25 16:05:29 16:05:34

discussed, application in more of the multiplex setting. 16:05:40 16:05:45

So, in the context as described here for genome walking, this was accurately described in the paper. 16:05:46 16:05:47 16:05:53

Q. So, when it says, "high specificity," it's walking in the region they want it to walk in and not walking at high rates in other regions that they don't want it to walk in, correct? 16:05:54 16:05:57 16:05:59 16:06:02 16:06:05

A. For the example that they describe and the particular gene that they used to demonstrate the utility. 16:06:07 16:06:09 16:06:11

Q. Right. 16:06:13

And you mentioned multiplex. 16:06:14

But, again, we have established already that the claims are not limited to multiplex reactions and, in fact, cover single loci, correct? 16:06:16 16:06:18 16:06:20 16:06:22

A. We have described that the -- we have agreed -- I -- let me restart my answer to that question. 16:06:25 16:06:27 16:06:31

As we've stated in the claims, there is no limitation as to whether you have 16:06:32 16:06:39

one or more -- rather, the claim state one or more -- let me restate it so that I don't misstate it. Pardon me. 16:06:44 16:06:48 16:06:53

As it states here, extending the one or more nucleotides annealed to the nucleic acid sequence so... 16:06:57 16:07:01 16:07:04

Q. And, in fact, this methodology of enrichment is quite similar to the methodology purportedly described as new in the '012 patent, right? 16:07:07 16:07:08 16:07:11 16:07:15

A. There are differences between this and what's described in the patent. 16:07:19 16:07:20

Q. But there are a lot of similarities too, right? 16:07:22 16:07:24

A. I would say "similarities" in the eye of the beholder. 16:07:26 16:07:27

Q. Well, it uses only a single primer, right, target-specific primer, right? 16:07:28 16:07:31 16:07:35

A. There is the single primer being used in this genome walking technique. 16:07:35 16:07:37 16:07:39

Q. And there's an adaptor ligated onto an end of a fragment that the single 16:07:39 16:07:41

primer anneals to, correct? 16:07:45

A. There is an adaptor ligated 16:07:46
to the end. 16:07:49

Q. And the amplification primer 16:07:50
only anneals and primes and amplifies to 16:07:55
the complement of the adaptor, right? 16:07:59

A. That would be accurate. 16:08:05

Q. So, in other words, the common 16:08:06
primer will only do amplification if the 16:08:10
target-specific primer hit its target and 16:08:15
extended through the adaptor sequence, 16:08:15
correct? 16:08:18

A. Correct. 16:08:18

There could also be off-target 16:08:21
binding. But they did not, presumably, 16:08:23
in this single example, see off-target 16:08:25
binding or reported only on the example 16:08:28
where they didn't see off-target binding. 16:08:32

Q. And Siebert and his other 16:08:33
authors, actually, design the adaptor such 16:08:35
that -- with a suppression effect, by 16:08:38
adding in an amine group on the three 16:08:43
prime end of the lower strand so that it 16:08:45
wouldn't ever extend, unless on its own, 16:08:48

correct? 16:08:54

A. I would say it's -- yes, 16:08:55
strand specific. 16:08:57

Q. So that the strand of the 16:08:59
adaptor, the lower strand of the adaptor 16:09:02
is not going to extend, correct? 16:09:08

A. As described in the paper, 16:09:14
that's a feature of this vectorette 16:09:17
system. 16:09:21

Q. So that diminishes situations 16:09:22
where you're going to get common primers 16:09:27
creating extension products when they're 16:09:30
not supposed to, correct? 16:09:32

A. In the genome walking setting, 16:09:35
where you're trying to extend into a 16:09:39
region of unknown sequence. 16:09:41

Q. So the main issue, I believe, 16:09:51
that you've identified in the Shapero 16:09:56
paper that would steer people away from 16:10:00
using single primer extension is the 16:10:03
possibility that the target-specific 16:10:06
primer is going to anneal to sequences 16:10:09
that you don't want it to anneal to, 16:10:14
that's the thing that's going to create 16:10:16

the greatest amount of off-target amplicons, correct? 16:10:17 16:10:22

MS. CIPRIANO: Objection to form. 16:10:23 16:10:24

A. Would you mind simplifying the question for me? 16:10:26 16:10:28

Q. As we've been discussing today, in Shapero, if you had to attribute one factor to creating the most off-target amplicons, would it be fair to say that, as reported in Shapero, the thing that you would point to is the target-specific primer, actually, annealling to and extending -- annealling to target sequence that it's not supposed to anneal to? 16:10:31 16:10:33 16:10:39 16:10:45 16:10:48 16:10:51 16:10:54 16:10:56 16:10:59

A. That's one of the factors that could generate off-target products. That's one concern. 16:11:00 16:11:02 16:11:06

Q. Possibility? 16:11:09

A. One possibility. 16:11:09

Q. But, as far as the data goes, we didn't see any possibility of primer dimers creating amplicons that were not wanted, right? 16:11:10 16:11:12 16:11:15 16:11:17

A. There's no data presented in the gel. It may or may not have primer dimers; don't fully conclude that since we'd need to know a bit more. And, again, because hybridization does the bulk of the work here, it's hard to know the degree of off-target amplicon generations, since only high affinity molecules are binding to the predefined approach on the array. 16:11:18 16:11:20 16:11:24 16:11:31 16:11:34 16:11:37 16:11:39 16:11:46 16:11:51 16:11:54

Q. So are you saying that looking at the gel Figure 2(A) in Shapero Exhibit 1006, that you can't tell whether there are any amplicons that are 100 bases or less? 16:11:55 16:11:58 16:12:01 16:12:05 16:12:09

A. What I said was, you know, in the image that I have before me, I don't see a band on the ladder for the hundred base pairs. It could be a bad reproduction. And I can't summarize just from this image the degree of primer dimerization. There is no evidence of primer dimerization, as the image has been produced here. 16:12:09 16:12:12 16:12:14 16:12:18 16:12:20 16:12:24 16:12:27 16:12:30 16:12:32

But it's hard to fully interpret, since I don't see a clear band at a hundred base pairs, but that could just be the reproduction here. 16:12:33 16:12:35 16:12:38 16:12:39

Q. So, if the editors who approved the publication of the Shapero article were doing their job and they also, I assume, being skilled in the field were looking at those gels and they saw no -- they said, you can't draw any conclusion that the majority of amplicons are between 500 to 750 because they, actually, saw bands at 100 or less, they wouldn't have been doing their job, if they let the article be published with Shapero drawing the conclusion that the majority of amplicons were in the 500 to -- whatever it was? 16:12:42 16:12:44 16:12:46 16:12:47 16:12:51 16:12:53 16:12:56 16:13:01 16:13:04 16:13:08 16:13:09 16:13:12 16:13:15 16:13:20

A. The hundred to 500 base pairs is what they state in the paper. And that may be the limit of resolution on this gel. And, as we agreed, primer dimers would be well below a hundred. So, again, I don't know how long they, 16:13:21 16:13:23 16:13:24 16:13:28 16:13:31 16:13:33

specifically, ran the gel and how far you'd be able to detect. 16:13:36 16:13:39

But I'm happy to state for the record that if we saw a band at a hundred base pairs or likely below a hundred base pairs, we would assume there is not a strong evidence of a lot of primer dimers being generated. 16:13:40 16:13:43 16:13:47 16:13:51 16:13:54 16:13:58

Q. Well other than primer dimers and off-target hybridization of the single specific target primer, what else would be contributing to a lack of specificity in the library generation, as described by Shapero Exhibit 1006? 16:14:01 16:14:03 16:14:08 16:14:11 16:14:13 16:14:18

A. In general, those are the features that generally characterize artifacts that would be concerning for next generation sequencing. There could be additional artifacts generated through more nonspecific binding and sort of more random priming. Although, again, there's no necessary evidence of that in this paper given the high affinity in the readout through the array hybridization 16:14:31 16:14:33 16:14:40 16:14:44 16:14:47 16:14:52 16:14:58 16:15:00 16:15:02 16:15:05

technology. 16:15:09

(Deposition Exhibit Tecan 2047, Bioinformatics Original Paper titled, "A novel strategy to design highly specific PCR primers based on the stability and uniqueness of 3'-end subsequences," was previously marked for identification.) 16:15:32

Q. I'm passing you what has been marked as Tecan Exhibit 2047, which is a paper from 2005 published in Bioinformatics. First author is Fumihito Miura, M-I-U-R-A, first name F-U-M-I-H-I-T-O. 16:15:32 16:15:34 16:15:38 16:15:47 16:15:54 16:15:59

Are you familiar with this article? 16:15:59

A. I am familiar with this reference. 16:16:01 16:16:03

Q. And did you cite this as a reference which would tell you that single primer extensions are going -- 16:16:03 16:16:06 16:16:10

A. Give me a moment to turn to my part of the declaration where I discuss Miura. 16:16:12 16:16:14 16:16:16

Q. How are you pronouncing it? 16:16:18

A. Mee/you/ruh (phonetic) I believe is how it's pronounced, but that is just a guess. 16:16:20 16:16:21 16:16:23

Q. It's going to be Paragraph 58 of your Declaration. 16:16:25 16:16:27

A. (The witness reviews the exhibit.) 16:16:49 16:17:06

Q. Are you there? 16:17:06

A. I am. 16:17:06

Q. So have you satisfied yourself that you're familiar with this article and you discussed it in your Declaration? 16:17:07 16:17:08 16:17:10

A. I never said I hadn't discussed it. 16:17:11 16:17:14

I said, I wanted to turn to the portion of my Declaration to make sure I could accurately answer your questions around this paper. 16:17:15 16:17:16 16:17:18 16:17:19

Q. And you cited this paper in support of your contention that people of ordinary skill in the art prior to 2012 thinking about single primer extension would be steered away from using libraries 16:17:20 16:17:22 16:17:26 16:17:28 16:17:30

created by single primer extension, because they'd be creating libraries with a lot of off-target amplicons, right? 16:17:32 16:17:34 16:17:39

A. What I cited to here is that only the primer targeting the endogenous nucleotide sequence can be expected to confer specificity, which is consistent with this paper. 16:17:45 16:17:47 16:17:47 16:17:52 16:17:54

Q. I'll repeat it. "Only the primer targeting the endogenous [nucleotide] sequence could [sic] be expected to confer specificity." 16:17:59 16:18:03 16:18:05 16:18:06

I believe that's what you said, right? 16:18:09 16:18:10

Dr. Bustamante, is that what you said, because the Court Reporter was unable to capture what you said because you were speaking too quickly. So I tried to repeat it for her. 16:18:15 16:18:16 16:18:18 16:18:20 16:18:22

And what I said -- 16:18:25

A. I can restate what is in my Declaration. 16:18:28 16:18:30

Q. Go ahead. 16:18:33

A. "The importance of primer 16:18:34

specificity is compounded when" -- 16:18:36

MS. CIPRIANO: Read slowly. 16:18:37

A. "The importance of primer 16:18:38
specificity is compounded when using a 16:18:40
synthetic sequence such as an adaptor as 16:18:42
a primer binding sequence. As many 16:18:45
methods introduce a synthetic sequence 16:18:47
non-discriminately into the sample. In 16:18:50
these cases, only the primer targeting 16:18:52
the second endogenous nucleotide sequence 16:18:55
can be expected to confer specificity." 16:18:59

Q. But in the situation, as 16:19:04
described in Shapero, the adaptor sequence 16:19:05
is not going to create on its own 16:19:08
off-target amplicons, the only way the 16:19:13
adaptor sequence can be used as a priming 16:19:19
site for the adaptor primer is if the 16:19:24
target-specific primer anneals and 16:19:28
extends all the way through the adaptor 16:19:31
creating the complement? 16:19:34

A. That was a long question. If 16:19:39
you could repeat it or have the Court 16:19:41
Reporter repeat it for me, please. 16:19:43

(Whereupon, the question is

read back as follows:

"Question: But in the situation, as described in Shapero, the adaptor sequence is not going to create on its own off-target amplicons, the only way the adaptor sequence can be used as a priming site for the adaptor primer is if the target-specific primer anneals and extends all the way through the adaptor creating the complement?") 16:20:15

A. So, in Shapero, they -- where did I put Shapero? 16:20:15 16:20:23

So -- 16:20:25

Q. I can make it easy for you. It's the same as the '012. 16:20:27 16:20:29

A. So you are asking about Shapero and in Shapero -- here -- they also use a series of digestion reactions to further remove the products from the reaction, the incomplete products. 16:20:31 16:20:35 16:20:38 16:20:46 16:20:52

I'd have to think a bit about the degree to which the universal primer 16:21:01 16:21:05

would prime. But I believe that there are scenarios in which it would prime and generate off-target products. 16:21:11 16:21:17 16:21:21

Q. Do you think the universal primer will prime and generate off-target amplicons regardless of a situation where the target specific primer has not extended through the adaptor to create sequence complementary to the adaptor sequence? 16:21:22 16:21:24 16:21:29 16:21:36 16:21:39 16:21:42 16:21:45

A. No, you need to extend through in order to create sequence complementary to the adaptor sequence. That's why I said I want to take a moment to think about it, because it was a long question. 16:21:46 16:21:47 16:21:51 16:21:53 16:21:55

Q. So the thing that is conferring specificity in Shapero and other single primer extension reactions is the specificity of the target specific primer, right? 16:21:59 16:22:00 16:22:04 16:22:08 16:22:12

A. We agree on that. 16:22:13

Q. And Miura is, actually, publishing an article in which -- I'm assuming it's a he -- in which he 16:22:14 16:22:17 16:22:21

improves upon the primer design for the target-specific primer for single primer extension reactions, correct? 16:22:25 16:22:29 16:22:33

A. For various PCR-based applications. 16:22:37 16:22:39

Q. And Miura, actually, reports that using the particular algorithm that he has developed -- and this is 2005. 16:22:42 16:22:47 16:22:50

So, just a year after Shapero and, at least, six years before the '012 and '108 purported inventors filed their application, he reports on designing primers for single primer extension, which are 90 percent specific, correct? 16:22:54 16:22:57 16:23:01 16:23:04 16:23:09 16:23:12

A. In certain scenarios. 16:23:16

Q. So a person using the teachings of Miura and applying those teachings to design the target-specific primers in an assay like Shapero would be able to design primers that have a 90 percent specificity rate, correct? 16:23:18 16:23:22 16:23:27 16:23:30 16:23:33 16:23:35

A. I don't believe that is accurate, because I believe this paper, as I recall, was restricted to using 16:23:38 16:23:39 16:23:41

yeast. 16:23:45

Let me see if they used it in other settings, but I believe this is a yeast paper. 16:23:45 16:23:49 16:23:51

Q. So are you saying sequencing yeast is not covered by the '012 or '108 patent? 16:23:51 16:23:53 16:23:56

A. I'm saying sequencing yeast is a much simpler problem than trying to sequence the human genome. 16:23:56 16:23:57 16:24:00

Q. The question still stands. 16:24:01

A. In the -- 16:24:03

Q. Do the patents exclude sequencing yeast? 16:24:03 16:24:04

A. The patents, certainly, do not exclude sequencing yeast. 16:24:05 16:24:07

Q. Alright. So what -- 16:24:07

A. But what works in yeast often doesn't work in humans or other systems. 16:24:08 16:24:10

Q. Who cares. 16:24:13

A. So I think -- 16:24:13

Q. I -- 16:24:13

A. People working in human genetics care. People working in plant 16:24:14 16:24:16

genetics care. 16:24:18

Q. What we're talking about is 16:24:19
the patents and we're talking about its 16:24:20
validity and validity is evaluated based 16:24:22
on whether something comes within the 16:24:26
scope of the claims. 16:24:28

And if someone was motivated to try 16:24:29
using Shapero methodology with primers 16:24:32
designed, as Miura describes, in yeast, 16:24:38
that's still covered by the claims of the 16:24:40
patent, right? 16:24:42

A. I am not disputing that the 16:24:45
application of the technology described 16:24:51
in the patent can't be used -- can't be 16:24:55
applied to yeast. I'm, certainly, happy 16:24:59
to agree with that. 16:25:02

What I cannot agree with is what 16:25:03
works in yeast will work at the same level 16:25:06
in other systems. Yeast is a much simpler 16:25:09
genome. 16:25:12

Q. Well, whether it works in all 16:25:12
systems across the entire world is not 16:25:15
really relevant here to the inquiry we 16:25:17
have in front of the Patent Office. 16:25:20

A. You were asking me about a 90 percent accuracy in yeast, how well it works in other systems. I can't tell you. We need to look into that question. 16:25:23 16:25:25 16:25:27 16:25:29

Q. But, at least, the actual results, as opposed to the prophetic claims of the '012 and '108 patent with zero data, Miura, actually, presents data, which editors in a peer reviewed journal allowed to be published, which shows that by using his new algorithm to design primers for whatever the genome that was being sequenced was, whether it was yeast, whether it was eukaryotes, prokaryotes, who cares, he was able to design primers that improved the specificity to more than 90 percent of the target-specific primer, right? 16:25:31 16:25:33 16:25:37 16:25:40 16:25:42 16:25:46 16:25:49 16:25:57 16:26:00 16:26:02 16:26:10 16:26:12 16:26:14 16:26:17

MS. CIPRIANO: Objection to form. 16:26:19 16:26:23

A. The way I would read the paper in yeast, he was able to improve to 90, percent but the baseline was 10 percent. If anything, the paper would suggest that 16:26:23 16:26:25 16:26:29 16:26:31

much of the time you're not getting what you think you're getting in the primer design, if you read further on at Page 4368. 16:26:34 16:26:37 16:26:39 16:26:43

Q. So is a person of ordinary skill in the art supposed to have a lobotomy and only have certain knowledge that exists in the field, or is it your understanding that they have knowledge of all the teachings in the field -- 16:26:48 16:26:53 16:26:54 16:26:56 16:26:58 16:26:59

MS. CIPRIANO: Object -- 16:27:02

Q. -- to evaluate the novelty of the patent? 16:27:03 16:27:06

MS. CIPRIANO: Objection to form. 16:27:07 16:27:07

A. That is a -- can I please ask you to restate that question? 16:27:07 16:27:10

Q. Sure. 16:27:11

You're saying that the teachings in Miura can be discounted because the baseline that he started at before he created his improvement was only -- he only had 10 percent on target for a primer design, right, and you're saying, 16:27:12 16:27:15 16:27:16 16:27:19 16:27:22 16:27:24

well, somehow that shows you that everything is bad? 16:27:26 16:27:28

A. That's not what I said. 16:27:29

I said, Miura was able to develop an approach that sometimes works in yeast and yielded a result in this setting, but baseline was 10 percent. 16:27:30 16:27:33 16:27:36 16:27:39

So, again, it shows and demonstrates that in the field, there was variable success in getting primers and single primers to work as potentially expected. 16:27:41 16:27:43 16:27:46 16:27:49

The field was in flux and developing algorithms and approaches and at the time it was working perhaps in yeast and perhaps not that well in higher model organisms including humans. 16:27:52 16:27:57 16:28:00 16:28:02 16:28:05

So it might discourage somebody from attempting to apply this en masse to particularly humans and complex systems and using NGS given the nonspecific nature. 16:28:07 16:28:10 16:28:15 16:28:18 16:28:20

Q. When a sequencing instrument sequences something in yeast, right -- so let's say I'm going to get -- I'm 16:28:23 16:28:26 16:28:29

sequencing yeast on an Illumina sequencer, 16:28:32
right, and I am sequencing fragments that 16:28:34
are on an -- Illumina sequencer is 16:28:38
usually between 100 and 300 bases is what 16:28:39
they suggest and the nucleotides in yeast 16:28:43
are the same nucleotides in the human 16:28:47
genome, right? Yes or no? 16:28:49

A. Sir, I'm trying to answer 16:28:51
your question. 16:28:53

Q. It's a simple question. 16:28:53
Answer my question instead of the question 16:28:54
that you want to create for yourself. 16:28:56

Are the nucleotides in yeast the 16:28:57
same as the nucleotides in the human 16:28:59
genome? 16:29:02

MS. CIPRIANO: Objection, 16:29:02
argumentive. 16:29:03

Q. Yes or no; A, G, Ts and Cs? 16:29:03

A. Both the human genome and the 16:29:05
yeast genome are composed of A, C, Gs and 16:29:07
Ts. 16:29:10

Q. Okay. So, when you put a 16:29:10
fragment on an Illumina sequencer that 16:29:14
was derived from yeast, that Illumina 16:29:16

sequencer is totally agnostic, it has no idea whether those A, G, Ts and Cs came from yeast or came from a human (INAUDIBLE) -- 16:29:19 16:29:22 16:29:25 16:29:27

A. As you can -- 16:29:27

Q. -- that makes the call? 16:29:28

A. As you can appreciate, mapping to the yeast genome is a far simpler problem than mapping to the human genome. So a lot of the complexity comes from the post-sequencing processing of the data. 16:29:28 16:29:30 16:29:31 16:29:34 16:29:37 16:29:40

Q. Again, not the question you were asked. 16:29:42 16:29:43

When the read comes out -- when a basis is called on an Illumina sequencer and it's called as an A, G, T or C, it uses the exact same methodology on the instrument whether those A, G, Ts and Cs came from yeast or whether they came from a human, correct? 16:29:44 16:29:47 16:29:49 16:29:52 16:29:55 16:29:58 16:30:00

A. It is agnostic as to the source. 16:30:03 16:30:04

Q. Got it. 16:30:05

Is there anywhere in this paper that says that the methodology applied here for designing target-specific primers are only applicable to yeast genomes and no other genomes? 16:30:06 16:30:11 16:30:16 16:30:19 16:30:23

MS. CIPRIANO: Objection to form. 16:30:24 16:30:29

A. I -- I don't suspect the paper to even expect it to make that claim. But it does say that it works particularly for smaller genomes, such as those of viruses. 16:30:29 16:30:33 16:30:37 16:30:39 16:30:42

So it's unclear whether it would work for complex, you know, genomes. 16:30:42 16:30:44

Q. So are you saying that sequencing a virus is an unimportant thing? 16:30:47 16:30:48 16:30:51

So, for example, sequencing the COVID virus was not important at all? 16:30:51 16:30:53

A. I would never say that. Why would you put that in? 16:30:55 16:30:58

Q. How many bases in the COVID virus? 16:30:59 16:31:01

A. The COVID genome, as I recall, 16:31:01

is maybe 3 KB. I don't have the number exactly in front of me, but it's in that order. 16:31:05 16:31:08 16:31:11

Q. Three KB, that's a lot smaller than the yeast genome, right? 16:31:11 16:31:13

A. That's right. 16:31:15

Q. Yet it's extremely -- it was extremely important to sequence the COVID -- to sequence the COVID virus, right? 16:31:16 16:31:18 16:31:22

MS. CIPRIANO: Objection to form. 16:31:24 16:31:26

A. I wouldn't disagree with that statement. 16:31:26 16:31:27

MR. BILSKER: Alright. Why don't we take a break. 16:31:28 16:31:28

(Recess taken 4:32 to 4:47 p.m.) 16:31:30 16:45:46

Q. In 2009, 2010, are you familiar with Myriad Genetics and their clinical diagnostic products for BRCA 1, BRCA 2 detection? 16:47:50 16:47:54 16:47:58 16:48:02

A. In a general sense. 16:48:04

Q. "In a general sense," were they performing genotyping with massively 16:48:05 16:48:07

parallel sequencing for the BRCA 1 and BRCA 2 genes? 16:48:12 16:48:15

A. In order to answer that question, I need to spend some time referring the Myriad protocols in order to accurately answer what technology they were using. 16:48:16 16:48:17 16:48:20 16:48:23 16:48:25

Q. So, as a general premise, you don't know whether Myriad was performing -- was using next generation sequencing to genotype for BRCA 1 and BRCA 2 mutations? 16:48:26 16:48:29 16:48:33 16:48:35 16:48:37

A. I don't know when Myriad switched over to using next generation sequencing. It might well have been in 2009, 2010 or before then. 16:48:37 16:48:43 16:48:45 16:48:47

Q. You're not disputing, are you, that by 2010, whether for actual clinical diagnostic applications or for research applications, groups of people, scientists were genotyping using next generation sequencing, are you? 16:48:50 16:48:53 16:48:57 16:49:00 16:49:04 16:49:08

A. I am not disputing that. 16:49:08

Q. Okay. Let's take a look at 16:49:10

Tecan 2126. 16:49:22

(Deposition Exhibit Tecan 2126, Nucleic Acids Research article titled, "Multiplex amplification enabled by selective circularization of large sets of genomic DNA fragments," was previously marked for identification.) 16:49:39

(There is a discussion off the record.) 16:49:39 16:49:50

Q. Are you familiar with this paper, Tecan 2126? 16:49:50 16:49:51

A. I am. 16:49:54

Q. And do you know who these authors are? 16:49:55 16:49:57

A. They are at Uppsala. I don't know them personally. 16:50:00 16:50:05

Q. Do you know what they're well-known for? 16:50:06 16:50:08

A. In what sense? 16:50:12

Q. In the scientific sense, of selective amplification of targets. 16:50:14 16:50:19

A. If you can be more specific... 16:50:25

I'm familiar with this paper and I've reviewed this paper and, as I said, I don't know them personally. 16:50:26 16:50:28 16:50:32

Q. Are these -- is this group the group of folks who developed the MIPS technology for creating specific amplicons for enrichment, for library enrichment? 16:50:33 16:50:36 16:50:39 16:50:44

A. There are multiple groups have worked on MIPS. 16:50:47 16:50:49

Q. Is Mats Nielsen -- so padlock probes, are you familiar with those? 16:50:50 16:50:54

A. I am familiar with padlock probes. 16:50:55 16:50:58

Q. Was this group responsible for developing padlock probes? 16:50:58 16:51:00

A. As I said, multiple groups have worked in the development of that technology. 16:51:02 16:51:03 16:51:05

Q. Well, is this the group that's credited with the first achievement of using padlock probes to create enriched amplicon libraries? 16:51:05 16:51:07 16:51:10 16:51:14

A. They well could be. I know Mat Nielsen is very well regarded Swedish 16:51:18 16:51:21

biotechnologist. 16:51:30

Q. You cited this paper yourself, 16:51:33
correct? 16:51:35

A. I did. 16:51:35

Q. Tell me where in this paper 16:51:38
this group rejects Shapero. 16:51:43

A. Let me turn to my citation, so 16:51:48
I can put it into reference, into context 16:51:50
please. 16:51:53

So I cite to the Dahl paper in -- 16:53:08
on Page 176 of my Declaration on Page 1 16:53:16
and discuss their -- their discussion of 16:53:23
Miura. 16:53:34

Q. Where do you see their 16:53:34
discussion of MARA where they reject it? 16:53:36

MS. CIPRIANO: Objection to 16:53:40
form. 16:53:40

A. Give me a moment to point to 16:53:42
the specific location. 16:53:44

Q. We're going to be here for a 16:53:49
long time because they never do, but go 16:53:51
ahead. 16:53:53

A. (The witness reviews the 16:53:56
exhibit.) 16:54:03

So what I cited to is in the middle of the paragraph where they're talking about adaptor PCR methods where they state the only way to amplify many defined sequences in the same reaction is by combining several different PCR primer pairs. 16:54:03 16:54:08 16:54:12 16:54:15 16:54:17 16:54:20 16:54:23

Q. And you think that's a rejection of Shapero and MARA? 16:54:23 16:54:24

A. If I could continue. 16:54:29

And what I have a crucial problem with this approach is the appearance of amplification artifacts, which is -- 16:54:31 16:54:33 16:54:33

(Stenographer clarification.) 16:54:37

MS. CIPRIANO: Go a little slower. 16:54:37 16:54:37

A. "A crucial problem with this approach is the appearance of amplification artifacts such as primer dimers, truncated fragments or amplification products of irrelevant sequence." 16:54:37 16:54:39 16:54:40 16:54:43 16:54:44 16:54:46

And they had cited to the Shapero reference, I believe, in Reference 7, as 16:54:47 16:54:50

part of that section where they're discussing the potential issues with the existing PCR technology at the time. 16:55:00 16:55:02 16:55:06

Q. Alright. So let's stick to the English language here and read very grammatically, alright? 16:55:09 16:55:11 16:55:14

So what you just said is currently the only way to amplify many defined sequences in the same reaction is by combining several different PCR primer pairs. 16:55:15 16:55:17 16:55:20 16:55:22 16:55:25

Is that referring to a single primer extension methodology or to, quote, "traditional" PCR where you're using a pair, your forward and reverse primers are specific? 16:55:25 16:55:29 16:55:31 16:55:33 16:55:37

MS. CIPRIANO: Objection, argumentive. 16:55:38 16:55:39

A. (The witness reviews the exhibit.) 16:55:43 16:55:43

I believe this sentence could refer to PCR primer pairs, which would include traditional PCR. And depending on context, whether or not they are thinking 16:55:43 16:55:54 16:55:58 16:56:05

of single primer extension in that setting, they had referenced it above and put it in the section on adaptor PCR methods. 16:56:10 16:56:14 16:56:18 16:56:21

Q. This is not referring to adaptor PCR methods. 16:56:24 16:56:26

This is referring to primer pairs, right? 16:56:28 16:56:31

A. That's correct. 16:56:31

Q. Okay. And when it says "a crucial problem with this approach," that's the primer pairs, not the adaptor PCR, right? 16:56:32 16:56:37 16:56:40 16:56:43

That's what it's referring to, "this approach," which directly follows the previous sentence, right? 16:56:44 16:56:45 16:56:47

A. I -- I agree with that. 16:56:50

Q. And, in fact, it's even further elucidated by the fact that it says, "a crucial problem with this approach" -- traditional primer pairs -- "is the appearance of amplification artifacts, such as primer dimers, truncated fragments or amplification 16:56:54 16:56:58 16:57:01 16:57:03 16:57:06 16:57:09 16:57:11

products of a relevant target sequences. The risk of generating such artifacts" -- the one just mentioned in the prior sentence -- "in multiplex PCR tends to increase roughly as the square of the number of added primer pairs." 16:57:14 16:57:18 16:57:20 16:57:22 16:57:25 16:57:27

Now, the fact that they're talking about the square of the number of primer pairs is referring to not the single primer extension situation, it's referring to what you termed or what we've referred to as traditional PCR, where you're using two target specific primers, right? 16:57:30 16:57:32 16:57:34 16:57:38 16:57:39 16:57:42 16:57:45

A. It is in the use of two target -- two prior traditional PCR where the risk would increase as the square of the primer pairs. 16:57:51 16:57:54 16:57:58 16:58:01

Q. Right. 16:58:02

So he is not, actually, referring to these problems as existing in single primer, which he terms so-called adaptor PCR, right? 16:58:03 16:58:05 16:58:09 16:58:13

A. Yes. But, as we've also addressed, the double primer pair PCR was 16:58:13 16:58:17

considered more accurate than the single primer pair extension. And so some of the artifacts from the single primer extension would also be problematic or even more problematic in the context of what they're discussing. 16:58:22 16:58:25 16:58:26 16:58:28 16:58:32 16:58:35

Q. There is no rejection of Shapero's MARA, which is Reference 7 on this right-hand column, by this group from Sweden, correct? 16:58:36 16:58:38 16:58:42 16:58:45

MS. CIPRIANO: Objection to form. 16:58:48 16:58:51

A. The author cite the MARA paper here and they neither use it nor contemplate using it with an NGS, as part of this paper. 16:58:51 16:58:53 16:59:01 16:59:02

Q. Right. 16:59:03

And, actually, when they mention it, they say a few methods exist that permit the user to amplify subsets of genomes using variants of so-called adaptor PCR. A subset of a genome would be an "enrichment," right? 16:59:03 16:59:04 16:59:05 16:59:09 16:59:11 16:59:13

A. Amplify a subset of the 16:59:16

genome. 16:59:18

Q. And it doesn't say, and by the way, these methods don't work and I reject them, does it? 16:59:19 16:59:21 16:59:23

A. The paper rarely would state something in that form. 16:59:25 16:59:28

Q. So, if the paper doesn't, actually, state that and papers would rarely state that, why do you say and why does Tecan say in their patent and response this paper, quote, "rejects" Shapero? 16:59:29 16:59:31 16:59:32 16:59:36 16:59:40 16:59:43

MS. CIPRIANO: Objection, form and speculation. 16:59:44 16:59:45

A. What I wrote in my Declaration is that they were aware of the -- this is in the section where I discuss papers that cite the MARA method. 16:59:50 16:59:52 16:59:57 16:59:59

They were aware of the MARA method. Yet as they write in -- clearly, as you state here, the only way to amplify many defined sequences in the same reaction is by combining several primer pairs. 17:00:01 17:00:03 17:00:09 17:00:11 17:00:14

Q. We know that's not true, 17:00:15

because Shapero itself amplifies at 250 plex, right? 17:00:17 17:00:20

So whoever wrote this was maybe an overzealous graduate student trying to promote their own technology, but did not, actually, read the Shapero paper because we know for a fact that Shapero amplified a 250 plex, a 750 plex and a 4300 plex, right? 17:00:21 17:00:25 17:00:27 17:00:29 17:00:31 17:00:33 17:00:36

MS. CIPRIANO: Objection to form. 17:00:38 17:00:39

A. Perhaps I can't put myself in the mind of Dahl or Nielsen and their collaborators but perhaps they wrote what they wrote because they were convinced that MARA, as a method, was as amenable to utilization as the double primer parent approach. 17:00:39 17:00:43 17:00:47 17:00:50 17:00:54 17:01:02 17:01:07

Q. Even though you -- even you in this deposition today and many other papers have said that two primer pairs -- primer pairs are only good to about ten or a dozen or maybe two-dozen at most loci multiplexing. And the Shapero paper 17:01:08 17:01:10 17:01:14 17:01:18 17:01:22 17:01:24

actually talks about orders of magnitude above that, correct? 17:01:29 17:01:31

A. In a -- 17:01:33

MS. CIPRIANO: Objection to form. 17:01:33 17:01:34

A. In a restricted setting where they're using genotyping out arrays as the readout. So it's a very restricted setting. I wasn't the editor of this paper. 17:01:34 17:01:37 17:01:40 17:01:42 17:01:46

Q. Yeah. 17:01:47

If you were the editor, you would not have allowed that statement in there, because it doesn't make any scientific sense, right? 17:01:47 17:01:49 17:01:50 17:01:52

MS. CIPRIANO: Objection to form, scope. 17:01:53 17:01:54

Q. I know you're laughing again or chuckling but it's true? 17:01:55 17:01:57

MS. CIPRIANO: Same objections. 17:01:59 17:02:00

A. I'm not going to hypothesize about what I would or would not have suggested at the time about how they 17:02:02 17:02:04 17:02:06

might modify the paper. 17:02:08

Q. Let's take a look at Tecan 17:02:11
2130. 17:02:14

(Deposition Exhibit Tecan 2130, Chapter 6 authored by Howell, et als., titled, "Detection Techniques for Single Nucleotide Polymorphisms," was previously marked for identification.) 17:02:25

MR. BILSKER: Incoming. 17:02:25

Q. Are you familiar with Tecan 17:02:34
Exhibit 2130? 17:02:37

A. I am. 17:02:37

Q. It looks like a book chapter. 17:02:38

A. It's a book chapter. 17:02:40

Q. First author is Mathias 17:02:41
Howell? 17:02:44

A. That is correct. 17:02:44

Q. And, again, you cited this for 17:02:45
the proposition that somehow this teaches 17:02:48
you that the method of Shapero, the 17:02:51
single primer extension, is not going to 17:02:54
give you or get specific libraries? 17:02:55

A. Give me a moment to review 17:03:02

this. 17:03:06

(The witness reviews the exhibit.) 17:03:07

So I cited to Page 160 of the publication where they discuss the MARA method in the context of multiple approaches that make use of, quote, "so-called adaptor ligation methods." 17:04:13 17:04:17 17:04:21 17:04:24 17:04:28

And further on in the last paragraph in the section that breaks on Page 160, they, quote, "none of these methods above achieve the ideal goal of amplifying a large set of arbitrary sequences without the production of undesired amplification products." 17:04:32 17:04:35 17:04:40 17:04:43 17:04:45 17:04:47 17:04:49

Q. Well, let's take a look at Page 160, the second full paragraph. And I'll read. "A subsequent PCR amplification" -- let's start at the full paragraph. 17:04:51 17:04:53 17:04:58 17:05:03 17:05:05

"As briefly noted previously, the so-called adaptor ligation method uses restriction and/or nucleuses to digest the genomic sample into fragments of a known distribution. A common adaptor 17:05:06 17:05:09 17:05:12 17:05:14 17:05:18

oligonucleotides are then ligated to the ends of the generated fragments. A subsequent PCR amplification with a single pair of primers can be adjusted to preferentially amplify fragments within a certain range of sizes." 17:05:21 17:05:23 17:05:25 17:05:28 17:05:33 17:05:35

Well, actually, that doesn't even make sense. You can't amplify with one primer, right? 17:05:37 17:05:38 17:05:40

A. That's what they wrote. 17:05:43

Q. Yeah. 17:05:45

But you, as a scientist, know it's not possible in PCR to amplify with one primer, right? 17:05:45 17:05:47 17:05:49

A. I believe what they are saying here is in the context of using one primer and a universal primer, giving them the benefit of the doubt. 17:05:50 17:05:52 17:05:55 17:05:58

Q. This way a subset of the genome is amplified and a reduction of sequence complexity is achieved, right? 17:06:01 17:06:03 17:06:07

So a reduction of only a subset of the genome is amplified using that methodology and you reduce the complexity 17:06:09 17:06:14 17:06:17

of the genome, right? 17:06:19

A. That's what they wrote. 17:06:22

Q. And that's "enrichment," 17:06:23

right? 17:06:24

A. Depending on one's definition 17:06:24

of "enrichment." 17:06:26

Q. Well, you're starting with a 17:06:27

population and you're cutting it down in 17:06:28

size and complexity, right? 17:06:31

A. Again, we can -- we can agree 17:06:34

that under certain definitions of 17:06:42

"enrichment" this would -- this reduction 17:06:45

in complexity would qualify under the 17:06:49

definition of "enrichment" when we're 17:06:56

comparing to next generation sequencing 17:06:57

that's not necessarily what's being 17:06:59

achieved. 17:07:01

Q. Well, it actually then says, 17:07:01

"a variant of the method," one that was 17:07:04

just discussed above -- "a variant of the 17:07:07

method uses adaptors, one common primer 17:07:13

and a single specific primer per target 17:07:17

sequence to achieve amplification of 17:07:20

specific genomic sequences." 17:07:23

Do you see that? 17:07:27

A. I do. 17:07:27

Q. So it actually says -- and 17:07:28

that's a cite to -- 17:07:29

A. Shapero. 17:07:31

Q. -- Shapero. 17:07:31

It, actually, says, "it achieves." 17:07:32

To achieve amplification of specific 17:07:34

genomic sequences, right? 17:07:36

A. Further down it says, "None 17:07:40

of the methods above achieved the ideal 17:07:41

goal of amplifying a large set of 17:07:44

arbitrary sequences without the 17:07:44

production of undesired amplification 17:07:46

products." 17:07:49

Q. So did the NuGEN method 17:07:49

achieve 100 percent specificity? 17:07:53

MS. CIPRIANO: Objection to 17:07:59

form. 17:08:00

A. I don't believe I ever 17:08:00

claimed that. 17:08:01

Q. So, when these guys say the 17:08:02

ideal of only amplifying one thing and 17:08:04

not amplifying anything other, that's a 17:08:07

goal which is not required by the patents, right? 17:08:10 17:08:12

A. A hundred percent -- let me restate that. 17:08:15 17:08:20

The patents do not require you to achieve a specific level of enrichment or on target. 17:08:21 17:08:26 17:08:33

Q. Right. 17:08:34

And these guys are being kind of -- I don't know what the right word is. 17:08:34 17:08:41

But they're, actually, saying that the ideal goal is to amplify only what you want to amplify and nothing else, right? 17:08:43 17:08:48 17:08:52 17:08:54

A. Without the production of undesired amplification products. 17:08:57 17:08:58

Q. Right. 17:09:00

So that would be 100 percent target specificity, right? 17:09:01 17:09:04

A. It depends on how you would define it. 17:09:07 17:09:08

Q. But that's a reasonable interpretation of what they wrote? 17:09:09 17:09:10

A. That's one interpretation. 17:09:11

Q. Do you know any methodology at this point even padlock probes that achieves 100 percent target specificity across all genomes? 17:09:16 17:09:17 17:09:20 17:09:23

A. I'm not claiming to have a methodology that achieves a hundred percent efficiency, right. That's not part of what I've claimed in my declarations. 17:09:27 17:09:36 17:09:37 17:09:41 17:09:46

Q. So the goal of achieving 100 percent target specificity is something that is not required in the claims of the '012 or the '108 patent, as you understand them, right? 17:09:49 17:09:52 17:09:54 17:09:57 17:09:59

A. A hundred percent efficiency is not required by the '012 and '108 patents. 17:10:00 17:10:01 17:10:05

Q. That would be an ideal? 17:10:05

That would be aspirational? That's what you're shooting for, right? 17:10:07 17:10:09

A. As stated here by Howell and colleagues. 17:10:10 17:10:13

Q. Right. 17:10:13

So, again, in the paragraph, in the 17:10:14

second full paragraph on Page 160, last sentence, "A variant of the method uses adaptors, one common primer, and a single specific primer per target sequence to achieve amplification of specific genomic sequences." 17:10:17 17:10:20 17:10:23 17:10:26 17:10:29 17:10:33

And the variant he's talking about which "achieves amplification of specific sequences" is among others Shapero, Exhibit 1006, right? 17:10:34 17:10:36 17:10:38 17:10:42

A. It achieves amplification, specifically, genomic sequences and also undesired amplification products. 17:10:46 17:10:48 17:10:51

Q. Right. 17:10:52

Potentially not the ideal of zero unintended amplification products? 17:10:53 17:10:56

A. Again, I'm simply citing to what they wrote in their paper, which is that none of the methods above are free of undesired amplification products. 17:11:00 17:11:02 17:11:04 17:11:07

Q. And nor is the methodology -- nor is NuGEN's commercial product, is it? 17:11:09 17:11:11

A. I can't speak to the efficiency. But nothing is a hundred 17:11:16 17:11:18

percent efficient. 17:11:20

Q. Well, sure, you can speak to 17:11:21
the efficiency, if you're to believe what 17:11:22
Brooks claimed in his Declaration that he 17:11:25
got the unexpected result of 90 percent. 17:11:27

That's not a hundred percent, right? 17:11:30

A. Ninety percent is not a 17:11:32
hundred percent. 17:11:33

Q. You know, if somebody got -- 17:11:34
I mean, if Brooks had, actually, got only 17:11:36
like 88 percent and then decides to puff 17:11:38
it up to greater than 90 percent, would 17:11:42
you say that's academically honest? 17:11:44

MS. CIPRIANO: Objection to 17:11:46
form. 17:11:52

A. I don't -- I cannot speak to 17:11:52
how he rounded, if he rounded at all. 17:11:55

Q. Would you do that? 17:11:58

If your results, actually, showed 17:11:59
88 percent on-target specificity, would 17:12:01
you put in a paper that you'd achieved 17:12:03
greater than 90 percent? 17:12:06

A. If I had only achieved 17:12:07
88 percent, I would write I achieved 17:12:09

88 percent. 17:12:11

Q. Why? Why not puff it up to 17:12:12
greater than 90 percent? 17:12:15

MS. CIPRIANO: Objection to 17:12:16
form. 17:12:17

A. Because 88 is not greater 17:12:17
than 90 percent. 17:12:18

Q. At least, in your ethics 17:12:20
system, reporting greater than 90 percent 17:12:22
when you only achieved 88 percent is not 17:12:23
ethical? 17:12:26

(Stenographer clarification.) 17:12:26

Q. Not ethical. 17:12:28

MS. CIPRIANO: Same objection. 17:12:28

A. Again, I don't have the data 17:12:28
in front of me. I don't know why -- if 17:12:30
he rounded, how he rounded and where that 17:12:32
came from. 17:12:35

Q. Well, we're not talking about 17:12:36
him. 17:12:37

I'm talking about your ethical 17:12:38
system. 17:12:40

If your data showed 88 percent 17:12:40
on-target specificity, in your ethical 17:12:43

system, you would not report, for example, a scientific journal that you had achieved greater than 90 percent on-target specificity? 17:12:46 17:12:48 17:12:50 17:12:52

MS. CIPRIANO: Objection to form. 17:12:52 17:12:57

A. It's a highly speculative question. But, in general, I would report as accurately as I could what the achieved upon efficiency was. 17:12:57 17:12:59 17:13:01 17:13:03

Q. Accuracy and scientific reporting is important, right? 17:13:04 17:13:06

A. I would agree that accuracy and scientific reporting is important. 17:13:07 17:13:09

MR. BILSKER: Alright. Why don't we take another break and I'm pretty close to being done. 17:13:10 17:13:11 17:13:13

MS. CIPRIANO: Okay. 17:13:15

(There is a discussion off the record.) 17:13:31 17:13:38

Q. Have you seen any evidence which demonstrates to you that QIAGEN copied NuGEN's/Tecan's enrichment protocol? 17:13:38 17:13:40 17:13:43 17:13:50

A. What I have written in my declarations under the section of "Secondary Considerations" is the strong similarity between the QIAGEN description of their technology and the description of the technology from NuGEN. 17:13:50 17:13:54 17:13:57 17:14:00 17:14:03 17:14:06

Q. Right. 17:14:08

And if we, actually, put those two things side by side, right? 17:14:09 17:14:10

A. That's what -- if we can point to that part of my Declaration, happy to answer questions about it. 17:14:12 17:14:14 17:14:16

Q. You can find it. I don't know what page it's on. 17:14:17 17:14:18

A. Okay. 17:14:19

Q. But I think you have side by side the steps of target enrichment, right? 17:14:20 17:14:22 17:14:24

MR. BILSKER: Do you know what page it's on? 17:14:31 17:14:32

Q. What's your Declaration Exhibit Number? 17:14:57 17:14:59

DR. METZKER: 2907. 17:15:02

Q. So what paragraph are you on, 17:15:08

Dr. Bustamante? 17:15:09

A. 302. 17:15:09

Q. Alright. So, in Paragraph 302, you identify as evidence of copying the flow for the target enrichment for the library, right? 17:15:24 17:15:26 17:15:29 17:15:31

A. As I write, in my opinion, the work flows are nearly identical, if not identical. 17:15:33 17:15:36 17:15:39

Q. Right. 17:15:40

If you were to place the Shapero library generation method -- let's say you created a third column, it would also be identical to these, right, to these steps identified here, right? 17:15:40 17:15:43 17:15:45 17:15:47 17:15:51

A. I wouldn't say it would be "identical." The figures are different. 17:15:53 17:15:55

Q. Well, the figures in Ovation and the QIAGEN ones are not exactly the same, right, but they're representing the same -- you're claiming they're representing the same steps, even though they look different, right? 17:15:57 17:16:01 17:16:03 17:16:06 17:16:08 17:16:10

A. As I said, the work flows are 17:16:11

nearly identical. 17:16:13

Q. Right. 17:16:14

So, in Shapero, Shapero fragments, 17:16:15
right? 17:16:16

A. Shapero fragments. 17:16:19

Q. And then just like in QIAGEN, 17:16:21
Shapero adds an adaptor, a partially 17:16:25
duplexed adaptor, right? 17:16:29

A. Shapero adds a partially 17:16:32
duplexed adaptor. 17:16:34

Q. And in the step which is the 17:16:35
third step in QIAGEN, Shapero also uses a 17:16:36
gene specific primer to extend through 17:16:40
the adaptor, correct? 17:16:42

A. That is accurate. 17:16:46

Q. And just like as shown in 17:16:47
QIAGEN in the fourth step, Shapero also 17:16:50
uses an adaptor primer, which anneals to 17:16:54
the complement of the adaptor sequence, 17:16:58
and extends through that to create double 17:17:01
strands, correct? 17:17:04

A. That is accurate. 17:17:07

Q. So, in fact, QIAGEN is just 17:17:08
as similar, if not more similar, to 17:17:11

Shapero than it is to Ovation, right -- 17:17:14

MS. CIPRIANO: Objection -- 17:17:17

Q. -- as far as the targeted 17:17:17

library enrichment steps, right? 17:17:19

MS. CIPRIANO: Objection to 17:17:21

form. 17:17:22

A. I wouldn't necessarily agree 17:17:26

with that statement. 17:17:28

Q. Well, why is it closer to one 17:17:28

than the other? 17:17:31

A. Let's recall that the Shapero 17:17:44

method is making use of a very specific 17:17:46

set of restriction enzyme digestion. 17:17:53

This is using -- this is agnostic 17:18:00

as to the form of fragmentation. 17:18:03

Q. By "agnostic" you mean it's 17:18:06

completely random, the size of the 17:18:09

fragments you're going to get? 17:18:10

A. No, I'm saying there are 17:18:12

multiple ways that you can achieve the 17:18:13

fragmentation. 17:18:15

Q. Well, do you, actually, know 17:18:15

how QIAGEN developed its fragmentation 17:18:16

system? 17:18:19

A. We could dig into the spec sheets for QIAGEN and discuss that in detail. 17:18:21 17:18:25 17:18:28

Q. Well, you actually just testified that it's completely "agnostic" as to how you fragment. 17:18:28 17:18:30 17:18:32

A. So I said the Ovation target is the -- the Ovation target enrichment is representative of the work flow as embodied in the patent where multiple approaches are available to do the fragmentation. 17:18:33 17:18:36 17:18:38 17:18:43 17:18:48 17:18:50

Q. Well, actually, when you take a look at the Ovation target enrichment, that very first line, you get a blunt ended double-stranded molecule, right? 17:18:50 17:18:51 17:18:55 17:18:57

A. As depicted. 17:19:02

Q. Yeah. 17:19:03

And in the QIAGEN side, you don't get a blunt ended double-stranded molecule, do you, in that first line? 17:19:03 17:19:05 17:19:08

A. You have an overhang. 17:19:11

Q. Right. 17:19:13

And you get an overhang when you 17:19:13

actually, do enzymatic fragmentation, right? 17:19:15 17:19:18

A. You can get an overhang with enzymatic fragmentation. 17:19:19 17:19:21

Q. And when you do sonification, you don't get overhangs, do you? 17:19:23 17:19:24

A. Typically, you get blunt end. 17:19:26

Q. Right. 17:19:28

So they, actually, fragment differently, QIAGEN and Ovation, right? 17:19:29 17:19:31

A. As potentially depicted here. 17:19:33

Q. And what you chose to depict, right? 17:19:36 17:19:38

A. I -- 17:19:38

Q. And you've read -- you've read the Shapero article. 17:19:39 17:19:39

How does Shapero fragment; enzymatically or sonically? 17:19:40 17:19:42

A. Enzymatically. 17:19:44

Q. Right. 17:19:45

So, actually, at least, with respect to the first line, QIAGEN is closer to Shapero than it is to what you depicted for Ovation, right? 17:19:46 17:19:47 17:19:50 17:19:52

A. If you would like to argue that QIAGEN copied Shapero, we can go through that line of questioning as well. 17:19:53 17:19:56 17:19:58

Q. Well, you have not -- you have not disputed the fact that Steps 1A to 1D in the '012 patent are disclosed in Shapero. 17:20:00 17:20:03 17:20:07 17:20:10

All these steps that are depicted here in QIAGEN's and the thing that you put in Paragraph 302 are actually disclosed in Shapero, right? 17:20:11 17:20:12 17:20:14 17:20:18

A. As I said, Shapero is a very specific work flow meant to target existing SNPs using a microarray technology. 17:20:20 17:20:23 17:20:26 17:20:31

It is not a general purpose primer extension system for targeting and sequencing in the way that was described in the patent. 17:20:31 17:20:38 17:20:40 17:20:42

Q. Well, according to you. 17:20:43

So QIAGEN's targeted panel is targeting SNPs, right, or do you not have a clue? 17:20:48 17:20:52 17:20:57

MS. CIPRIANO: Objection to 17:20:57

form. 17:20:58

A. In this particular example it's working through what appears to be a variant in the middle of the amplicon. 17:20:58 17:21:04 17:21:08

Q. Which would be a SNP, right? 17:21:12

A. Potentially could be a SNP, could be an Indel. It could be some other variation. 17:21:15 17:21:16 17:21:16

(Stenographer clarification.) 17:21:16

A. An Indel. 17:21:20

Q. So one other thing. 17:21:20

So like in the QIAGEN system where you got an overhang and you got to get the adaptors attached, right, which is -- it was fragmented enzymatically and Shapero also attaches adaptors, right? 17:21:23 17:21:24 17:21:26 17:21:31 17:21:34

If you have blunt end versus overhangs, would you attach the adaptors in exactly the same way? 17:21:37 17:21:39 17:21:42

A. You would attach them differently. 17:21:43 17:21:44

Q. Okay. So given that both QIAGEN and Shapero have overhangs and they attach the adaptors, it's much more 17:21:45 17:21:48 17:21:50

likely that the adaptor attachment is more similar between QIAGEN and Shapero than it is between QIAGEN and the Ovation, right? 17:21:52 17:21:54 17:21:57 17:22:00

A. It -- it -- it -- I'd need to walk through the protocol in order to accurately answer that. 17:22:01 17:22:09 17:22:14

Q. So you threw this out here saying that it shows copying, even though we see that the fragmentation is different, even though you see Ovation is blunt ended double-stranded and QIAGEN's overhang double-stranded after fragmentation and you have no idea how Ovation, actually, attaches its adaptor? 17:22:15 17:22:18 17:22:19 17:22:21 17:22:24 17:22:27 17:22:30 17:22:32

A. That's not what I said. 17:22:35

I said in order to answer this accurately, I would like to work through the spec sheets, as discussed. 17:22:36 17:22:39 17:22:40

Q. So you didn't bother doing that before making the claim that QIAGEN copied Ovation, huh? 17:22:42 17:22:44 17:22:46

A. I want to -- 17:22:47

MS. CIPRIANO: Objection to 17:22:47

form. 17:22:48

A. I want to answer your 17:22:48
questions accurately. So we can go 17:22:49
through the exhibit. 17:22:51

Q. Well, it's a very simple 17:22:52
question. 17:22:54

Before making this claim that QIAGEN 17:22:54
copied Ovation, you didn't bother to see 17:22:57
whether they attached adaptors in the 17:23:00
same way QIAGEN and Ovation? 17:23:03

MS. CIPRIANO: Objection, 17:23:05
argumentive. 17:23:06

A. If we can please turn to 17:23:07
Exhibit 2083 and we can discuss that in 17:23:09
detail. 17:23:12

Q. I don't have 2083 with me. 17:23:12

But you certainly -- you don't know 17:23:14
sitting here today, right? 17:23:17

A. I want to answer your 17:23:18
question accurately, sir. 17:23:19

Q. Well, how do you attach an 17:23:21
adaptor to a blunt ended double-stranded 17:23:22
nucleic acid? 17:23:25

A. Through ligation. 17:23:27

Q. And how do you attach an adaptor to an overhung double-stranded nucleic acid? 17:23:28 17:23:31 17:23:35

A. Usually, through end repair. 17:23:35

Q. So ligation and end repair are not the same methodologies, are they? 17:23:38 17:23:40

A. Ligation often follows end repair, but there's usually an end repair step. 17:23:45 17:23:48 17:23:51

Q. Alright. Is there anything else that's evidence to you that QIAGEN copied NuGEN? 17:23:54 17:23:56 17:23:58

A. (The witness reviews the exhibit.) 17:24:14 17:24:16

I have no evidence that QIAGEN developed the work flow independent of NuGEN. 17:24:16 17:24:18 17:24:22

Q. And you have no evidence that QIAGEN copied it from Ovation, you're just speculating, right? 17:24:22 17:24:24 17:24:27

A. What I'm drawing attention to is the similarity between the work flows. 17:24:28 17:24:31

Q. And there's as much, if not more similarity between QIAGEN and 17:24:33 17:24:36

Shapero than there is QIAGEN and Ovation? 17:24:39
MS. CIPRIANO: Objection, 17:24:42
asked and answered. 17:24:43
A. I believe we've discussed 17:24:44
this matter before. 17:24:46
Q. Well, 1, 2, 3, 4, 5. 17:24:47
So, in the Ovation methodology, you 17:24:49
have six steps identified. 17:24:54
In the QIAGEN method, there are 17:24:56
five steps identified in the process. 17:24:58
Two of the five steps in the QIAGEN 17:25:01
process are different than the Ovation 17:25:04
process. 17:25:07
So that's like 40 percent different, 17:25:07
right, there in the five steps that 17:25:10
you've listed, right? 17:25:11
A. We could go through and 17:25:13
understand that many of the minor 17:25:19
differences here a POSA would understand 17:25:23
to be a standard approach towards 17:25:26
implementing the method. 17:25:36
Q. I mean, back in the 2010 to 17:25:40
2015 timeframe, have you ever worked with 17:25:46
fragmentation to see the differences 17:25:48

between sonication and enzymatic fragmentation? 17:25:50 17:25:54

A. I have worked in and developed libraries using both approaches. 17:25:54 17:25:58

Q. And it's not trivial, the differences. There are big differences between those two approaches. 17:26:00 17:26:02 17:26:03

A. I wouldn't disagree with that. 17:26:05

Q. Okay. Why don't we take our break. 17:26:06 17:26:08

(Recess taken 5:26 to 5:38 p.m.) 17:26:08 17:38:13

Q. During the break, did you talk to your attorney about this deposition at all? 17:38:13 17:38:14 17:38:16

A. No. 17:38:16

Q. Alright. If we can just turn back quickly to -- if you still have them -- Tecan 2130, which was the book chapter that we just went over. 17:38:17 17:38:19 17:38:23 17:38:26

A. Give me a moment to find it. 17:38:29

Q. This thing. (Indicating.) 17:38:31

A. I know which one you're referring to. There's just a lot here. 17:38:32 17:38:35

Here it is. 17:38:38

Q. And then also Tecan 2126, which is the Dahl paper; also, one of the chapters that we talked about before. 17:38:38 17:38:42 17:38:47

A. Here's the Dahl paper. 17:38:48

Q. Yeah. 17:38:50

There is an overlap in 2130. 17:38:51

Three of the authors in 2130 are also authors on 2126, right? 17:38:56 17:38:58

A. I see that Mats Nilsson is an author on both papers. 17:39:06 17:39:11

Ulf Landegren is an author on both papers. 17:39:15 17:39:17

And, I believe, Johan Stenberg is an author on both papers. 17:39:17 17:39:21

Q. Okay. I don't have any other questions. 17:39:22 17:39:27

MS. CIPRIANO: Okay. I don't have any questions today either. 17:39:27 17:39:28

You're done. 17:39:33

THE WITNESS: We're done. 17:39:34

(Time noted: 5:39 p.m.) 17:39:42

([RESERVATION] Ms. Cipriano reserves signature.) 17:39:42 17:39:43

CARLOS D. BUSTAMANTE, Ph.D.

(Ms. Cipriano's order for regular delivery on the final and rough is recorded on the Stenographer's software.) 17:41:21 17:42:19 17:42:22

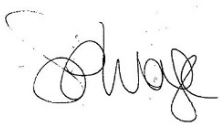
CARLOS D. BUSTAMANTE, Ph.D.

CERTIFICATE OF REPORTER

I, SILVIA P. WAGE, CSR, CRR, RPR, herby certify that the witness in the foregoing deposition was by me duly sworn to tell the whole truth, nothing but the truth; said deposition was taken down in shorthand by me, a disinterested person, at the time and place therein stated. The testimony of said witness was thereafter reduced to typewriting by computer under my direction and supervision. Before completion of the deposition, review of the transcript [X] was [ ] was not requested. If requested, any changes made by the deponent (and provided to the reporter) during the period allowed are appended hereto.

I further certify that I am not of counsel or attorney for either or any of the parties to the said deposition, nor in any way interested in the event of this cause, and that I am not related to any of the parties thereto.

October 14, 2025



DECLARATION

I hereby declare I am the deponent in the within matter; that I have read the foregoing transcript and know the contents thereof; and I declare that the same is true of my knowledge except as to the matters which are therein stated upon my information or belief, and as to those matters, I believe them to be true.

I declare under the penalties of perjury under the laws of the United States that the foregoing is true and correct.

This declaration is executed this _____ day of _____, 20___, at _____, _____.

_____

CARLOS D. BUSTAMANTE, Ph.D.

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Lcipriano@goodwinlaw.com

October 14, 2025

RE: Qiagen Sciences, LLC v. Tecan Genomics, Inc.

10/7/2025, Carlos D. Bustamante, Ph.D., (#7619957).

The above-referenced transcript has been completed by Veritext Legal Solutions and review of the transcript is being handled as follows:

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Qiagen Sciences, LLC v. Tecan Genomics, Inc.

Carlos D. Bustamante, Ph.D. (#7619957)

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(Carlos D. Bustamante, Ph.D.) Date

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Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

DISCLAIMER: THE FOREGOING FEDERAL PROCEDURE RULES ARE PROVIDED FOR INFORMATIONAL PURPOSES ONLY. THE ABOVE RULES ARE CURRENT AS OF APRIL 1, 2019. PLEASE REFER TO THE APPLICABLE FEDERAL RULES OF CIVIL PROCEDURE FOR UP-TO-DATE INFORMATION.

VERITEXT LEGAL SOLUTIONS

COMPANY CERTIFICATE AND DISCLOSURE STATEMENT

Veritext Legal Solutions represents that the foregoing transcript is a true, correct and complete transcript of the colloquies, questions and answers as submitted by the court reporter. Veritext Legal Solutions further represents that the attached exhibits, if any, are true, correct and complete documents as submitted by the court reporter and/or attorneys in relation to this deposition and that the documents were processed in accordance with our litigation support and production standards.

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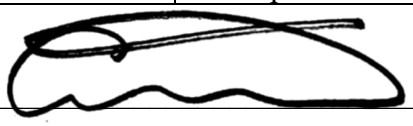
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ERRATA SHEET FOR THE TRANSCRIPT OF:

QIAGEN SCIENCES, LLC., v TECAN GENOMICS, INC.
IPR2025-00028; IPR2025-00029
Deponent: Carlos Bustamante
Deposition Date: October 7, 2025

I wish to make the following changes for the following reasons:

Page:Line	Presently Reads	Should Read	Reason
8:6	"CBD Consulting Group"	"CDB Consulting Group, Inc."	Transcription Error
9:4	"Stamford"	"Stanford"	Transcription Error
27:20	"who have"	"who had"	Transcription Error
49:21	"multiply binding"	"multiple binding"	Transcription Error
77:5	"regions with genome"	"regions of the genome"	Clarification
79:22	"how many time"	"how many times"	Transcription Error
84:13	"there your"	"there are"	Transcription Error
96:20	"multiply blind"	"multiply bind"	Transcription Error
102:5	"side selection"	"size selection"	Transcription Error
104:24; 105:3	"basis"	"bases"	Transcription Error
118:21	"allel"	"allele"	Transcription Error
162:10	"date"	"data"	Transcription Error
163:18	"brut"	"brute"	Transcription Error
167:13	"to answer to that"	"to answer that"	Clarification
179:9	"implement he something"	"implement something"	Transcription Error
187:15-16; 188:15; 188:18-19; 188:20	"miss priming"	"mispriming"	Transcription Error
204:10	"allel"	"allele"	Transcription Error
206:19	"deployed"	"diploid"	Transcription Error
223:2-3	"called it a PCR"	"called it traditional PCR"	Clarification
227:3	"date"	"data"	Transcription Error
233:18	"'102 patent"	"'012 patent"	Clarification

/s/ 

Carlos Bustamante

This 11th day of November 2025.