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

FORESIGHT DIAGNOSTICS INC.,	)
	) IPR2023-00546
Petitioner,	) U.S. Patent No.
	) 10,450,611
V.	) and
	) IPR2023-00545
PERSONALIS, INC.,	) U.S. Patent No.
	) 11,299,783
Patent Owner.	)
	)

DEPOSITION OF JOHN QUACKENBUSH, PH.D.
APPEARING REMOTELY
October 20, 2023
10:05 a.m., Eastern Standard Time

Reported by: Lori J. Goodin, RPR, CLR, CRR,
RSA, California CSR #13959

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7 EXHIBIT DESCRIPTION PAGE

8 Exhibit 1006 Mertes reference 186

9 Exhibit 1012 Ley reference 230

10 Exhibit 1020 Declaration for IPR matter

related to U.S. Patent

11 Number 11,299,783 10

12 Exhibit 1030 Forshew reference 118

13 Exhibit 1032 Forshew Supplemental Material 122

14 Exhibit 1042 Ley Supplemental Material 240

15 Exhibit 1043 Newman reference 58

16 Exhibit 1061 Declaration for IPR matter

17 related to U.S. Patent

18 Number 10,450,611 16

19 Exhibit 1070 Dawson reference 159

20

21 (All exhibits were provided

22 electronically to the reporter.)

FRIDAY, OCTOBER 20, 2023, 10:05 a.m. EST

PROCEEDINGS

THE VIDEOGRAPHER: We are now on the record. My name is Henry Marte. I am a videographer on behalf of Digital Evidence Group.

Today's date is October 20, 2023, and the time is 10:05 a.m.

This proceeding is being held in the matter of Foresight Diagnostics, Inc., versus Personalis, Inc.

The deponent today is Dr. John Quackenbush.

All parties to this deposition are appearing remotely and have agreed to the witness being sworn in the remotely.

Counsel, please identify themselves for the record. Afterwards, the court reporter will administer the oath to the witness.

MR. LUMAN: Hi. My name is Nate Luman. I am from the law firm of Knobbe Martens. I'm here on behalf of patent owner, Personalis.

I am joined by Derek Walter from the law firm of Weil Gotshal, and also Stephen Moore from Personalis.

MR. KRAUSE: Andrew Krause from Irell & Manella on behalf of Foresight Diagnostics. And I am joined by my colleague, Amir Naini, from Naini P.C.

* * *

Whereupon,

JOHN QUACKENBUSH, PH.D.,

a witness called for examination, having been first duly sworn, was examined and testified as follows:

* * *

EXAMINATION

BY MR. LUMAN:

Q. Good morning. My name is Nate Luman. I will be taking the deposition today.

Dr. Quackenbush, can you hear me okay?

A. Yes, I can.

Q. And would you please state your full name and your home address for the record.

A. My name is John Quackenbush, Q-U-A-C-K-E-N-B-U-S-H.

And I live at 86 Walpole Street, W-A-L-P-O-L-E, in Dover, Massachusetts.

Q. Do you understand that you are under oath today?

A. Yes, I do.

Q. Is there any reason that you would be unable to give truthful and accurate testimony today?

A. No, there is not.

Q. So today, I will be asking questions and the court reporter is going to be taking down my questions and your answers.

Do you agree to give verbal responses today?

A. Yes, I do.

Q. I am going to endeavor to refrain from speaking over you, and I would ask that you do the same, to try to not speak over me.

Is that okay?

A. Yes, it is.

Q. If you don't understand a question, please let me know. Otherwise, I'm going to assume that you understood my question.

Is that fair?

A. Yes.

Q. And your attorney may object from time to time, but you will still need to answer my questions unless you are specifically instructed by counsel not to answer.

Do you understand that?

A. Yes, I do.

Q. And I will probably take a break every hour or so. And if at any point you would like to take a break, let me know.

But I do ask that you would first answer any pending question before we take a break.

Is that okay?

A. That is perfectly reasonable and fine with me. Yes, thank you.

Q. So, you have been deposed before in this case and I understand several other times.

Can you give me an estimate about how many times you have been deposed before?

A. I don't have my records in front of me. I guess sitting here right now, and it is probably not that accurate, 10 to 15, maybe more.

Q. Were all of those in patent cases or a mixture of patent cases and something else?

A. I believe they were all patent related litigation, yes. Some IPR matters, some District Court matters.

Q. Have you ever testified in court before?

A. Yes, I have.

MR. LUMAN: Let's see.

So, what I would like to do is I would like to bring up Exhibit 1020.

Henry, would you be able to do that

for us?

(Exhibit 1020 marked for identification.)

BY MR. LUMAN:

Q. So, Exhibit 1020 is on the screen. Dr. Quackenbush, do you recognize this document?

A. Yes, it is the declaration I submitted in this IPR matter.

Q. And would you turn with me to Paragraph 86.

A. So, could I have a copy of it, please?

MR. LUMAN: Yes. Henry, how would --

THE VIDEOGRAPHER: You can refresh the page, that link on the exhibit.

THE WITNESS: Okay, great. Thank you so much.

BY MR. LUMAN:

Q. Dr. Quackenbush, I will give you a minute to download it.

Can you just let me know when you've

1 got it?
2 A. All right. I have it, yes. Thank
3 you.
4 Q. And would you turn to Paragraph 86
5 with me, please?
6 A. Yes, I am there.
7 Q. And this paragraph mentions
8 cell-free DNA and kind of refers to small
9 fragments of DNA.
10 Do you see that?
11 A. Yes, I do.
12 Q. And the second sentence talks about
13 apoptosis and cell death.
14 Do you see that?
15 A. Yes, I do.
16 Q. So, apoptosis and cell death is a
17 process that can release cell-free DNA into the
18 bloodstream; is that right?
19 A. Yes. If you read on further, it
20 says part of that process, apoptosis and cell
21 death involve cellular mechanisms that cause the
22 DNA of the cells' chromosomes to be cleaved and

fragmented.

And then the fragmented DNA, along with other parts of the cells, are released into the bloodstream.

Q. And when it says, "along with other parts of the cells," what is that referring to?

A. A cell, I often describe to my students is a little machine made of proteins. So, there are lots of proteins. There are also nucleic acids, including RNA and DNA.

So, really, you know, the cell ruptures and the components of the cell are released into circulation.

Q. So, it is not just the cell-free DNA that is released into the bloodstream. It is the cell-free DNA and those other parts of the cells that you have mentioned, right?

A. Generally, yes. That is a fair way of characterizing it.

Q. So, there is a fair amount of cellular debris that enters the blood through apoptosis and cell death?

A. There are many things that enter the blood. If you look at the bloodstream itself, it is filled with cells, white blood cells, red blood cells, a variety of different proteins.

And so this releases additional proteins and nucleic acid into circulation.

Q. And the last sentence mentions waste products.

Do you see that?

A. Yes, I do. The fragmented DNA, it is in the bloodstream. And just like with many bodily waste functions, they are typically cleared out through the urine.

Q. And what type of waste products are you referring to?

A. You know, cellular proteins. Probably bacterial and viral proteins.

Things that -- the kidneys filter the blood and remove proteins, free DNA from the bloodstream and excrete it through the urine.

Q. Were you thinking of like antigens as being waste products as well? Or is that

1 something else?
2 A. I'm not sure if antigens are
3 cleared. Many different proteins, protein
4 fragments -- I'm not sure everything that gets
5 cleared out of the body through the urine.
6 But definitely you have cellular
7 waste products that are cleared out. And the
8 nucleic acids can be detected in the urine as
9 well as in the blood.
10 Q. And so other than apoptosis and cell
11 death, are there other mechanisms by which
12 cell-free DNA enters the bloodstream?
13 A. There could be others. There are --
14 there is the potential for cells to excrete DNA
15 themselves.
16 There are small particles called
17 exosomes, which are often excreted by the cells
18 which contain nucleic acid. Those may break down
19 and release nucleic acids.
20 There are -- you know, cells can be
21 ruptured in a variety of different ways.
22 So, other than apoptosis, you can

have viruses life cells. You can have cells ruptured through sheer stress.

It is -- well, when cells break open, the components inside can come out and one of those components is DNA.

Q. And so, is it fair to say that there is other ways for a cell-free DNA to enter the bloodstream besides apoptosis?

A. So, one of the primary natural processes in which cell-free DNA gets entered into the bloodstream is through programmed cell death, right. This process called apoptosis.

It happens in development. It happens in a variety of different biological situations.

But yes, DNA can be released into the bloodstream through a variety of processes.

Q. Can you name one of those other processes besides apoptosis by which cell-free DNA enters the bloodstream?

A. So, if we characterize cell-free DNA as that DNA which is outside of cells, the simple

process of cellysis can release blood -- DNA into the bloodstream.

So viruses can lyse cells. Stress can break open cells, sheer stress.

It really would depend on the characteristics of the particular event.

Q. And is there any other ways besides cellysis that cell-free DNA enters the bloodstream?

A. Again, DNA could be exported through -- from the cells themselves. I would have to think about how that might occur.

It is not something I really studied before in preparation for my deposition today.

MR. LUMAN: What I would like to do is also bring up your second declaration.

Can we bring up Exhibit 1061, please?

(Exhibit 1061 marked for identification.)

BY MR. LUMAN:

Q. So, on the screen is Exhibit 1061,

Dr. Quackenbush.

Do you recognize this document?

A. Hold on. Just let me download it, please. All right, I have it.

Q. And do you recognize this document?

A. Yes, it is the second declaration that I submitted. This one for the IPR matter concerning the '611 patent.

Q. And this declaration is for U.S. Patent Number 10,450,611. Correct?

A. That is correct.

Q. And the previous declaration that we were looking at which is Exhibit 1020, that one was for -- let me just make sure I get the number right so the record is clear.

That one is for U.S. Patent Number 11,299,783. Correct?

A. That's correct.

Q. In Exhibit 1061, would you please turn with me to Paragraph 167.

A. Yes, I am there.

Q. Do you see the first sentence talks

about it being desirable for increasing accuracy; do you see that sentence?

A. Yes, I do.

Q. And can you provide any additional explanation about why it is desirable to increase accuracy of detecting and quantifying mutations in tumors in the year 2016?

A. So --

MR. KRAUSE: Objection to form.

THE WITNESS: So, I think it has always been recognized. The Lander/Waterman equation, which this refers to, is an analysis that was published, I think in 1998.

And it was by Eric Lander and Mike Waterman. And it described, at that time, mapping of clones for mapping the genome.

And it describes using -- it describes an analysis based on the size of the fragments and the depth of coverage to estimate coverage in the genome, and the average cover of a particular location or locus of a genome?

1 From the start of DNA sequencing, it
2 was recognized in the context of this
3 equation, but also for the simple logic, that
4 to get a more accurate read at any given base
5 in the genome, that what one would want to do
6 is typically increase coverage.
7 And there are a wide variety of
8 different ways that one could do that that we
9 can talk about.
10 But, you know, as early as the early
11 2000's, when people were thinking about
12 genome sequencing and using it in a clinical
13 setting, it was recognized that by sequencing
14 deeper, one wanted to make, say, a robust
15 discovery in the laboratory, or if one were
16 interested in developing the clinical assay,
17 that sequencing deeper would provide more --
18 a more accurate result.
19 So, you know, it is simple
20 measurement theory. The more times you
21 measure something the better, the better you
22 measure it. And this was known well

before 2016.

BY MR. LUMAN:

Q. Were there problems with the accuracy of detecting and quantifying mutations and tumors that were recognized in the field in 2016?

MR. KRAUSE: Objection to form.

THE WITNESS: So, you know, there has been constant progress in sequencing genomes.

I think outside of the draft genomes, the first personal genome I know that was sequenced, was that of James Watson. It was done by a group at Baylor College of Medicine.

And increasing sequence depth was an important way that they used to try to be as accurate as possible when they were looking at mutations in genes that were associated with disease.

And, you know, as early as 2005, 2006, there were many discussions at meetings

about the importance of carrying out this kind of analysis.

So, one of the references I cite in my report is the Ley reference in which an individual with AML is sequenced in targeted regions at great depth to be able to identify mutations.

So, there is always room for improvement. And again, this was something that was well known for quite some time.

BY MR. LUMAN:

Q. And so it was well known to a person of skill in the art that it would be desirable to increase the accuracy of detecting and quantifying mutations in tumors?

MR. KRAUSE: Objection to form.

THE WITNESS: So, again, you know, it is -- it has been well known that making accurate measurements of mutations and tumors could be important for clinical, for clinical applications such as assigning patients to different therapeutics or matching patients

to therapeutics.

It was also known that in research the confidence one has in a mutation call is going to depend on, among other factors, the depth of the sequence.

BY MR. LUMAN:

Q. And when you say it was known, that was known in at least the year 2016, right?

MR. KRAUSE: Objection, vague.

THE WITNESS: So, this has been -- the importance of making many measurements has been known since -- well, I don't know, the early days of modern science.

I used to teach a physics course at UCLA where I would have my students make many measurements of the same basic object to teach them about statistical distributions of measures and how we make estimates of any kind of measure.

And this was back in the, the 1980's. And, that was old news then.

So, you know, we have always known

that making repeated measurements is a good way to reduce errors. There are other potential ways to reduce errors in assays like this.

But the importance of making accurate measurements has been known for quite some time.

And ways to do that have been known with sequence data since the earliest days of DNA sequencing.

BY MR. LUMAN:

Q. I don't mean to hide the ball on the year 2016. Let me clarify that.

Can we turn to Paragraph 33 of your report.

A. The Exhibit 1060 -- 61, excuse me?

Q. 1061.

And you say in the, what is it, in the third sentence, "I have considered May 27, 2016 to be the relevant date for assessing prior art invalidity in my analysis."

Do you see that?

A. Yes, I do.

Q. And so, you haven't changed your position on the relevant date for assessing prior art invalidity since you filed this -- since you signed this declaration, right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, on the front page of the patent, the '611 patent, at line, maybe it is 60, it is annotated 60. It says provisional application and gives a number. It says that provisional application was filed on May 27, 2016.

If I look at my report in Paragraph 33, I quote that, in fact, that the application was filed on May 27, 2016.

I write, "I have considered that date to be the relevant date for assessing prior art invalidity in my analysis, although I offer no opinion on whether or not the '647 provisional application in fact provides sufficient support for the issued claims."

And then I have a footnote which

1 says, "I am not aware of any evidence
2 suggesting the patent owner is entitled to an
3 earlier priority date."
4 So, I have seen no, no evidence to
5 suggest this date is incorrect, and
6 therefore, that is the date that I have used.
7 BY MR. LUMAN:
8 Q. And so, earlier when we were talking
9 about the desirability of the increasing
10 accuracy, that desirability was something that a
11 person of ordinary skill in the art would have
12 known at least in the year 2016. Right?
13 MR. KRAUSE: Objection to form.
14 THE WITNESS: So, that desirability
15 to increase accuracy is something that I
16 would say dates back to the early days of
17 modern science.
18 And so, if we are talking
19 specifically about DNA sequencing, it -- I
20 would say it dates back to the earliest days
21 of sequencing with Fred Sanger and -- the
22 names of the other sequencing methods elude

me since Sanger's dominated.

But, back to the 1970's, when DNA sequencing was first discovered through the sequencing of the Huntington disease locus, the early sequencing of genes like hemoglobin beta.

So, we have known long before 2016 that increasing accuracy is important. We know that one way to do that is to increase sequencing depth.

BY MR. LUMAN:

Q. And the desire to increase the accuracy continued up until 2016, right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, any sequencing -- anyone performing any assay is constantly trying to be as accurate as possible.

And there are many methods which people have developed and continue to develop, both laboratory and analytical, that attempt to improve the accuracy of the measurements we make.

So, this started long before 2016. And as good scientists, our drive for accuracy continues to this day.

BY MR. LUMAN:

Q. Can you turn back to Paragraph 167 with me, please.

A. Sure.

Q. And I'm looking at the last sentence. There is a portion of the last sentence that says, "A person of ordinary skill knew reducing sequencing costs further was desirable."

Do you see that?

A. I do, yes.

Q. And can you provide any explanation about why the person of skill in the art knew that reducing sequencing costs was desirable?

A. Sure. I can give you an example from my background.

So, I think it was in 2009, maybe 2010, I was with the Dana-Farber Cancer Institute. And I believe that was the date when

they launched an assay called Profile. At least we were talking about it.

Profile was an attempt to sequence cancer-associated genes in every patient who walked through the doors of the Dana-Farber Cancer Institute.

In performing those assays, we had to make a number of different choices. And the choices we made were largely driven by the -- our interest in generating high quality sequence.

So there are a number of choices we made in the laboratory protocols. Sequencing at relatively large depth so that we had good confidence in the accuracy of our calls.

And then also doing it in a way that was cost efficient.

So, you know, at least in my own personal experience in a clinical setting, you know, we were making those kinds of choices because we wanted to offer a cost efficient service to the hospital, also our patients, and to the insurance companies or others who would

1 reimburse it.
2 And I can talk about lots of other
3 ways in which reducing cost is important in
4 laboratory settings, in clinical settings, in
5 others.
6 Q. Do you feel that reducing sequencing
7 costs was a real consideration for the person of
8 skill in the art?
9 Or is it really just merely a dollar
10 sign? You can always write another grant
11 application to get more dollars and it is not
12 really that much of a consideration.
13 MR. KRAUSE: Objection, calls for
14 speculation.
15 THE WITNESS: So, you know, based on
16 your questions, you have never written a
17 grant application, so you don't know how
18 challenging it is to receive one.
19 The budgets are fixed and often
20 require balancing many different things.
21 In our assays, you know, with a
22 fixed budget, as a laboratory scientist, we

have always striven to be as cost efficient as possible, because that typically allows us to collect data on larger numbers of subjects, which in some applications is, is really driving some of the science that we do.

So, a person of ordinary skill in the art would consider that. If the assay was simply too expensive, then one could not effectively run this assay.

In a, you know, if we look at the '611 patent, there is nothing presented in the patent that wasn't already known in the art that would give us a way to reduce cost or improve accuracy, because these are things, like getting greater sequencing depth or choosing a specific number of targets rather than, rather than a larger number of targets.

Those were all methods known in the art to both potentially reduce cost and to increase accuracy.

BY MR. LUMAN:

Q. And how about in a clinical setting? Are the budgets fixed in that setting as well?

MR. KRAUSE: Objection to form.

THE WITNESS: So, you know if, from having worked at many clinical sites and diagnostic testing laboratories over the years, one of the things that typically is concerning is how much someone will be reimbursed for the test.

If you can't get paid for the test, then -- you know, most clinical laboratories are not charities, and so they have to be able to be paid for the assays that they run.

So, if the assays are more expensive than what they are reimbursed, they can't provide the service they would like to provide.

So, like, with any business, reducing, reducing cost is an important part of doing -- of providing a service.

And, you know, again, if I look at

the '611 patent, which we cite to in Paragraph 167, there is, as I write, even though sequencing would become less expensive over the years prior, that a person of ordinary skill in the art would understand that smaller sequencing panels were one way to reduce cost.

And this is, actually again, something that was known for quite some time.

BY MR. LUMAN:

Q. Would you turn with me to the next paragraph, Paragraph 168.

A. Sure.

Q. And I'm looking about halfway through the paragraph. There is something about simplifying -- a simplifying factor in capture panel design and production.

Do you see that?

A. I see where it says that, yes.

Q. What were you referring to when you mention a simplifying factor in capture panel design and production?

A. So, would you repeat the question, please?

Q. What were you referring to by referencing this simplifying factor in capture panel design and production?

A. So, there are many aspects to that. And if you read farther in the paragraph, it points out that there are approximately 25,000 genes encoded in the genome, right.

So -- and one of the important things in eukaryotes, so, organisms that have nuclei, which humans are an example of eukaryotes. One of the things we know is that genes tend to be modular.

One of the other things -- by which I mean there are coding regions that encode proteins, and they are called exons, and intervening sequences called introns.

And while a gene may span 1,000 bases of coding sequence, that can be over, or more or less, but that can be distributed over sometimes tens of thousands of bases of DNA.

1 So, if one were to probe all 25,000
2 genes, and let's say there is an average of five
3 exons per gene, so, 125,000 exons, to get all of
4 the coding sequence in the genome.
5 Designing -- and given the fact that
6 some of those regions may need multiple PCR
7 primers, depending on your laboratory or other
8 types of capture probes, depending on your assay.
9 Then, if one would try to sequence
10 the entire exome, one would have to do, as one
11 example, a highly multiplex PCR which introduces
12 some laboratory complications that can require
13 additional optimization, right.
14 So, if one were to sequence the
15 entire exome, right, one would generate -- or the
16 whole genome, one would generate for a fixed cost
17 a certain amount of data, which would provide
18 some degree of coverage.
19 And, again, it would depend on the
20 particular assay and how it was run.
21 So, we would do the whole genome.
22 We would do the whole exome. And there are

complications in doing that kind of amplification.

We then could focus on a subset of genes, as an example, Ley had done.

And in focusing on that subset, now -- I forget the number Ley profiled. I think it was ten. That is an example of going from the whole genome down to ten genes.

So, 125 hundredth of the complexity of just doing the laboratory assay.

And then in terms of the analysis, if we are doing those follow-on assays that Ley does, then in doing the analysis, one doesn't have to search the sequences across the entire genome. One just searches the sequences against the set of informed mutations that came from the original sequencing analysis that Ley had done.

So, you can simplify the laboratory protocol, and there is a lot that goes into that. You can increase the read depth by concentrating your sequencing on a small region, other than the whole genome or 25,000 genes.

1 You can simplify the downstream
2 analysis. And again, all of this was well known
3 in the art prior to 2016.
4 I remember it being discussed at
5 meetings at Cold Spring Harbor as far back as
6 2005.
7 Q. And so, a person of ordinary skill
8 in the art, in the year 2016, would have been
9 motivated to simplify the capture panel design
10 production. Is that correct?
11 MR. KRAUSE: Objection to form.
12 THE WITNESS: So, a person of skill
13 in the art would have followed what had been
14 established in the literature as ways of
15 simplifying assays to be as informative and
16 as cost effective as possible.
17 And, you know, again, I think Ley is
18 a really nice example of doing this in a
19 human setting where they follow exactly those
20 same steps to sort of simplify the process
21 and reduce cost.
22 BY MR. LUMAN:

Q. You had mentioned in one of your answers that multiple PCR primers can introduce some laboratory complications.

What laboratory complications were you referring to?

A. So, we refer to PCR -- there are many ways people refer to PCR.

The sort of canonical PCR assay is that patented by Kary Mullis.

And in PCR, what one typically does is uses two primers to capture a region of DNA by selectively annealing and amplifying it. And we can talk about the PCR process.

PCR is one example of a way of capturing a portion of the genome, but it is a commonly used one.

And so, as an example, one could imagine doing PCR as a way of analyzing all 25,000 genes. That would require a large number of PCR primers. There is a cost involved in synthesizing those.

There are also considerations that

have to be done to -- instead of running one PCR, to run multiple PCRs together. And we can talk about those.

They include intelligent approaches to primer design. They include optimization of laboratory protocols.

So, what one really wants to try to do is to ensure that the PCR is specific in many cases, depending on the application, uniform.

And so, doing that with ten genes just, you know, is conceptually far simpler for a wide variety of practical reasons, is far simpler than doing it for 25,000.

Q. When you mention the intelligent approaches to primer design using multiple PCR primers together, what were you -- can you elaborate on that a little bit?

A. Sure. There are many aspects to that. I don't think I speak about that in my report. But -- and I don't think anywhere in either the '611 or '783 patent is there a discussion about optimal primer design.

1 But one of the things that one would
2 have to do in designing primers is to ensure that
3 they avoid repetitive elements in the genome.
4 Another thing that someone would
5 have to do is to ensure the melting temperature
6 of the primers didn't differ wildly across the
7 collection.
8 Another approach that is typically
9 used in primer design is to use software tools
10 that help avoid what are called primer dimers, or
11 the formation of primer dimers, where the primers
12 have sequences that are complimentary to each
13 other, right.
14 One could also develop other
15 strategies for doing PCR amplification, ligation
16 and amplification strategies.
17 In general, any of these is far
18 easier with a smaller number of targets. By
19 targets, I mean the genes that one is going to
20 sequence.
21 So, you know, to talk about the
22 complexities, I would really have to look at a

1 particular assay.
2 But I have just given you a flavor
3 of a few that one of skill in the art would
4 consider depending on the application in which
5 they were looking to do highly multiplexed PCR.
6 Q. You had mentioned laboratory
7 protocols would have to be considered for using
8 multiple PCR primers at the same time.
9 What type of laboratory protocols
10 were you thinking of?
11 A. So, again, I don't think I comment
12 on this in my declarations. I don't think there
13 are any -- I don't recall any particular
14 laboratory protocols which are laid out in either
15 of the two patents at issue today.
16 But, you know, there are many
17 factors which go into designing a laboratory
18 protocol for PCR or any other molecular biology
19 assay.
20 That would include primer
21 concentration, target DNA concentration, salt
22 concentrations in the buffer, the choice of DNA

1 polymerase one would use, the nucleotide
2 concentrations one might use in that PCR
3 reaction, the annealing temperature one selected,
4 the annealing times.
5 So, there are many, many different
6 factors that would be involved in establishing a
7 PCR reaction.
8 But again, I don't think the -- I
9 don't think the -- I am talking about this
10 hypothetically. All of these things are things
11 that a person of ordinary skill in the art would
12 have understood and incorporated into their
13 particular laboratory assay design, right. It
14 would really depend on the application.
15 So, you know, I, at this point I'm
16 just speculating about different things,
17 depending on the assay that might be run.
18 Q. Turning back to Paragraph 168. The
19 last sentence mentions simplified computational
20 analysis. Do you see that?
21 A. Yes, I do.
22 Q. Why would a person of ordinary skill

in the art have been motivated to simplify the computational analysis in the year 2016?

A. So, people would have always been interested in simplifying computational analyses.

Again, this was something that was well known in the art for quite some time, you know.

The easiest analogy I can give you is, you know, if you had an encyclopedia and you had to look something up and you didn't know what volume to look in, it is much harder than knowing it is in Volume 3, right.

Just knowing that the matter you want to learn about is in the particular volume makes it easier to find it.

In the same way, if I have a fixed number of genes, I can do my mapping analysis much more efficiently, because I don't have the map to the entire genome. I map to the set of genes, for example.

And, you know, I might, again hypothetically, be able to invest in greater

1 detail studying what was known about those
2 particular genes of interest.
3 One of the things, for example, that
4 comes up in Ley is the use of two fixed genes,
5 BRCA1 and TP53.
6 And one of the nice things about
7 those fixed genes in the panel that Ley used was
8 that Ley had the opportunity to go in and provide
9 a good deal of information about what was known
10 about those individual genes, right.
11 And understanding that and reading
12 it as a scientist could give -- or a clinician,
13 could give one insight into that individual's
14 particular AML case.
15 Q. Can you provide any more detail in
16 what you mean by computational analysis? What is
17 the computational analysis you are referring to
18 here?
19 A. So, I am referring to the entire
20 process. It would depend on the particular
21 application.
22 It could include, among other

1 things, many elements that were well known in the
2 art, including identifying genes in the genome,
3 annotating those genes based on information from
4 the literature. Designing primers based on the
5 assay that would be run.
6 Processing the sequencing data,
7 mapping that sequence data back to a reference,
8 which could either be the entire genome or the
9 subset of genes when we are profiling, depending
10 on the application.
11 And then as we talked about earlier,
12 if one were to increase the sequencing depth,
13 identifying high confidence variance based on the
14 data that were available.
15 So, there were many, many different
16 aspects of this and it would depend on what one
17 would do.
18 But methods for doing this, again,
19 were well known in the art prior to 2016.
20 MR. LUMAN: Let's see, can we look
21 at Paragraph 167 and 168 together on the
22 screen at the same time. Thanks.

BY MR. LUMAN:

Q. So, between increasing accuracy, reducing sequencing costs, simplifying capture panel design and production and simplifying computational analysis, which of those four things would have been more important to a person of ordinary skill in the art, in the year 2016?

MR. KRAUSE: Objection to form.

THE WITNESS: So, this is a section in which I am talking -- I am providing an opinion regarding obviousness based on Ley and what a person of ordinary skill in the art would understand.

I think a person of ordinary skill in the art, long before 2016 -- and I believe the Ley reference is from 2008. So, even as far back as 2008, the person of skill in the art would have understood that all of these factors are factors which should be considered.

And it is hard to say that one is more important than the other, right.

Obviously increasing accuracy was important. And so, one of the things that Ley did was, from an initial whole genome sequencing analysis, narrowed the analysis down to, I believe ten individual genes, right.

So, Ley knew that by having a smaller number of genes, for the same cost he could generate deeper sequence, right. So -- and that deeper sequence would lead to increased accuracy.

Ley would have also understood that the design of the assay would be simplified with a small number of genes. That the conduct of the assay in the laboratory with ten genes versus 25,000, would have been far easier.

And that in analyzing the data at the very end -- if you will recall in Ley, there was a long pipeline for the original analysis getting down to the ten genes.

But once those ten genes are

identified, essentially the analysis once you map the sequences back to the genes becomes a lookup, right.

You look up what is known about those genes in therapeutic interventions.

And I think one of those that is referred to in Ley is the FLT3 gene which, I believe, a mutation in which I believe contraindicated stem cell transplant, right.

So, rather than searching through all 25,000, by having that fixed panel, that small number, Ley was able to simplify that kind of computational analysis.

And again, all of these things are important. It is going to depend on the particular application. But, it is hard to say one is relatively more important than the other. They are all factors that one has to consider.

BY MR. LUMAN:

Q. Well, specifically for modifying Ley's disclosure, which of the four motivations

in Paragraphs 167 and 168 would the person of ordinary skill in the art found to be the most important?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I don't know what you mean by modifying Ley's disclosure.

But, you know, again, I think a person of ordinary skill in the art reading Ley would understand that Ley describes a process which I believe fully anticipates Claim 1 of the '611 patent and the '781 patent -- or '783 patent, excuse me.

But that, you know, one of ordinary skill in the art, too, would also be constantly trying to improve the assays that one runs. You know, scientists are always trying to make things better.

And, it would be hard to place a value judgment on any one of these.

Again, I think they are all important and we have talked about reasons why. Deeper sequencing gives you better

accuracy, typically, along with other factors.

Simplifying laboratory assays reduces the risk of errors, also typically helps provide cleaner data.

Simplifying computational analyses can speed the interpretation of the results of an assay.

So, you know, we can go on. They are all important, but you know, they are all well known in the art prior to 2016.

BY MR. LUMAN:

Q. And, let's look up at Paragraph 166. It is the one right above 167.

A. All right.

Q. And do you see that Paragraph 166, the first sentence, I guess it is just one sentence long.

A. Yes.

Q. Says, "Then modifying Ley's disclosure." Do you see that?

A. I see where it says that, yes.

Q. And you had mentioned that you weren't sure what I was referring to when I said modifying Ley's disclosure.

Does this help you understand what is meant by modifying Ley's disclosure?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I believe elsewhere in my report I provided an analysis of the ten genes that Ley disclosed he used in subsequent assays of the individual who had AML and also tested in a population.

In that analysis, I looked at the length of the coding sequences of the genes, because Ley tells us that he only analyzed coding sequences.

I summed up the size of those coding regions and they were 45,000 base pairs in line.

So, the analysis I did required something other than just reading Ley to understand that Ley's coverage was less than 175 kilobases which I believe appears in

the -- I believe it is Claim Element E, but I would have to look. That those 45,000 base pairs are less than 175 base pairs.

But, if one didn't recognize that immediately, then what one would recognize is that using a capture panel smaller than 175,000 base pairs would have been obvious in the sense that it would do all of the things we talked about.

It would reduce some of the laboratory complexity. It would give us the opportunity to generate greater sequencing depth. And it would reduce the computational, the computational burden of analyzing the data.

So, you know, again, my own practical experience with the profile assay at Dana-Farber really speaks to this.

That we were trying to choose a relatively small subset of targets for our analysis that would have been smaller than 175,000 bases for exactly the same reasons

1 outlined here.
2 BY MR. LUMAN:
3 Q. So, still focusing on Paragraph 167
4 and 168. If a person of ordinary skill in the
5 art were looking to have an assay for a clinical
6 setting, which of the four motivations would
7 drive the POSA the most?
8 Those four motivations being
9 increasing accuracy, reducing sequencing costs,
10 simplifying capture panel design, and simplifying
11 computational analysis.
12 MR. KRAUSE: Objection to form.
13 Vague. Calls for speculation.
14 THE WITNESS: So, I can't really
15 speculate on what a individual laboratory
16 director -- in your case, a clinical lab --
17 might feel is most important.
18 I think all of these are important.
19 One wants to offer assays that are as
20 accurate as possible. One wants to do that
21 in as cost effective manner as possible.
22 If I look at the assays we were

1 deploying at Dana-Farber prior to 2016, a
2 large part of what we were interested in
3 doing was simplifying the computational
4 pipeline and the laboratory complexity, for
5 pretty obvious reasons.
6 You know, part of which in our case
7 was getting CLIA/CAP approval for the use of
8 these assays.
9 So, they are all important. Each
10 individual might weight them differently.
11 But all of the things that appear in
12 Paragraph 167 and 168 were very well known in
13 the art prior to 2016, and could have been
14 applied to Ley's 2008 disclosure if someone
15 found any part of it lacking.
16 I don't -- I see, for example, we
17 are talking about the size of coverage
18 provided by the capture panel. And Ley
19 clearly discloses something less than 175,000
20 bases.
21 BY MR. LUMAN:
22 Q. So, let's explore the interplay

between some of these two motivations -- some of these four motivations.

So, if a person at Dana-Farber had a working assay, would they have wanted to increase the accuracy at the expense of cost?

MR. KRAUSE: Objection, calls for speculation.

THE WITNESS: You would have to ask the individual person.

I think some of it would depend on the degree of accuracy. Some of it would depend on the cost. Some of it would depend on the reimbursement structure.

Some of it would depend on the particular goal of the assay that one was running.

So, it is -- you would have to ask the person running the assay. Again, all four of these I think are important parts of optimizing any kind of laboratory protocol.

BY MR. LUMAN:

Q. If you would turn with me to

Paragraph 189 in this declaration.

A. All right, I am there.

Q. And do you see that you've got a quote from Newman. It says, "Sequencing was performed using 2 times 100 or 2 times 150 paired-end reads." Do you see that?

A. I see where it says that, yes.

Q. And then you also discuss in that paragraph -- you've got a reproduction of a table from Newman and Rows 286 and 287 are highlighted.

Do you see that?

A. Yes, I do.

Q. And I see in that Row 286, there is the GBM relapse.

Do you see that?

A. Yes.

Q. What is the GBM relapse referring to?

A. So, GBM is glioblastoma multiforme.

It is a type of brain tumor. I would have to go back and refresh my memory about the individual samples that were profiled here.

But the relapse is almost certainly a tumor sample from a patient who had the disease, had gone into remission, but then relapsed.

Q. And then the next sample is GBM PBL. What is that sample?

A. So, again, I'd want to read the Newman reference to ensure that I'm not making an error.

But it is says sample type PBL, GBM PBL. So, I believe that is peripheral blood lymphocytes.

So, this would be an attempt to obtain two samples of DNA in the Rows 286 and 287, and then to perform sequencing on those, on those samples.

Q. And the peripheral blood lymphocyte sample, is that a cancer sample or is that the germ line sample?

A. So, it would be a representation of the germ line sample.

Lymphocytes do contain some

rearrangements in immune associated genes. But they are commonly used in the analysis of cancer because they are an easy to obtain sample.

And to the best of my knowledge for bunker genes and tumor suppressor genes, other cancer related genes, there aren't substantial modifications that occur in the formation of lymphocytes, modifications to those genes.

Q. When Newman performed sequencing on the GBM relapse and PBL samples, we don't know if Newman did it as 100 X or 150 X, correct?

MR. KRAUSE: Objection to form.

BY MR. LUMAN:

Q. Let me ask it differently, I don't think that is a good question.

So, when Newman performed sequencing on the GBM relapse and PBL samples, we don't know if the read length was 100 or 150, right?

A. So, I'm not sure. I believe I quoted 150 because there was -- well, strike that.

I would have to go back and actually

read the reference. But one doesn't -- I don't know sitting here today whether it was 150 bases or 100 bases that Newman read in this particular example.

But, you know, one of ordinary skill in the art would understand that one could -- if one fell below this 12 gigabyte threshold that appears in Claim 1a, that as the patent instructs us, that sequencing could be performed on molecules from at least one biological sample so that one could simply sequence additional samples to rise above the, the threshold of 12 gigabases.

So, I provide a calculation down below that simply shows that combining those two samples gives us greater than 12 gigabases of sequence.

Q. And so the, the first sentence where you are quoting from Newman is Exhibit 1043 and it is in the Online Methods.

MR. LUMAN: Let's pull that up. Can -- Henry can you pull up Exhibit 1043?

(Exhibit 1043 marked for

1 identification.)
2 BY MR. LUMAN:
3 Q. And the Online Methods --
4 A. Sorry, I don't have it yet.
5 Q. I'm going to have -- try and get it
6 on the screen, too, while you are downloading it.
7 MR. LUMAN: Henry, can you scroll
8 down on that. It is several pages down.
9 Keep going. It is near the end.
10 THE VIDEOGRAPHER: Oh, near the end.
11 Do you want to give me maybe a page number?
12 MR. LUMAN: The page numbers are
13 tough on this one because when they get into
14 the Online Methods, they don't have page
15 numbers. So --
16 THE VIDEOGRAPHER: No problem.
17 MR. LUMAN: We need to find -- let's
18 see.
19 THE VIDEOGRAPHER: Maybe if you can
20 tell me what you need I can find it. Online
21 Methods you are looking for, right?
22 So, that is Page 10 of the PDF.

MR. LUMAN: Can we start zooming in a little bit. Yeah, there we go.

Okay. Perfect. You've got it on the screen.

BY MR. LUMAN:

Q. Dr. Quackenbush, do you see the heading, Library Preparation and Sequencing?

A. I see where it says that, yes.

Q. And then, after Supplementary Figure 1a it says, "Sequencing was performed using 2 times 100 or 2 times 150 paired-end reads.

A. Yes, I do.

Q. That is the section of Newman that you were quoting in Paragraph 189 of your declaration. Correct?

A. Yes, I call that out. It is in library preparation sequencing of the Online Methods, so that is right.

Q. So, Newman does not specify whether the 100 read length was used or the 150 read length was used for the GBM samples, right?

A. I would have to read this further to understand. My -- I would actually have to spend some time reading this reference.

My guess would be that since this is one of the later samples in the analysis that was done, it was probably the 150.

But as, you know, I point out in Paragraph 189 of my report, that whether it was the 150, in which each individual sample was more than 12 gigabases, or if it was the 100, the combination of samples is greater than 12 gigabases.

One of ordinary skill in the art would simply understand that if one wanted to get greater sequencing depth, all one had to do was sequence more.

Q. And so, sitting here today, you don't know whether the GBM sample was sequenced at 100 read length or 150 read length; is that right?

A. So, I'm going to spend some time and look at the reference to see if there is anything

that would inform my answer.

So, in the Online Supplemental Methods, I can't find anything that provides that information. There are also a number of supplementary figures and tables which I don't have before me that may provide some additional information about the depth.

But, you know, as I wrote in my report, whether it is the 150, where each individual sample exceeds the 12 gigabase limitation in the claim, or the combination of samples, which exceeds 12 gigabases, one of ordinary skill in the art would have known that to get greater sequence depth, all one would have to do is generate more sequence reads.

Q. A 150 base pair read is 50 percent longer than a 100 base read, right?

A. Yes, it is. But again, one of ordinary skill in the art would have understood that to get greater sequence depth, and greater total sequence -- greater total amount of sequence, all one would have to do is sequence

more.

Q. So, the 150 read length would generate 50 percent more data than the 100 base pair read length; is that right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, 150 base pair read length absent any other considerations would generate 50 percent more data.

But again, one of ordinary skill in the art would have understood that to generate more sequence data, one would only have to run the sequence -- run the sequencer with some additional samples or load more sample into the flow cell.

BY MR. LUMAN:

Q. If a person of skill in the art were choosing between a 100 base pair read length and a 150 base pair read length, is there anything they would have to take into consideration on costs?

Is there a difference in cost between those two?

A. The difference in cost was -- I would have to look back at the cost of Illumina kits. The difference in cost would have been minimal to run 150 base pairs.

I believe this is at a time when Illumina was improving their kits at a pretty rapid rate.

And, you know, even looking back at the table that I excerpted into Page 98 of my report at Paragraph 189, you will see there were -- there are many samples that had far greater total numbers of reads including some cell line data, some cell-free DNA data, some spike in experiments.

So, one of ordinary skill in the art would have really easily understood that generating more data was something that could be accomplished without great effort.

Q. Is there a difference in cost per gigabase when you are sequencing at a 2 times 100 read length versus a 2 times 150 read length?

MR. KRAUSE: Objection to form.

THE WITNESS: I don't recall the cost of the kits that were provided. I think they were roughly comparable. It was really just an improvement in Illumina's overall reaction protocols.

So, the library preparation would have been the same. You load the kit onto -- you load the libraries onto the sequencer. And I believe the cost of the 150 base pair and 100 base pair kit were comparable, but sitting here today I couldn't tell you what they were.

BY MR. LUMAN:

Q. Did the longer read length of 150 cause any phasing problems on an Illumina sequencer?

MR. KRAUSE: Objection to form.

THE WITNESS: Sitting here today, I couldn't tell you. I believe that when the kit was released, it was optimized. And that Illumina felt that it was a kit that would meet its standards of accuracy. I forget

what they quote as their sequence accuracy.

But I believe it would have met their, their advertised accuracy and likely wouldn't have caused any great problems.

BY MR. LUMAN:

Q. How about length of time? Does it take longer to sequence at 2 times 100 than to sequence at 2 times 150 read lengths?

A. So, when we look at time, time is -- the time of each individual step is -- can't be thought of alone, right.

If you think about this process in running a diagnostic, you go from sample collection to library preparation, to sequencing, to downstream analysis.

I can't tell you, sitting here today, in 2016 how long it would take the Illumina sequencer to run.

There would be imaging 150 bases. And when I say imaging, the Illumina sequencer uses an imaging protocol to collect data on the sequence.

So, collecting an additional 50 images would have added some time, but it wouldn't have increased the sequencing time by 50 percent because there are many other elements of sequencing that are involved.

And it likely would have had a small impact on the overall entire diagnostic workflow.

So, I mean it -- there would have been some marginal difference in time.

But again, you know, a person of ordinary skill in the art would recognize that one could have carried out these assays using commercially available kits, and that one could adjust the number of gigabases of sequence generated by making very simple changes in laboratory protocols.

Q. And you would agree that if, if the person of ordinary skill in the art chose to run the sequencer at the 2 times 150 read length, then they would only be able to sequence fewer samples per unit of time than if they had chosen the shorter 100 base pair read length. Right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, the amount of time the sequencer runs is typically not the rate limiting step in the process.

The way these assays tend to get run is a technician will set them up late in the day and run them overnight. And they would come in the next morning.

We had an Illumina sequencer that -- in the Center for Cancer Computational Biology at Dana-Farber -- first an Illumina GA II and then an Illumina HiSeq.

And as we increased the read length given the Illumina kits, there was basically no substantial change in our overall data generation workflow, largely because these samples do get run overnight.

MR. LUMAN: So, we have been going for a while. Would it be a good time to take a break?

MR. KRAUSE: Works for us.

THE WITNESS: I would be fine with

that.

THE VIDEOGRAPHER: All right, the time is 11:24 a.m. Off the record.

(Recess taken -- 11:24 a.m.)

(After recess -- 11:37 a.m.)

THE VIDEOGRAPHER: The time is 11:37 a.m. We are back on the record.

BY MR. LUMAN:

Q. Dr. Quackenbush, before the break, we have been discussing the costs of sequencing of 100 read length versus 150 read length. And some of the answers that you had provided were in the context of the cancer center at the Dana-Farber Institute.

I would like to focus on a clinical laboratory setting. And so my question is, would the time for running a sequencing assay at 100 versus 150 read length have any importance in a clinical laboratory setting?

A. You would have to ask a clinical laboratory director. My assessment as a person of ordinary skill in the art, as of 2016, is that

any impact would have been minimal.

The time it takes to run a sequencer is really a small part of the entire laboratory process.

I know for some clinical labs it can take weeks to produce a result, and the time it takes to run a sequencer is generally small.

From my interactions with clinical laboratories, most of them, to the best of my knowledge, run their sequencers overnight. And the slight difference in the time of running the sequencer wouldn't have a major impact on the overall process that runs from collecting samples to producing reports.

Q. So, I would still like to look in Newman. This is Exhibit 1043.

And let me do a little bit of orientation on the parts of Newman and then I will ask the question.

A. All right.

Q. Can you let me know when you've got Newman handy and let's turn to Page 551.

A. All right. I am on Page 551.

Q. And in the right-hand column there is the heading, Detection Limit.

Do you see that?

A. Yes, I do.

Q. And then on the next page, still under that heading, it talks about Figure 5a. There is like a -- it kind of splits up. It talks about Figure 5a there.

A. Oh, I'm sorry. Let me go to the next page. Figure 5a and Supplementary Figure 12a and b, yes.

Q. I'm still on the orientation then.

If we go to the next page, Page 553, there we do have Figure 5.

And do you see down underneath Figure 5, there is the heading, Ultrasensitive ct Monitoring?

A. Ultrasensitive ctDNA Detection and Monitoring.

Q. Yes. Thank you.

A. Yes.

Q. And then underneath that heading there is a discussion of some different portions of Figure 5. There is a discussion there of Figure 5b, and Figure 5c and Figure 5d, all under that heading.

Do you see that?

A. Yes.

Q. Okay. So, I would like to now look at Figure 5. And let's -- I want to see what parts of Figure 5 relate to different things so I will do the question.

The question is, so, Figure 5a is in the caption. And it says Figure 5a is the ctDNA detection limits using a hypermutated GBM tumor mixed into the normal control. Do you see that?

A. Yes, I do.

Q. So, Figure 5a relates to the GBM tumor sample, right?

MR. KRAUSE: Objection to form.

THE WITNESS: Would you repeat the question, please?

BY MR. LUMAN:

Q. Yes. Figure 5a is providing data for the GBM tumor sample, right?

MR. KRAUSE: Same objection.

THE WITNESS: So, I'm not sure that is fully accurate. You referred back to Page 551. In the section that says, "Detection Limit of iDES-enhanced CAPP-Seq."

So, just for orientation, iDES is the Integrated Digital Error Suppression Method. They describe -- which is part of their cancer personalized profiling by deep sequencing CAPP-Seq.

And this is an experiment designed to understand what the detection limits might be for this iDES-enhanced CAPP-Seq method.

So, what they tell us on Page 551 on the right-hand side near the bottom, "To establish the detection limit of iDES-enhanced CAPP-Seq, we designed a personalized selector covering 1,502 non-synonymous mutations identified by exome sequencing of a glioblastoma multiforme

tumor."

And then they created a series of DNA spiked mixtures. So, this is a glioblastoma.

Since you were asking earlier about the table that appeared in my report and also in the supplemental materials for this, I'm not sure if it was the same. It may have been a different one. I would have to read further to understand this.

As they tell us on Page 551, this is -- they created a series of 32-nanogram DNA mixtures, in which the GBM DNA was spiked into healthy control cell-free DNA in defined proportions down to 2.5 times 106 molecules.

So -- and then they assessed reproducibility. So, my best read of Figure 5 is this an analysis of the synthetic construct they made to assess detection limits.

And they are comparing their method, the iDES method to methods that include

1 polishing bar coding or bar coding and no bar
2 coding or polishing.
3 BY MR. LUMAN:
4 Q. Let's turn back to your declaration,
5 Exhibit 1061. And would you please turn with me
6 to Paragraph 198.
7 A. All right.
8 Q. And you talk about Newman disclosing
9 a 157 kilobase selector.
10 Do you see that?
11 A. I see where it says that, yes.
12 Q. And how is it that the 157 kilobase
13 selector meets the limitation from 1e about
14 sequencing at a coverage of 175 kilobases or
15 less?
16 A. So, the simple read of this is
17 that -- and I believe this is correct -- that
18 Newman's 175 kilobase selector is the capture
19 panel they designed.
20 I believe it targets a region in
21 genes that has a total length of 157 kilobases.
22 And so, the claim language says

subjecting said sequencing library to sequencing at a coverage of 175 kilobases or less.

So, 157 kilobases is less than 175 kilobases.

Q. And so the 157 kilobase selector has to capture by hybridization --

What does it have to capture in order to meet the 175 kilobase or less limitation?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I'm not sure what you mean by meets the limitations in this context.

This is -- Newman is a prior art reference. And Newman on Page 548 tells us that they applied a redesigned CAPP-Seq selector, i.e. a capture panel, to maximize the number of mutations per, in this case, non-small cell lung carcinoma, NSCLC, patient while minimizing panel size and sequencing cost.

So, you know, this speaks to what we

1 were discussing earlier about the importance
2 of trying to do, use a targeted approach.
3 I believe that when Newman refers on
4 page -- I can't see the page number. But
5 when Newman refers to the personalized
6 selector, they say we designed 157 kb
7 personalized selector to cover these
8 mutations.
9 It is 1,500 mutations found in a
10 glioblastoma. Employing the same
11 biotinylated oligonucleotide synthesis
12 processes described for the non-small cell
13 lung carcinoma selected for the design above,
14 that they were targeting 150,000 base pairs
15 of sequence within the genome.
16 And that 150,000 base pairs, as a
17 selector, would be, as I state in my report,
18 a method that would generate sequence over
19 157,000 base pairs, which is smaller than the
20 175,000 base pairs that is specifically
21 called out in Claim 1e of the patent.
22 BY MR. LUMAN:

Q. How does Newman's 157 kilobase selector result in sequencing at a coverage of 175 kilobases or less?

A. If the sequencing covers 157 bases of the genome, -- 157,000 bases of the genome, that is a coverage of less than 175,000 kilobases, right.

The coverage is the region of the genome. In reading this, the coverage is the region of the genome that is sequenced.

And so, the claim says subjecting said sequencing library to sequencing at a coverage of 175,000 kilobases or less.

So, sequencing 157 kilobases of genomic area is less than what is called out in the claim.

Q. And what if the capture panel pulls down a region of the gene that is longer than -- in totality that is longer than 157 kilobases; is that possible?

MR. KRAUSE: Objection to form.

THE WITNESS: There are lots of

1 things that are hypothetically possible.
2 The sequencing process would involve
3 sequencing and analysis. And so, the region
4 that they are targeting is substantially
5 smaller than 175,000 bases.
6 And so, they are disclosing the use
7 of a selector to do sequencing of that -- of
8 that region, right.
9 Other experimental noise that might
10 factor in is irrelevant.
11 One skilled in the art would also
12 know that one could target a smaller number
13 of mutations. In this case they targeted for
14 their 157 kb set of mutations, almost 1,500
15 coding mutations that had been discovered
16 previously.
17 So, depending on the application,
18 this is typically at the high end -- it is
19 way at the high end of what one would
20 generally try to profile.
21 Yeah, it is going to depend on
22 whether your application is discovery driven

1 or potentially driven by some criterion in a
2 clinical trial or by offering a clinical
3 assay.
4 In the work I did in the company
5 GenoSpace that I founded, we worked with a
6 lot of clinical laboratories. And their goal
7 was to identify the number of actionable
8 mutations that they would report on.
9 And for any individual tumor type,
10 those that were linked to a therapy, you
11 could typically count on one or two hands.
12 So, you know, this is sort of the
13 extreme. But even in this extreme, the
14 region they are targeting is smaller than 175
15 kilobases.
16 BY MR. LUMAN:
17 Q. So, when Newman runs the experiment
18 for using this personalized selector, 157
19 kilobases, he runs it and it interacts with sheer
20 DNA.
21 And the sheer DNA that is pulled
22 down could be, in totality, quite a bit larger

than 157 kilobases, right?

MR. KRAUSE: Objection, form.

THE WITNESS: Sorry, can you repeat that, please?

BY MR. LUMAN:

Q. So, Newman uses the 157 kilobase selector on tumors, GMB tumor sample that the DNA has been sheared into many different fragments.

And the fragments that are pulled down by the 157 kilobase selector, they could in totality add up to much more than just 157 kilobases because the size of the fragments could be much -- each fragment pulled down could be more than what is one of the capture probe's length, correct?

MR. KRAUSE: Objection, incomplete hypothetical. Calls for speculation.

THE WITNESS: So, first, I don't believe the DNA was sheared. There is sequencing circulating tumor DNA.

Circulating tumor DNA is fragmented. The average size of a DNA fragment is about

160 bases, although there is a distribution in that size.

What Newman is targeting is 157,000 bases. And what I am sure Newman is analyzing is those same 157,000 bases when the sequence is generated and mapped to the reference.

So, again, recall that this is an example with 1,500 mutations which is far larger than what would typically be profiled.

And, you know, one skilled in the art would understand that 157,000 base selector could easily be reduced in size depending on the application.

But, irrespective, the -- this is the region that they were targeting. Hypothetically, there could be something else there. But, you know, the goal here was really to sequence 157,000 bases.

MR. LUMAN: Could we turn to Exhibit 1043, which is Newman. I would like to go to the last page of Newman. And if you

1 could zoom in on the right column a little
2 bit more.
3 The paragraph that starts with
4 Based.
5 BY MR. LUMAN:
6 Q. It says based on our modeling, they
7 used a glioblastoma GBM tumor and they applied a
8 selector to the GBM tumor.
9 That doesn't say -- Dr. Quackenbush,
10 that doesn't say they applied the 157 kilobase
11 selector to fragmented circulating tumor DNA,
12 correct?
13 A. So, you are right. I may have
14 misremembered pieces of this. But now it is
15 coming back to me.
16 So, it says, "Based on our modeling
17 and given considerations of cost and molecule
18 recovery, we used a glioblastoma tumor that was
19 found to harbor 1,500 coding mutations by whole
20 exome sequencing," and that data is provided in
21 Supplementary Table 2.
22 So, I believe that those are

Rows 286 and 287 that we referred to with tumor and the control where over 100 and -- or over 12 gigabases of initial sequence data were generated.

Based on the analysis, they then designed a personalized selector to cover these mutations. And that personalized selector selected the region of 157,000 base pairs.

And they use the same process described for their non-small cell lung carcinoma selector designed above, so you can go back and look at that.

They then applied the selector to perform deep resequencing of the GBM tumor, so they did a resequencing.

And I provide an analysis of how much data came out of that in terms of total sequence reads and confirmed it.

And then they performed the dilution series, the synthetic series in -- described in the next paragraph.

And this was the graph, the

1 sensitivity analysis that they had done that we
2 were talking about earlier in Figure 5.
3 So, they applied this 157 kilobase
4 selector both to DNA from the GBM tumor and then
5 to this model of cell-free DNA where they spiked
6 in DNA fragments from the GBM into the
7 circulating, into the cell-free DNA from a
8 healthy control.
9 So, there are actually multiple
10 sequences that are described here. And initial
11 whole exome sequencing of the GBM of resequencing
12 of the 157,000 bases of the GBM tumor to validate
13 the mutations.
14 And then the spike in the experiment
15 to look at sensitivity described in, presented in
16 Figure 5.
17 Q. Do you know the length of the DNA
18 molecules that were captured by the 157 kilobase
19 personalized selector that Newman used?
20 A. I don't think that information is
21 provided. But the goal was to target 157,000
22 base pairs that contain 1,500 mutations.

1 And again, as a prior art reference,
2 it would have been obvious to one skilled in the
3 art that 1,500 is a large number of mutations.
4 That it was used really in this sensitivity
5 analysis.
6 And that by decreasing the number of
7 coding mutations one was targeting, one would
8 fall well below the 157,000 base pairs that
9 Newman targeted.
10 Q. Let's go back to your expert report
11 which is, your expert declaration, Exhibit 1061.
12 A. All right.
13 Q. I would like to look at the
14 paragraph right above what we were looking at,
15 Paragraph 197. Can you let me know when you
16 arrive there?
17 A. Yes, I am.
18 Q. I want to clarify. You cite the
19 median depths of 62 and 65. And there is a
20 citation to Exhibit 1045 with Rows 286 and 287.
21 Do you see that?
22 A. Yes, I do.

Q. And Row 286 is the -- I just want to clarify -- that is the GBM relapse sample, right?

A. I included that table in my report. And if I recall correctly, that is the relapse sample.

Q. Yes. Row 287 is the GMB PBL sample, right?

A. That is the peripheral blood lymphocyte sample that was used as a control to identify the primary -- it uses a control to identify these 1,500 mutations.

Again, that is what I recall from the table. I'm trying to find it in my report, I'm not sure where it appeared.

Q. It is in Paragraph 189.

A. Okay.

Q. Just to keep the record clear, Row 286 is the GBM relapse sample, right?

A. Yes, according to the table, it is the GBM relapse.

Q. And 287 is the GBM PBL sample, right?

A. Yes.

Q. Let's put that declaration aside and turn to your other declaration. Exhibit 1021 from the IPR on the '783 patent.

I'd like to go to Paragraph 117.

A. Exhibit 1020?

Q. Yes.

A. Okay.

Q. And I will just state for the record we are now looking at Exhibit 1020 from IPR 2023-00545.

A. Regarding the '783 patent.

Q. Yes.

A. Thank you.

Q. And would you let me know when you arrive at Paragraph 117?

A. I am there.

Q. This is the -- this paragraph recites Subpart 4 of Claim Limitation 1a and it has got a variable portion and a fixed portion.

Do you see that?

A. I see where it says that, yes.

Q. And then in Paragraph 118 and 119, you provide a discussion about the variable portion.

Do you see that?

A. Yes, I see that.

Q. So, what is your understanding of what the variable portion recited by Limitation 1a, what does that mean? What is a variable portion?

A. So, this is referring to Subpart 4 of Claim 1 of the '783 patent. Subpart 4 of Claim 1a which says, "Further, wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising at least one variable portion from a result of said sequence data, and at least one fixed portion independent of said result of said sequencing data."

So, as I write in Paragraph 118, Ley's personalized probe set comprises nucleic acid probe molecules, in this case PCR primers, that are directed to the genes described on the

1 personalized tumor panel.
2 And, I refer you to Ley where he
3 talks about the putative variants that were
4 found.
5 Such PCR probes by their nature
6 contain oligonucleotide-directed genomic content,
7 specifically oligonucleotide sequences that
8 base-pair or hybridize to their complementary
9 sequences, right.
10 And then go on to talk about the
11 variable portions in Paragraph 119, where Ley
12 detected and targeted single-based changes, none
13 of which, as Ley says, has previously been
14 detected in an AML genome.
15 And in addition to those, Ley
16 targeted two other genes BRCA1 and BRCA2. And
17 then in Figure 3 -- I don't have Ley in front of
18 me, but this appears on Page 78.
19 What this shows is data from the
20 primary tumor, the relapsed tumor in the skin.
21 And you can see that in the first --
22 I believe, in the first ten genes that Ley

1 targeted, these are the ones that he found to be
2 variable in his analysis between skin and tumor.
3 Q. And so, that is a discussion about
4 what Ley discloses. And before we can talk about
5 whether Ley discloses something that meets a
6 variable portion, you have to know what a
7 variable portion is.
8 That is the order of analysis.
9 So, we have to back up and first
10 understand what you believe variable portion
11 means.
12 So, what is your understanding of
13 what a variable portion is?
14 A. So, my understanding is that in
15 interpreting the claims of the patent -- of a
16 patent, what one should do is look to the
17 specification of the patent to understand what
18 the inventors believed that they have invented.
19 And if we look back at Column 8, the
20 variable portion is actually defined in a variety
21 of different places.
22 And so in Column 8 at Line 3, it

1 begins, "In some embodiments at least one
2 variable portion corresponds to potential
3 neoantigen causing genetic variance of the
4 subject."
5 And then goes on, "Wherein the at
6 least one fixed portion corresponds to -- " and
7 then list: cancer driver genes, genes involved
8 in pharmacogenomics, genes involved in Mendelian
9 immunological diseases, genes related to
10 inherited forms of cancer and so forth.
11 The next paragraph on Line 14, "In
12 some embodiments, at least one variable portion
13 corresponds to genetic variants responsible for
14 Mendelian phenotypes of a proband."
15 And then it goes on to contrast that
16 with a fixed portion.
17 And then in Column 18. Let's see if
18 we have arrived there yet. "In some embodiments
19 the oligo-directed genomic content of the second
20 assay comprises," and this is a variable portion
21 selected for the second assay, "at least one
22 variable portion based on results from the first

assay."

So, you will recall that Ley does a whole genome sequencing analysis of -- the cancer in this case it is an acute myeloid leukemia, AML.

And then uses skin as a reference.

And identifies eight -- eight or 10 -- I forget the number, but identifies a set of genetic variants that had not previously been seen before.

So, as Ley describes in Paragraph 18, right, these, the variable portion is defined based on the results of the first assay. And this stands in contrast to the fixed portion which are genes known to be involved in cancer.

And, I believe the two genes that Ley included, that are well known to be involved in cancer, in his second assay were TP53, sort of the canonical cancer gene, and BRCA1.

It could be BRCA2, but one of the BRCA genes that again is known to be involved in

1 cancers.
2 So, the variable pieces are the
3 pieces as we are told in Column 18. The variable
4 portion is defined based on the results of the
5 first assay. And that is in contrast to the
6 known cancer driver genes.
7 Q. And you pointed me to the
8 specification to talk about the meaning of
9 variable portion.
10 Have you seen the term, variable
11 portion, in connection with nucleic acid probe
12 molecules been used in the prior art literature?
13 MR. KRAUSE: Objection to form.
14 THE WITNESS: I'm sure that phrase
15 appears somewhere in different applications.
16 Again, what is important in
17 interpreting these claims is what the
18 patentee teaches us they mean by variable
19 portion and fixed portion.
20 So, the best place I can turn to
21 understand what that, the patent owner means
22 is to look at what is disclosed in the

1 written description of the patent.
2 And, you know, Column 18 very
3 clearly states at least one variable portion
4 defined based on the results of the first
5 assay and at least one fixed portion
6 independent of the results of the first
7 assay.
8 So, as we are told earlier that
9 independent -- or that fixed portion would be
10 known oncogenes and tumor suppressor genes as
11 an example. And there is a longer list but
12 it would include those, like TP53 and BRCA1.
13 BY MR. LUMAN:
14 Q. So, you mentioned the fixed portion.
15 To understand the meaning of fixed
16 portion, do we need to turn to the specification
17 to interpret what that means?
18 A. So, my understanding of how one
19 interprets a patent is that if the term is
20 presented and it is not a term with an
21 unambiguous description to a person of ordinary
22 skill in the art, that the best way to interpret

it is to look at the context of the patent.

In this case, that would mean looking at the written description.

So, here the patent owner, you know, very clearly lays out the -- what a variable portion is and contrasts that with his definition of what a fixed portion is.

Q. If you would turn to Paragraph 260 in this declaration with me, please.

A. I'm sorry. It is BRCA2, not BRCA1.

So, we are in declaration, Exhibit 1020?

Q. Correct. 1020, Paragraph 260.

A. All right.

Q. And Paragraph 260 is in the section where you talk about Limitation 1c, right?

A. So, you will recall in this declaration I provide a number of different grounds for obviousness or anticipation.

This is in a section entitled Ground 3, Obviousness over Forshew in view of Dawson.

And in the context of that argument, Paragraph 260 appears in a section in which I am describing my analysis of Claim Element 1c.

Q. And we can see the language from Limitation 1c is that bolded language above Paragraph 260.

Do you see that?

A. Right. Starting on Page 115.

Q. Yeah. And Limitation 1c includes -- let's see.

It says, "To identify a presence or absence of at least a subset of said genetic variants."

Do you see that?

A. I see where it says that, yes.

Q. Now I'm looking at figure, Figure 4D, which is reproduced there in Paragraph 260.

Do you see at the bottom there is, there is the yellow line with stars on it? That is the ADAMTS1 line. Do you see that line?

A. Yes, I see that.

Q. And, like before Day 200, there is a point -- a day that has a fraction of mutant allele of something around 10-3. Do you see that?

A. Yes, I see that.

Q. Is that fraction of a mutant allele a presence or is it an absence of the ADAMTS1 mutant allele?

A. So, I believe this is a figure from the Forshew reference. And this is, if I recall correctly, since I don't have the reference -- maybe I do have it. No, I haven't provided it.

So, this is a figure from the Forshew reference. And I believe there, this is one individual patient. If I recall correctly they are monitoring the presence or absence of tumors in circulating cell-free DNA.

And they are detecting the presence of a mutation in this one individual, in the ADAMTS1 gene, along with other mutations.

And that it appears, based on my read of this graph without the paper in front of me, to be about one molecule out of 1,000, down

at 10-3.

So, in this case they are detecting a very low presence of this gene as well as with the other genes, consistent with the tumor having responded to the initial course -- excuse me -- the initials course of therapy.

And I don't recall -- sorry -- excuse me.

Responding to the initial course of therapy. And then after about 400 days, detecting a relapse. And then beyond 400 days, about 500 days, detecting response to second line therapy with a decrease in the presence.

So, in this case, I would say the ADAMTS1 variant was detected at a very low frequency, but its presence was detected.

Q. And same question with the dark blue line. The dark blue line with the circles on it. That is K -- that is the second one from, on the legend, it is the second one up from the bottom.

A. Yes, KIAA0406.

Q. Yeah. Do you see at the time point,

1 right before 200, it is kind of overlapping with
2 the yellow star one.
3 At that point is that a presence or
4 an absence of the KIAAO406 mutation?
5 A. So, in this particular individual,
6 like with the last example, the KIAA0406 mutated
7 allele was identified at a very low frequency --
8 about one molecule out of 1,000 -- indicating
9 that this person still had some residual disease.
10 If the person were cured, one could
11 also imagine that dropping to zero, being
12 undetectable.
13 Q. And so, it is it is your opinion
14 that this patient has identified the presence of
15 the ADAMTS1 and KIAA0406 mutations; is that
16 right?
17 A. So --
18 MR. KRAUSE: Objection to form.
19 THE WITNESS: Excuse me, Andrew.
20 You were going to say?
21 MR. KRAUSE: I will make it clear
22 for the record. Objection to the form of the

1 question.
2 THE WITNESS: So, in this single
3 individual -- and, again, I don't have the
4 reference in front of me.
5 But, in this single individual, all
6 of these variants were detected in the
7 original disease.
8 They were detected at lower levels
9 in response to the therapy and they declined
10 through therapy.
11 And then they increased. So, in
12 this individual, based on their own response,
13 their presence was detected, but one skilled
14 in the art would know that if this individual
15 was cured of the disease, or if the molecular
16 characteristics of their disease somehow
17 changed, that one might, in fact, detect the
18 absence of these markers.
19 BY MR. LUMAN:
20 Q. So, in the context of Limitation 1c,
21 when you see the to identify language, that means
22 that you have to identify a presence or an

absence of a genetic variant.

Is that right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, you know, I'm not sure what you are asking. The claim language says, "Subjecting said sequencing library to sequencing to identify the presence or absence of at least a subset of said genetic variants and at least said additional biological sample."

So, we are looking in an additional biological sample. So, the original sample is taken at Day 0. There are multiple individual additional biological samples.

In this case the mutations that were found, right, the genetic variants that were found in the original sample are also found at later time points.

And that indicates that in this individual there was still some residual disease.

So, Forshew -- and again, I think

this is from Forshew. Forshew clearly shows that they can detect the presence of these variants in the individual as residual disease.

But one skilled in the art would also understand that if this individual had been cured, and this is just one example, if this individual had been cured then one would potentially detect the absence of all of these variants.

BY MR. LUMAN:

Q. So, yeah, let me ask a more pointed question. Do you see in Limitation 1c the language, "to identify"?

What was your understanding of what it means to identify something in the context of this claim language?

MR. KRAUSE: Objection, asked and answered.

THE WITNESS: So, farther up in my report, I provide the entirety of Claim 1.

And Claim 1 is fairly long. It has

1 D parts. And it is a method for personalized
2 genetic testing comprising.
3 And then Part A talks about
4 attaining a personalized probe set for a
5 subject, which personalized probe set
6 comprises a plurality of nucleic acid probes,
7 and then it lists characteristics of that
8 probe set including some of the things we
9 talked about earlier, namely a probe set that
10 includes or targets a variable portion and a
11 fixed portion.
12 And then Claim D is using said
13 personalized probe set to selectively enrich
14 or amplify sequences comprising said set of
15 genetic variants over other sequences in at
16 least in additional biological sample from
17 said subject to generate a sequencing
18 library.
19 And then in Step C, subjecting said
20 sequencing library to sequencing to identify
21 the presence or absence of at least said
22 subset of said genetic variants.

So, we identify genetic variants -- I'm sorry. We construct a personalized probe set. And then we target samples from -- or we use it to probe samples from that individual.

And then we -- to selectively enrich or amplify sequences from a number of samples from that individual. And then use sequencing to detect the presence or absence of at least said subset of said genetic variants.

So, in this section as I talked about earlier, I was laying out my analysis of obviousness in Ground 3 which was Forshew in view of Dawson.

And I believe the analysis I'm presenting in the paragraphs we have been discussing, all refer to what was presented in Forshew is at least in this graph.

And that Forshew is detecting, in this case, the presence of all of these different variants.

1 But again, in presenting this
2 argument of obviousness I'm looking at two
3 references and also using my understanding of
4 a person of ordinary skill in the art.
5 And a person of ordinary skill in
6 the art would understand that an assay could
7 detect either the presence, which my best
8 interpretation of this graph is that we are
9 seeing the presence of all of these variants.
10 Or, if the disease had been cured in
11 this case, because I believe this is a
12 cancer, the absence of those same mutations.
13 So, in this case I would say you are
14 identifying the presence. But, one skilled
15 in the art would also know that one could, in
16 a different individual with a different
17 response to therapy, identify the absence of
18 those same variants.
19 BY MR. LUMAN:
20 Q. So, I had asked what to identify
21 means and you took me on a tour of all of the
22 claim language.

But, let's focus on "to identify."

And you had just mentioned that -- it sounded like you were equating "to identify" with "to detect."

Is that fair or were you -- is that not what to identify means?

MR. KRAUSE: Objection to form.

THE WITNESS: So, you know, again my understanding is that this claim should be read in its entirety and shouldn't be taken out of context. All right.

So, we are identifying something in a sequencing library. That sequencing library comes from somewhere. It comes from a selection of personalized probes that in Step B is used to create a sequencing library.

And that is when personalized probes is selected based on the -- based on the criteria laid out in Claim Element 1a.

The plain language of Claim 1c says, "Subjecting said sequencing library," okay,

so we are going to take the sequencing library, "to sequencing," so it is going to be sequenced, "to identify a presence or absence of at least a subset of said genetic variants, in at least said additional biological sample from said subject." Right.

And then it talks about the sequencing footprint.

So, we are going to identify, identify what, the presence or absence of at least said subset.

That is going to require -- that is going to require both the identification of the individual variants that were targeted and then assaying their presence or absence based on the available data.

And so what Forshew is showing in Figure 4d is, to the best of my recollection in reading this graph, data that shows the presence.

But then, again, one of skill in the art would also realize that one would also

identify in an individual that had been cured the absence of these very same markers.

BY MR. LUMAN:

Q. So, in order to meet this claim limitation, first you have to identify the individual variants and then assay their presence or absence. Is that right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, we are not talking about infringement here. So, I can't offer an opinion on what it would take to meet the claim limitation.

But rather what we are doing is really looking at this in the context of whether or not this is -- this claim is obvious, given Forshew and Dawson, and what one of ordinary skill in the art would understand.

And so, in looking at Figure 4d, it is very clear that in the additional biological sample, Dawson -- or Forshew has identified the presence of genetic variants

and reports those out.

And the presence of those genetic variants, their relative representation changes over time indicating the natural history of the disease.

So, you know, reading this claim, it is very clear that the claim is obvious in light of Forshew. That at least this claim element is obvious in light of Forshew.

And that the entire claim is obvious in light of Forshew and Dawson and the understanding of a person of ordinary skill in the art.

BY MR. LUMAN:

Q. So, you have to understand the first step in an obviousness analysis is to determine what the claim means.

And you just told me that you couldn't offer an opinion on what it would take to meet the claim limitation. And I don't want to leave the record like that.

I would like you to tell me what you

interpret the claim language that says, "to identify a presence or absence of at least a subset of said set of genetic variants."

What does that mean?

MR. KRAUSE: Objection. Testifying. Asked and answered. And form.

You can answer the question, Dr. Quackenbush.

THE WITNESS: So, again, you are asking me to read a portion -- one phrase out of the claim without the context of the rest of the claim language.

So, you know, Claim 1a discusses the selection of a personalized probe set. And that personalized probe set is selected based on a number of criteria that are laid out in Claim Element 1a. So --

BY MR. LUMAN:

Q. I don't want to take this language out of the context of the claim. I agree. The context of the claim as a whole is important.

But when we get down to figuring out

what the language in Limitation 1c means, what is your understanding of what it means to identify a presence or absence of at least a subset of said set of genetic variants within the context of all of the claim language?

MR. KRAUSE: Same objections.

THE WITNESS: So, in the context of the entire claim, the claim is obvious in view of -- based on Forshew in view of Dawson.

BY MR. LUMAN:

Q. But, that is obviousness --

A. Because, because they disclose all of the claim steps.

So, I can take you through the analysis of Claim Element 1a. And I present that over multiple pages.

I also then -- so, I talk about in -- my analysis in Claim Element 1a, how Forshew describes obtaining a personalized probe set for a subject and the criteria that were used.

1 I talk about, you know, Forshew's
2 TAm-Seq method. How Forshew discloses selecting
3 his probe set PCR primers using a program called
4 Primer3. How he used the cosmic database, which
5 is a database of human cancer sequences to select
6 some of the polymorphisms and how he selected
7 others.
8 In this -- and, again, this goes on
9 for many pages where we can discuss how Forshew
10 renders this obvious in detail.
11 If we come down to Claim Element 1b,
12 right, this discusses using said personalized
13 probe set to enrich or amplify sequences in at
14 least an additional biological sampling
15 generating a sequencing library.
16 Again, I point to Forshew. There is
17 a really nice diagram in Forshew that discusses
18 or provides an overview of their protocol.
19 Step C, "Subjecting said sequencing
20 library to sequencing to identify the presence or
21 absence of at least a said subset of genetic
22 variants."

1 And so, what Forshew does is Forshew
2 sequences the library. We can see that in the
3 figure on Page 115. And applies this to
4 additional biological samples. We can see this
5 in the figure on the bottom of Page 116.
6 And, in this case, since the person
7 still has residual disease and then relapses,
8 identifies at subsequent time points the presence
9 of genetic variants that appear in this one
10 individual patient.
11 But of course, if the patient were
12 cured, then Forshew likely would have also found
13 the absence.
14 So, my reading is that Forshew
15 renders this obvious because he, at the very
16 least, detects the presence of these genetic
17 variants which arose through the work that he had
18 done in generating these data.
19 Q. So, Dr. Quackenbush, that was
20 nonresponsive.
21 I had asked you what the claim
22 language means and you took me on a tour of the

prior art.

Before we can compare the prior art to the claim language, you have to understand what the claim language means.

So, what is your understanding of what Limitation 1c means when it says, "to identify a presence or absence of at least a subset of said genetic variants"?

MR. KRAUSE: Same objections.

THE WITNESS: So, I'm trying to be as clear as I can. Right.

My understanding is that to interpret these claims we have to take them as a whole. And we have to take them as a -- we have to, we have to interpret them in the light of what is in the written description and in light of what a person of ordinary skill in the art would have understood at the time this patent was -- as of the priority date of the patent.

So, the analysis I am performing here is an analysis on -- an analysis of

1 obviousness.
2 So, I can't set out the breadth or
3 width or length of what "to identify" might
4 mean in all possible contexts.
5 I can tell you that Forshew, in
6 Figure 4d and these additional biological
7 samples, which are part of Claim 1c, performs
8 sequencing on libraries that were generated
9 and identifies in his data, at the very
10 least, the presence of these different
11 variants.
12 So, one might interpret identify in
13 different ways. But, Forshew very clearly
14 finds these mutations.
15 And so, based on my read as a person
16 of ordinary skill in the art, Forshew renders
17 Claim Element 1c and 1d, which is report --
18 generating a report identifying a presence or
19 absence. Renders both of those obvious
20 because that is what Forshew does.
21 So, I can't, you know, testify as to
22 the extent of how one might interpret this.

But, very clearly, Forshew does identify the presence or absence of these variants.

MR. KRAUSE: We have been going about an hour and 15 minutes. Would this be a good time for a break?

THE WITNESS: Fine with me.

MR. LUMAN: I just want to clarify, I still feel that that answer was nonresponsive. But we can take a break.

THE WITNESS: All right. Thank you.

THE VIDEOGRAPHER: The time is 12:53 p.m. Off the record.

(Recess taken -- 12:53 p.m.)

(After recess -- 1:27 p.m.)

THE VIDEOGRAPHER: The time is 1:27 p.m. We are back on the record.

BY MR. LUMAN:

Q. Okay. I would like to talk about the Forshew reference.

MR. LUMAN: Can we put Exhibit 1030 on the screen? That is the Forshew reference.

(Exhibit 1030 marked for identification.)

BY MR. LUMAN:

Q. And, Dr. Quackenbush, I will let you download that. Can you let me know when you've got it available?

A. Sure. It hasn't appeared in -- oh, there it is. It just appeared in Box. And, it just popped open in Acrobat. So, I have it.

Q. We are looking at Exhibit 1030 which is Forshew. Dr. Quackenbush, this was a reference that you considered in rendering your opinions in these matters. Right?

A. Yes, I believe I referenced it in both of my declarations. Let me check. Sorry.

Q. This reference is something called TAm-Seq, right? Can we go to Page 1.

A. Yes, they have an application, Tagged Amplicon mutation Sequencing or TAm-Seq.

Q. And TAm-Seq is an acronym for Tagged Amplicon deep sequencing, right?

A. Yes.

Q. If you will turn to Page 10 with me. Would you look -- there is the first full paragraph on the left side that starts with the word, Using.

Do you see that one?

A. Yes.

Q. Okay. And it says, "Using standard amplification primers tailored to the mutation loci, we also use TAm-Seq to monitor the dynamics of ten mutations in plasma DNA of a single patient with metastatic breast cancer."

Do you see that?

A. I see where it says that, yes.

Q. And the breast cancer patient, that is one of the patients disclosed in Forshew that you relied on for part of your analyses, correct?

A. I don't recall exactly. If you can point me to where I discussed that in my report. I would be happy to refresh my memory.

Q. Okay. Let's try Paragraph 240 of your declaration. The Exhibit 1020 in the IPR for 2023-00545.

A. All right. I'm at Paragraph 240. I see. Yes.

Q. The patient with breast cancer from Forshew is a part of the Forshew reference that you rely on in rendering your opinions in these matters, right?

A. Yes, I disclose it or discuss it in my obviousness analysis in Ground 3 of Claim 1.

Q. So, back in Forshew on Page 10, we were just looking at that sentence about using standard amplification primers.

What is a standard amplification primer?

A. So, I'm not sure exactly how Forshew is using the term, standard, here. It says, "Using standard amplification primers tailored to the mutation loci, we also use TAm-Seq to monitor the dynamics of ten mutations in plasma DNA of a single patient."

So, there are -- they are amplification primers. They are tailored to the low side that are being analyzed. The TAm-Seq

1 protocol is being laid out, I believe, in
2 Figure 1.
3 But, the details of the primer --
4 like many modern papers in biology, this paper
5 has multiple supplements. And if you look at the
6 same page we were referring to, on the right-hand
7 column, there are supplemental materials.
8 And Figure S -- or, sorry.
9 Supplementary Figure 1, so Figure S1, has a PCR
10 strategy and primer design. Table S1 has target
11 specific primers.
12 So, to understand what he means
13 there, we would have to look at some of the
14 supplemental materials.
15 Q. Okay. And so maybe Table F7 would
16 be good because that is the one about the breast
17 cancer patient.
18 A. So, those are the mutations in
19 amplicons. That may have information about the
20 primers, I'm not sure. I don't recall all of
21 these supplements.
22 MR. LUMAN: Can we make Exhibit 1032

available to Dr. Quackenbush? You don't have to put it on the screen, but if you can put it in the room for him.

THE VIDEOGRAPHER: 1042?

MR. LUMAN: 1032. Here, let me upload it into the box.

(Exhibit 1032 marked for identification.)

MR. LUMAN: This 1032, Dr. Quackenbush, was not submitted with your declaration in this case. It was submitted in another case.

THE VIDEOGRAPHER: If you can put it in the box. I don't see it here.

BY MR. LUMAN:

Q. So, Dr. Quackenbush, without Exhibit 1032, which is the supplemental materials for Forshew, would you be able to answer my question about what a standard amplification primer is referred to in Forshew?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I might be able to

1 offer an opinion. I would want to read
2 Forshew in its entirety.
3 In presenting my analysis of this --
4 for example, in Paragraph 240, I really
5 didn't focus on the meaning of standard.
6 What I was doing is really using
7 Forshew to show the idea that -- to show that
8 the idea of designing patient specific sets
9 of primers, so a set of primers that are
10 tailored to mutational loci.
11 And then using those serially to
12 perform an assay to look for mutations and to
13 monitor the state of an individual's disease.
14 That that was something that Forshew
15 disclosed that renders Claim 1 obvious.
16 So, in particular, the argument I
17 presented was Forshew in view of Dawson.
18 So, I really didn't focus on
19 standard because it was -- it wasn't really
20 germane to the argument I was making.
21 BY MR. LUMAN:
22 Q. Uh-huh. And can you tell me what

standard means in this context? Why is -- what the word, standard, is being used for to modify the amplification primers that are used for the breast cancer patient?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I don't have the exhibit you were going to upload. As I said earlier, I would -- to understand -- or to try to understand what Forshew meant in this context, I would really want to read the paper in its entirety.

And I would want to go through the supplemental materials to try to see if there is some additional information there.

The word, standard, I could speculate on what he might have meant here. But it wouldn't be an informed -- anything I said wouldn't really be informed as to what Forshew may have meant.

BY MR. LUMAN:

Q. Uh-huh. Can you turn to Paragraph 256 in your Exhibit 1020 declaration on

1 the '783 patent.
2 A. So, 1020, what paragraph? 256?
3 Q. Yeah.
4 A. Okay.
5 MR. LUMAN: That is the -- that is
6 Paragraph 156. Let's try 256, please. Okay.
7 BY MR. LUMAN:
8 Q. In the first sentence you see it
9 says that "Forshew does not expressly disclose,
10 including PCR primers for sequences"?
11 A. I see where it says that, yes.
12 Q. So, we don't actually know what PCR
13 primers Forshew used for the breast cancer
14 patient. Right?
15 MR. KRAUSE: Objection to form.
16 THE WITNESS: So, I don't think that
17 is true, right.
18 As we were discussing earlier, on
19 Page 10 of Forshew, Forshew told us that
20 primers were designed -- I am trying to see
21 the paragraph.
22 He said, "Using standard

amplification primers tailored to the mutation loci, we also used TAm-Seq to monitor the dynamics of ten mutations in the plasma DNA."

So, Forshew clearly designed primers that targeted ten mutations. And he is using plasma DNA, so you can start to speculate about what some of the characteristics of the primer pairs might have been.

Table S1 has target specific primers. I don't have that in front of me. But, I am assuming the supplemental table may have those primers.

You point out also to Table S7. I don't know if that supplemental table has information.

But, as I point out in my report, it is clear that Forshew here is disclosing PCR primers for sequences that represent these variable sequences. Forshew doesn't explicitly talk about a fixed portion of his target set.

But it would have been obvious to one skilled in the art that one could do that.

BY MR. LUMAN:

Q. You keep mentioning the tables, Figure S1 and some of the tables in the supplemental materials.

Are those materials important for your opinion in Exhibit 1020?

MR. KRAUSE: Objection to form.

THE WITNESS: You are asking me questions about specific language being used in Forshew.

And so I'm trying to find that language in the references that we are discussing. And, it is not immediately apparent from the text, so the best place to try to find that would be to look at those individual references -- look at the reference in its entirety.

In the argument I present here on obviousness, and we can go through it if you

would like, the material in the -- in the main published paper that I cite to was sufficient to really show that Forshew in light of Dawson was actually carrying out all of these steps.

Or the person skilled in the art would realize that one could carry out all of the steps in Claim 1 of the '783 patent by reading what was disclosed in Forshew.

So, if I needed something from one of the supplements to support my argument, I would have cited to that, as I did, in one of the previous references we were discussing and which I cited to the sequencing of the GBM tumors.

BY MR. LUMAN:

Q. So, I'm looking at Paragraph 255 in your declaration, if you go there.

A. Okay.

Q. And you say, "Forshew expressly discloses the use of a variable portion from a result of the whole genome sequencing data in the

1 context of its breast cancer patient."
2 And so, what is it about the breast
3 cancer patient's PCR primers that makes them a
4 variable portion?
5 A. So if you read at the bottom of that
6 paragraph, Forshew explicitly tells us, "Whole
7 genome sequencing of tumor material was used to
8 identify tumor mutations in a patient. Ten
9 mutations were selected."
10 And in the portion of the reference
11 we were talking about, using standard
12 amplification primers tailored to the mutation
13 loci.
14 So, Forshew selected a set of
15 mutations based on the original sequencing that
16 was done, and those were mutations found in this
17 patient. And so they represent the variable
18 portion of the primer types that are mentioned in
19 this Claim 1a.
20 And of course one skilled in the art
21 would recognize, we could also have known genes
22 like TP53 or others.

Q. And so what -- how do we know that they are variable portions in Forshew's breast cancer patient when he is using standard amplification primers to analyze the breast cancer patient?

MR. KRAUSE: Objection, form. Mischaracterizes the document.

THE WITNESS: So, the document actually says, "standard amplification primers tailored to the mutation loci."

They were specifically tailored to these loci.

So, again, I would have to read through the supplemental material to understand how they were tailored.

If you are suggesting that one could simply buy, you know, a set of primers for every mutation in the genome, including some that might not have been known until Forshew sequenced them, that doesn't make a whole lot of sense, right.

The fact that Forshew is telling us

they were tailored means that they were -- that, you know, they were selected and that -- well, I can't speak to the protocol he used, but he specifically selected these.

It might be useful to go back and review, review actually the written description of the patent. Because if I recall, the, the written description when it laid out the criteria for being variable and fixed, even there doesn't specify what kind of capture probes or PCR primers one would use, whether one would call them standard or not.

Really they had to represent types of genetic variants. Some of which were discovered in the patient; I believe those were variable. And some of which were previously known.

So, we can go back and review that language if it is helpful.

But whether or not the primers were called standard, they were clearly selected

and tailored to the individual patient's mutation.

BY MR. LUMAN:

Q. And so is it the selection that makes them tailored?

I'm not quite understanding what your testimony is. What is it about selection that is important?

MR. KRAUSE: Objection to form.

THE WITNESS: So, if we go back to the written description in the patent itself, in the '783 patent in Column 8, right.

And we have looked at this previously. "In some embodiments at least one variable portion corresponds to potential neoantigen causing genetic variants of the subject."

And, "When at least one fixed portion corresponds to one or more of," and there is a fairly long list that includes cancer driver genes, genes involved in pharmacogenomics of cancer drugs, right,

genes related to inherited form of cancer and so on, right.

So, the fixed portion would correspond to a set of well known, well established targets.

And in this one passage here, "In some embodiments, at least one variable portion corresponds to potential neoantigen causing genetic variants of the subject," right.

The next paragraph, "In some embodiments, at least one variable portion corresponds to genetic variants responsible for Mendelian phenotype of a proband," and then goes on.

If we read all of -- further down in Column 7. "At least one variable portion from a result of the sequencing assay," right.

And so if we read what Forshew is telling us, Forshew is selecting a set of mutations. That set of mutations is a subset

of what was found using whole genome sequencing of tumor material, and these were targeted.

So, the claim language itself doesn't actually speak to the characteristics of the primers as being fixed or variable. It is really the targets that are fixed or variable.

And so in this instance, the primers that Forshew uses are primers that target this variable portion of his assay panel.

BY MR. LUMAN:

Q. So, hold on. You said that the primers -- the claim language doesn't speak to the characteristics of the primers being fixed or variable.

But, I mean, you can see in Paragraph 253 of your report, you have reproduced the claim language, and it does require the probes have a variable portion and a fixed portion, right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I think you are mischaracterizing what appears in Claim 1.

So, if we go back to the patent, and we read Claim 1a, right, it says, "Wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-directed genomic content," right.

So, the probe set contains probe molecules that have oligonucleotide-directed genomic content comprising at least one variable portion from said sequence data -- from a result of said sequence data and at least one fixed portion independent of said result of said sequencing data."

So, we are not talking about probes that have variable and fixed pieces, right. And I don't think that is referred to anywhere in the two patents in question.

We have a probe set and that probe set comprises nucleic acid probe molecules having nucleotide directed genomic content.

And the content comprises a variable portion and a fixed portion.

So, what Forshew is telling us explicitly in the paragraph that you called out in, on Page 10, is it is using amplification primers.

So, he has a set of primers tailored to the mutation loci, right, that he had discovered -- as I referred to in the paragraph in my report we were talking about earlier, I believe it is Paragraph 256 -- that target the variable sequences that were discovered from the analysis of that individual's genome.

BY MR. LUMAN:

Q. So, let me make sure we understand the claim. I'm looking at Paragraph 253.

A. Okay.

Q. And the nucleic acid probe molecules, they need to have at least a variable portion and at least a fixed portion.

And you had talked about the genomic

content.

So, what was the distinction you were trying to draw about the genomic content?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I am reading the claim language. You are asking me if the probes themselves had to be based on this claim language variable and fixed.

And so I could imagine different things one could do to maybe call a PCR primer having a variable and a fixed piece. Right? But that is not what the claim language says.

So, if you read the claim language, and it is in Paragraph 253, "Wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-directed genomic content," right.

So, the probe set has oligonucleotide-directed genomic content, so it is the content that comprises at least one

variable portion.

So, some of the content targeted by that probe set represents a variable portion from a result of said sequence data.

And the sequence data is way back up in the claim. And at least one fixed portion independent of said result of said sequencing data.

So, the probe set has to have a variable portion and a fixed portion. And that probe set, in the case of Forshew, targets ten different variants, you will recall, that were selected based on an analysis of the original -- I believe whole exome sequencing. Maybe whole genome sequencing that was done.

So, if the probe sets are the things, as the claim language explicitly tells us, were the result of said sequence data, right, that variable portion from an analysis of the sequence of the individual, that is exactly what Forshew has, is a set of

variable -- probe sets targeting this variable portion.

BY MR. LUMAN:

Q. Is the genomic content part of the nucleic acid probe molecules or is it part of the targets?

MR. KRAUSE: Objection to form.

THE WITNESS: I don't understand your question, right.

It says, "Wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising," right, "at least one variable portion from said -- from a result of said sequence data." Okay.

BY MR. LUMAN:

Q. Uh-huh.

A. So, my read of this in the context of what Forshew is doing, and my understanding from the point of view of a person of ordinary skill in the art, is that what Forshew did was based on the analysis of the original sequence

1 data that he generated. He identified ten
2 mutation loci, to use his language.
3 If Forshew is using PCR, right --
4 and now I will use the word, standard, because
5 you can come up with all sorts of variants.
6 But, a typical way of doing this --
7 and I believe that is what Forshew did and we can
8 dig through the supplemental material if that
9 would be helpful.
10 But, if we have a mutation at a
11 particular place in the genome and we are going
12 to sequence that, the way one would design
13 primers in a kind of standard way is to select
14 primers that bracket that mutational point, okay.
15 So, the primers would be designed
16 with oligonucleotide-directed genomic content,
17 right. It would be targeted to that genomic
18 region.
19 And in the case of Forshew's ten
20 mutation loci that were discovered in the
21 patient, that would represent at least one
22 variable portion of said oligonucleotide set,

right.

So, his oligonucleotide set, the probes, the PCR primers, are oligo-directed toward the genomic content where the mutations occur.

Q. So, looking at Paragraph 253, and I see that the language of Subpart 4 of 1a, requires genomic content.

And so is the genomic content part of the nucleic acid probe molecules, or is it part of the targets?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I tried to answer this question and I will try again.

So, in Paragraph 254, for example, I write, "A person of ordinary skill in the art would understand that Forshew's PCR primers or probes are nucleic acid molecules having oligonucleotide-directed genomic content, i.e., sequences that are designed to bind or hybridize to nucleic acids in a sample having a complementary sequence."

255. "Forshew expressly discloses the use of a variable portion from a result of the whole genome sequencing data in the context of its breast cancer patient.

"As discussed above, in the breast cancer patient, whose cancer was tracked using TAm-Seq following an initial whole genome sequencing set -- step," excuse me, "the set of ten nucleic acid probe molecules used to generate the amplicons for sequencing constitute a variable portion resulting from a result of said sequencing data."

And then I have -- I quote from Forshew. And I believe it is the one you read earlier about targeting tumor mutations, right.

So, these are the mutations that were identified from the sequencing data. The language of the written description tells us that the variable portion are those which are determined expressly from the patient's sequence data.

1 And Forshew's set of primers are
2 primers that have -- they are nucleic acid
3 molecules that have an oligo-directed genomic
4 content, right. They amplify the target
5 mutations.
6 BY MR. LUMAN:
7 Q. So, in Paragraph 254, you've got
8 your example of PCR primers and how they would
9 have genomic content being the sequences that
10 bind or hybridize to the nucleic acids in a
11 sample.
12 What if you were using
13 solution-based hybridization capture probes?
14 What would be the genomic content in a
15 solution-based hybridization capture probe?
16 A. So, again, I think you are sort of
17 dissecting this language in ways that don't make
18 a lot of sense, right.
19 The, the PCR primers do hybridize to
20 their complementary sequences in the genome.
21 Now, remember the genome is double
22 stranded.

1 So, by hybridizing to a
2 complementary portion -- in fact, the two primers
3 would hybridize to opposite strands.
4 In hybridizing to a complementary
5 portion, they do have genomic content. And that
6 genomic content was explicitly selected to be in
7 a region in which there is a mutation.
8 One could also use capture probes of
9 another form. So, you mentioned solution-based
10 hybridization. There are other types of capture
11 probes one could use.
12 And I believe I may cite to Mamanova
13 paper describing different capture technologies
14 or enrichment technologies.
15 But in that case, one could imagine
16 capture probes which could also by their nature
17 hybridize to their complementary sequences in the
18 genome.
19 And again, one could imagine,
20 hypothetically, that they would fall in the
21 region of -- fall in the region of particular
22 mutations, right.

What other things might happen really aren't important here.

What is important is that Forshew clearly describes a set of capture probes that target genomic regions that were selected from an analysis of the initial sequencing data to represent ten mutations which meet the definition of the variable portion of his probe set.

Q. Now, the genomic content referred to in Claim 1a, it has got to be specific to the variants in Forshew in order for the nucleic acid probe molecules to hybridize to them. Correct?

MR. KRAUSE: Objection to form.

THE WITNESS: So, again, I don't fully understand the question, right.

We can look at Forshew's PCR primers. Those are in the online supplements. And they may be there. I am pretty sure they are there.

I could take those and I could map them back to the genome, right.

I can almost invariably tell you

that the probe molecules have oligonucleotide-directed genomic content.

And the way in which Forshew almost certainly designed these primers was that he identified a mutation locus, right, and he tells us that he has ten mutation loci.

He designs those primers to amplify and sequence those genomic loci, right.

I don't have all of the details in front of me, but invariably what one would naturally do is design primers that bracketed those, that -- each locus that you wanted to sequence and follow, right.

So, it is oligo-directed genomic content, right. Each one of the oligos, as individual oligos, and PCR would hybridize to the genome.

And then once amplified, they would amplify the genomic content that included the mutational locus that he was trying to analyze.

So, what Forshew does is he finds

1 loci. He makes PCR primers. He amplifies
2 regions of the genome and sequences them.
3 And does this over time to follow the
4 trajectory of the patient. And that is what
5 Claim 1 describes doing.
6 BY MR. LUMAN:
7 Q. Let's return to Forshew, Exhibit 30.
8 A. Uh-huh.
9 Q. And back on Page 10, we were looking
10 at the paragraph that starts with using. And it
11 says, "Standard amplification primers tailored to
12 the mutation loci."
13 A. Uh-huh.
14 Q. So, is Forshew designing standard
15 amplification primers or is he just selecting
16 standard amplification primers from a -- from
17 some external source that he can purchase?
18 MR. KRAUSE: Objection to form.
19 THE WITNESS: So, I don't have all
20 of the details of what Forshew -- let's see.
21 Let me take a look.
22 So, the details of how Forshew

1 designed his primers isn't provided in the
2 main text. The main text of the paper
3 actually refers to supplementary methods.
4 And again this is a common practice
5 in modern biological -- in the modern
6 biological literature, that many times the
7 sort of standard methods which are well known
8 in the art, the details are provided in
9 supplementary materials, because they are not
10 important for understanding the main thrust
11 of the paper.
12 Based on my understanding of what
13 Forshew writes about selecting on Page 10, as
14 we talked about, these ten mutational loci
15 and targeting them with primers, right.
16 What he almost certainly did was
17 used a program, like Primer3, which was
18 widely used, or some other program to design
19 primers that targeted the genomic content
20 that he was interested in, right, those
21 mutational loci.
22 Using criteria that would allow them

to be effectively sequenced -- and I would have to read his sequencing protocol to understand what that might be.

But, understanding his protocol, you design the primers to be a certain distance apart from each other. You would use other criteria like their melting temperature, salt concentration of the reaction that you are going to use, et cetera.

And those were methods that were well known in the art.

The thing that is important here, whether or not the primers came off the shelf or were custom designed, is that the claim language itself says that the primer -- the probe set is a personalized probe set.

And that it has nucleic acid molecules having oligonucleotide-directed genomic content, the variable portion of which is a result of said sequencing data.

So, you know, whether he bought the probes or designed them himself, they are

1 targeting that variable genomic region that
2 were those mutations that were identified in
3 the patient.
4 And so, he is clearly practicing in
5 a way that renders the claim obvious, the
6 selection of a probe set that targets this
7 variable portion of regions selected from
8 said sequencing data.
9 BY MR. LUMAN:
10 Q. Let's look a little lower on Page 10
11 of Forshew.
12 Do you see the last paragraph that
13 starts with, "Previously proposed"?
14 A. Sure.
15 Q. And it says, "Previously proposed
16 methods for personalized monitoring of tumor
17 dynamics relied on expensive custom-designed
18 probes."
19 Do you see that?
20 A. I see where it says that, yes.
21 Q. And so, what is it about
22 custom-designed probes that makes them expensive?

MR. KRAUSE: Objection to form. Calls for speculation.

THE WITNESS: So, in this paragraph, Forshew is talking about what he perceives as some of the benefits of using the TAm-Seq protocol.

I would have to go back and review all of the TAm-Seq protocol to get a better understanding of what his argument might be here.

The cost of oligo synthesis in 2012, I can't tell you what the cost was per base, but Forshew characterizes it as expensive as compared to the TAm-Seq protocol that he is describing.

But the relative cost here doesn't seem to -- doesn't seem to matter to me for the obviousness argument that I lay out, namely that Forshew clearly demonstrates that one can sequence a genome, identify mutations, and then take a subset of those mutations and monitor them in samples

serially over time.

So, you know, in 2012, I don't know what, what criteria Forshew relied upon to come to the characterization of the custom design probes as being expensive and what that is relative to.

BY MR. LUMAN:

Q. Do you see the next sentence --

A. Uh-huh.

Q. -- it says that, "These have better analytical sensitivity than currently achieved by TAm-Seq but are difficult to implement on a routine basis."

Do you see that?

A. I see where it says that, yes.

Q. What is it about custom-design probes that are difficult to implement on a routine basis?

A. So, as of 2012, I don't know what Forshew was referring to here. I mean, clearly what Forshew was able to demonstrate is sequencing a -- doing a preliminary sequencing

assay, identifying a subset of mutations, designing probes to capture those mutations, and then sequencing and following them subsequently over time.

So, you know, Forshew makes some statements here that are based on his interpretation of his own results.

Q. And do you see, not the next sentence, but the sentence after that, it says, "Using TAm-Seq to identify cancer mutations in the plasma of most ovarian cancer patients and tracked dynamics of TP53 mutations without requiring any specially designed probes."

Do you see that?

A. I see that, yes.

Q. So, I mean TAm-Seq can be performed without designing any special probes, right?

MR. KRAUSE: Objection to form.

THE WITNESS: So that may be what Forshew is referring to here.

So, in the mid-2000's a lot of companies were coming out with whole exome

capture technologies. Some of those were PCR based, some of those were based on solid phase to solution capture probes, right.

So, Forshew may have been using a commercially available set of probes that targeted individual exons.

In reading this, that may, in fact, be what Forshew is referring to.

Nevertheless, rather than using the entire exome or the entire genome, what Forshew told us is that he selected ten mutational loci and specifically targeted those.

And those ten loci were -- whether or not he used standard probes or custom designed probes is kind of irrelevant.

That those ten loci represent a variable portion of the loci he analyzed, in fact, they were the only portion -- but one could easily extend this to other known genes -- and demonstrated that as of 2012, one could essentially carry out all of the

1 steps of the -- especially in light of
2 Dawson, all of the steps of Claim 1 of
3 the '783 patent, thus rendering it obvious.
4 BY MR. LUMAN:
5 Q. This paragraph that we have been
6 looking at in Forshew that begins with,
7 "Previously proposed," on Page 10, this is
8 telling the person of ordinary skill that the
9 advantages of TAm-Seq are that you do not need
10 specially designed probes, right?
11 A. Again, I would have to read the
12 whole paper. That is probably one way to
13 interpret it. But whether or not you need custom
14 designed probes doesn't mean they are custom
15 selected, right.
16 We are told, in fact, that Forshew
17 used standard amplification primers tailored to
18 the mutation loci, right.
19 So, what Forshew is telling us is
20 that these may have been standard primers that
21 could have been purchased.
22 Again, I don't recall all of the

1 potential sources of oligos that may have been
2 commercially available.
3 He may have selected these ten loci
4 because they fell within regions of interest
5 where those that were amenable to the probe sets
6 that he had available.
7 Again, we would have to read the
8 supplemental materials which I don't have in
9 front of me.
10 But, irrespective of how he selected
11 these, what they do is they represent probes that
12 capture the genetically -- sorry, what was the
13 phrase, the -- let's see Paragraph 256.
14 I'm sorry. I have to go back to
15 find this so I don't misquote it.
16 That he used a personalized probe
17 set, so personalized, that comprises nucleic acid
18 probe molecules having oligonucleotide-directed
19 genomic content with at least one variable
20 portion from a result of said sequence data."
21 He identified mutations. He
22 identified a probe set which, in reading this

1 further as we have been doing, could very well
2 represent a standard probe set that he purchased
3 off the shelf.
4 But the probe set -- the probes that
5 he used were specifically selected to target
6 mutations that were found based on said sequence
7 data that were obtained in his previous analysis,
8 right.
9 So, he sequenced. He identified
10 mutations. He picked a set of PCR probes to
11 capture those mutations and then sequenced them
12 and monitored them over time.
13 So, you know, where he got the
14 probes, doesn't seem to be -- doesn't seem to be
15 important to me. They were custom selected based
16 on the mutations.
17 Q. So, we have been talking about
18 Forshew for a bit.
19 Now, Forshew is the primary
20 reference you rely on for Ground 3 against
21 the '783 patent. Right?
22 Primary, meaning it is the first of

1 two references.
2 A. Yes. I, I -- so, the first one I
3 discussed in detail was Forshew.
4 Q. And, so Forshew would be important
5 to your analysis of the obviousness of the claims
6 in the '783 patent. Correct?
7 A. So, Forshew and Dawson, together
8 with knowledge of a person of ordinary skill in
9 the art, basically provide the rationale that I
10 lay out in Ground 3.
11 One of the things that Dawson does
12 is Dawson uses -- he is from the same group. He
13 uses the same TAm-Seq technique, but simply adds
14 in TP53, a well known cancer gene, in his
15 analysis of breast cancer patients.
16 So, TP53 is the type of gene that
17 would represent what the patent refers to as a
18 variable portion in Claim 8 because -- or, sorry,
19 in Column 8, because you recall that in Column 8
20 they referred to the -- excuse me, the fixed
21 portion in Column 8, because TP53 is one of the
22 canonical cancer driver genes that would be

profiled.

Q. So, you mentioned Dawson. We should talk about Dawson.

A. Okay.

Q. Can you turn to Paragraph 275 of your Exhibit 1020, please.

A. Sure. Can you drop a copy of Dawson in the file transfer box?

(Exhibit 1070 marked for identification.)

BY MR. LUMAN:

Q. Yes. Dawson Exhibit 1070.

A. Okay. I am at paragraph 275.

Q. Yes. I gave you the wrong paragraph. Let me get you --

A. Okay. All right. Well while you are finding the paragraph, the Dawson reference is up. And I have it open.

And I referred to Dawson as he, but in fact, it is Sarah-Jane. So, I am assuming she.

Q. Okay. It is 257, sorry.

Paragraph 257.

A. All right.

Q. Can you let me know when you get there?

A. Yes. Sorry, I just lost the document. Let me open it up again. All right. So, 257.

Q. Yeah, and --

A. There we go.

Q. Great. The second sentence, it refers to, "Dawson further describes applying the TAm-Seq technique." Do you see that?

A. Yes, I do.

Q. So, Dawson has the same type of tagged amplification deep sequencing disclosed in Forshew, right?

MR. LUMAN: I note for the record that it has been taking you quite a while to answer some of our questions about the very references that you are asserting is prior art against the patents such as the Forshew document and the Dawson document.

1 You don't seem particularly familiar
2 with them.
3 MR. KRAUSE: So, let's get back to
4 the colloquy and the testimony from counsel.
5 The record is quite clear that he is
6 answering your very open-ended questions.
7 And this seems to be sort of a
8 predetermined exercise to create a phony
9 record where you are going to claim
10 nonresponsiveness.
11 Just noting our position that it is
12 quite clear what is going on here.
13 MR. LUMAN: Sure. He has been
14 taking a long time to even review the very
15 references that he has asserted as prior art
16 against these patents. That is what I am
17 noting for the record.
18 MR. KRAUSE: You can sum the times
19 up and they are quite reasonable, given the
20 questions.
21 THE WITNESS: So, you are asking me
22 questions that actually do require some

review, right.

Forshew and Dawson were both part of the same research group working with Nitzan Rosenfeld, who is a senior author on these papers.

They are both at University of Cambridge at the Cancer Research UK facility.

They work together. You are asking me if the TAm-Seq method is the same, right.

The analysis I did didn't rely on the detail comparison of the TAm-Seq method in both documents, right.

So, I can't answer that question without performing some review.

There may have been some change in the way in which TAm-Seq was used between the original Forshew paper and the Dawson paper.

And so if you ask me that kind of question, I have to -- I have to answer -- I have to look to see if I can find information to be able to answer that question, right.

So, you know, if you asked me about

the arguments I made, I can very clearly lay them out in referring to Dawson.

Dawson explains that TP53 is, "known to be recurrently mutated in breast cancer." This is in Paragraph 257, the one you referred to.

Dawson further describes applying the TAm-Seq technique to detect variants of TP53 in breast cancer patients, right.

So, whether or not there is some tweak to the method in the argument I presented is less important than the fact that Dawson was able to detect TP53 in breast cancer and that TP53 and another gene, PIK3CA, that both of those are known to be recurrently mutated in breast cancer and both of them fall into the class of the fixed set of targets.

So, you know, I can't tell you whether or not the methods are identical. But I can tell you that they are probably the same and at the very least highly similar.

BY MR. LUMAN:

Q. Sure. And I didn't ask if they were identical or not.

Let's try a --

A. I believe you said the same. And, you know, to me that is asking whether or not they are identical.

Q. Let's try a question based right on Page 257 --

A. Okay.

Q. -- Paragraph 257?

A. Paragraph 257?

Q. Yes, second sentence. "Dawson further describes applying the TAm-Seq technique to detect variants of TP53 in breast cancer patients."

That is a sentence that you believed to be true at the time you signed your declaration, correct?

A. So, I believed it was correct when I submitted my declaration.

I can also point you to multiple

1 places in the Dawson reference that describes the
2 sequencing of TP53 from breast cancer patients.
3 Q. So, let's look in the Dawson
4 reference itself.
5 A. Uh-huh.
6 Q. I would like to turn to Page 1207.
7 Can you go there?
8 A. All right. All right. I am there.
9 Q. And I am looking in the right-hand
10 column. And there is the second full paragraph
11 that starts with, "The monitoring."
12 Do you see that one?
13 A. Yes, I do.
14 Q. I'm going to go down a couple of
15 sentences to the one that starts, "Here we have
16 demonstrated the use of two strategies."
17 Do you see that?
18 A. Yes, I do.
19 Q. And the two strategies were digital
20 PCR assay and targeted deep sequencing. Right?
21 A. That is what Dawson has written
22 there, yes.

Q. And it says the next sentence that "Digital PCR assay provides high accuracy and sensitivity but requires the design of personalized assays, an expensive and rate-limiting step."

Do you see that?

A. I see where Dawson wrote that, yes.

Q. What is it about designing personalized assays that are expensive?

MR. KRAUSE: Objection. Calls for speculation.

THE WITNESS: So, I can't -- yeah --

I can't really tell you what Dawson was referring to here. But I think in this case Dawson is referring to the potential cost of personalized digital PCR assays, right.

But as we read in both Forshew, and I'm sure we can find references here in Dawson, that Forshew and Dawson would both argue that their TAm-Seq approach, which as I believe we finally realized, were using

1 previously designed or available primers to
2 custom target variable portions of the genome
3 for further analysis.
4 That, then Dawson also shows that
5 one can use these to target a fixed portion,
6 right, the set of known oncogenes like
7 PI3CA -- PIK3CA and TP53, and perform those
8 assays.
9 So, what you are talking about in
10 that sentence you read was a statement that
11 Dawson had made about digital PCRs, a
12 personal assay.
13 In fact, she goes on to say,
14 "Targeted deep sequencing of plasma DNA
15 provides a cost effective alternative for
16 high throughput analysis and may overcome
17 limitations of initial tumor tissue
18 assessment by virtue of allowing," and it
19 goes on.
20 So, she is contrasting her TAm-Seq
21 approach, looking at a fixed portion of the
22 TP53 gene in its mutations as opposed to

1 digital PCR.
2 BY MR. LUMAN:
3 Q. So, the TAm-Seq that Dawson is
4 highlighting here is a fixed -- has a fixed
5 portion instead of a variable portion. Right?
6 MR. KRAUSE: Objection to form.
7 THE WITNESS: So, I believe that
8 Dawson's implementation of TAm-Seq was very
9 similar to Forshew's in that they performed
10 an initial sequencing analysis to identify
11 mutations.
12 And if you look at Figure 1 on
13 Page 1202, sort of in the middle of the
14 left-hand column, there was a targeted
15 sequencing of PIK3CA and TP53 mutations in 53
16 women.
17 And then whole genome sequencing to
18 identify mutations or SVs or both, in nine of
19 the 52 women, right.
20 And so they have 25 females who had
21 mutations in the two known oncogenes. And
22 the nine individuals who had mutations in

1 their own genomes.
2 And so, the SVs are structural
3 variants. And so they have identified those.
4 And then they selected a set of targets, some
5 of which represent the fixed portion, those
6 previously known oncogenes. So, TP53 and a
7 PIK3CA.
8 And, in addition, they identified
9 additional mutations. And they sequence
10 these over time in individuals.
11 So, if we look at patient --
12 Figure 2, we have plasma monitoring of four
13 different patients. Each one has a different
14 set of genes that were profiled.
15 So, Patient 6 has three structural
16 variants. There are deletions in PIK3CA in
17 Panel A.
18 Panel B, Patient 4 has a set of
19 mutations in one, two, three, four, five, six
20 genes, one of which is one of the fixed
21 portion, and the other five which would
22 represent the variable portion.

1 And then there are two individuals,
2 Patients 18 and Patient 16, in which only
3 that fixed portion was profiled.
4 But, you know, clearly if one can do
5 this for the variable set, one can do it for
6 the fixed set. And that is really what
7 Patient 4 demonstrates, that this can be done
8 for both.
9 So, Forshew and Dawson both present
10 an analysis that one of ordinary skill in the
11 art would recognize renders Claim 1 obvious.
12 BY MR. LUMAN:
13 Q. Now, what is it about personalized
14 assays that make them a rate limiting step for
15 digital PCR?
16 MR. KRAUSE: Objection to form.
17 THE WITNESS: So, I don't know what
18 Dawson was referring to here.
19 Dawson is simply trying to, in this
20 discussion of her method, to try to point out
21 what she believes are some of the advantages
22 over other techniques, like digital PCR.

1 But, you know, clearly what Dawson
2 demonstrates is that one can conduct an
3 assay, and could have as of 2003, that
4 involves sequencing, selecting targets, and
5 then monitoring those targets over time with
6 both a fixed set, which are those oncogenes
7 known ahead of time, and a variable set,
8 those known -- those targets that include
9 mutations that occurred in the individual,
10 that were identified through sequencing.
11 So, in a -- you know, I can't speak
12 to why she believes it was potentially rate
13 limiting. But it doesn't discount the fact
14 that this reference does demonstrate and
15 render obvious the method that is claimed in
16 Claim 1 of the '783 patent.
17 BY MR. LUMAN:
18 Q. Back to Page 1207 in Dawson.
19 A. Okay.
20 Q. And we are still in the same
21 paragraph. The very next sentence after the one
22 about rate limiting step. That one says,

"Targeted deep sequencing of plasma DNA provides a cost effective alternative for high-throughput analysis and may overcome limitations of initial tumor tissue assessment by virtue of allowing for the direct identification of mutations in plasma."

Do you see that sentence?

A. Yes, I do.

Q. So, this is Dawson saying that one of the advantages of TAm-Seq, targeted deep sequencing, is that you do not need to sequence the tumor. Right?

A. So, that is not actually what she is saying here. Right.

So, she is saying that by monitoring plasma, you can overcome some of the limitations of assaying a tumor itself.

So, this is something that I believe as of 2012, 2013, would have been very well known in the art.

And that is that tumors themselves tend to be very heterogenous, right.

1 So, what often happens is if we have
2 a tumor that is growing in an individual, one of
3 the first steps that is carried out is a core
4 biopsy is taken, so needles are inserted and
5 cells are removed.
6 And that sample is a portion of the
7 entire tumor, even if the tumor is surgically
8 resected.
9 The piece of the tumor that would go
10 to a laboratory for further analysis is a subset
11 of the entire tumor, right.
12 So, we know that tumors are
13 heterogeneous. And so, what you run into
14 actually looking at a tumor tissue is a potential
15 sampling bias. That you are not sampling all of
16 the mutations that may occur over the evolution
17 and development of the tumor.
18 And so what Dawson is speculating
19 about here is that if one were to sequence plasma
20 DNA, circulating DNA, where all of the cells in
21 the tumor are releasing DNA into circulation, one
22 might be able to find some mutations that were

otherwise mixed -- missed. Right.

Nevertheless, even without doing that initial plasma sequencing, one would identify patient-specific mutations by sequencing the primary tumor and having a matched control.

And then one could perform an analysis of those mutations and monitor them over time.

So, it doesn't obviate the need for doing an initial sequencing. It really just says that it could be done in a different way using plasma, potentially, instead of sequencing a solid tumor.

Q. It says that the targeted deep sequencing of the plasma DNA is an alternative to having to sequence the initial tumor tissue.

So, it is telling you that TAm-Seq avoids having to sequence the tumor tissue.

Do you disagree with that?

MR. KRAUSE: Objection. Objection to form. Mischaracterizes the document.

THE WITNESS: So, that is actually

not what it says, right. It says -- let's see.

"Targeted deep sequencing of plasma provides a cost effective alternative for high-throughput analysis and may overcome limitations of initial tumor tissue assessment."

What I'm going to go back and do is look at Claim 1 of the '783 patent, which is I believe the one we are discussing now.

So --

MR. LUMAN: For the record, I asked about Dawson. I didn't ask about Claim 1 of the patent.

THE WITNESS: Well, we have been referring back to my report on this '783 patent. You referred to Dawson in Paragraph 257.

This is part of Ground 3 in which I am discussing the obviousness of the -- the obviousness of the '783 patent in light of Forshew and Dawson.

So again, the arguments I present are presented in this context.

So, you know, the claim talks about said sequencing data from at least one biological sample that is used to select a section of probes, right.

What I would imagine that Dawson is referring to here, although you would have to ask her specifically, but what one would imagine that Dawson is referring to is using a large collection of probes to target many different regions in the genome and performing TAm-Seq.

And then reading these papers what one skilled in the art would recognize they could do is then take a subset of those probes that represent mutations that occur in the patient, right, the variable portion.

And then also as Dawson teaches us a fixed set of genes, like TP53 and PIK3CA, that represent known oncogenes and sequence them.

So, you know, Dawson isn't saying you don't have to do an initial analysis to monitor these samples over time.

Dawson is offering an alternative based on TAm-Seq that could replace whole genome sequencing which isn't required for Claim 1 of the '783 patent.

There are other possible ways of generating that initial data, right. And Dawson is speculating on that here.

MR. LUMAN: All right. We have been going for a little while. Should we take a break?

THE WITNESS: Sure.

THE VIDEOGRAPHER: The time is 2:50 p.m. Off the record.

(Recess taken -- 2:50 p.m.)

(After recess -- 3:06 p.m.)

THE VIDEOGRAPHER: The time is 3:06 p.m. Back on the record.

BY MR. LUMAN:

Q. Dr. Quackenbush, we were talking about Dawson. I would like to talk a little bit more about Dawson.

A. All right.

Q. Can you turn to Figure 1 of Dawson with me? That is on Page 1202.

A. All right, I am there.

Q. And I am looking at the part where there is a box, the one on the left that is Targeted Sequencing of PIK3CA.

And then there is another box next to it, Whole Genome Sequencing.

Do you see those two boxes?

A. Yes, I do.

Q. So, the box with targeted sequencing, that is referring to the part of Dawson dealing with the TAm-Seq assay, right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, again, I would have to read this reference.

I actually don't believe that was TAm-Seq. I would have to read the protocol.

I believe the TAm-Seq assay was carried out sort of down at the bottom, "126 samples underwent comparison of circulating tumor DNA versus circulating tumor cells."

And I don't know exactly the protocol they used. I'm not sure if this is TAm-Seq or not.

But they sequenced a -- they did an initial sequencing of PIK3CA and TP53 in 52 women. In the same women they did a whole genome sequencing.

And they identified 25 individuals who had mutations, 25 individuals -- or nine individuals who had either mutations or structural variations outside of the two targeted genes.

And then they performed the downstream analysis that we talked about where they did sequencing of cell-free DNA that appears in Figure 2.

So, I believed that the Figure 2

analysis here represents the use of the TAm-Seq assay. I would have to read the paper carefully, but I am pretty sure that is what is represented in Figure 2.

And so for each patient it is personalized. Only a set of genes are monitored.

And the example of Patient 4 has both a fixed PIK3CA and variable the five or six other genes that were monitored.

BY MR. LUMAN:

Q. And the box that has the whole genome sequencing, that is the portion of Dawson for the digital PCR assay, right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I'm going to have to read the Method section. The whole genome sequencing is not digital PCR.

BY MR. LUMAN:

Q. I think you are right, that the whole genome sequencing is not digital PCR.

Let me withdraw that question and

ask, it is the whole genome sequencing that informed the digital PCR that was conducted in Dawson. Right?

A. So, if you read, starting on Page 1201 at the very bottom, Quantification of Circulating Tumor DNA, "In the 30 women with somatic mutations or structural variants, circulating tumor DNA was quantified in a total of 141 serial plasma samples by means of either digital PCR assay or tagged-amplicon deep sequencing."

So, they were doing a comparison -- excuse me. They were doing a comparison of digital PCR or TAm sequencing --

Can you excuse me for a second. Hopefully I won't cough again. I have been talking a lot today.

But it says here they did either digital PCR or TAm-Seq. And they have more data on what was done.

So, on the bottom of Page 1202, it says, "As a high-throughput alternative to

1 digital PCR assay the remaining 44 samples
2 from the remaining 11 patients were analyzed
3 using TAm-Seq."
4 So, they did a comparison of digital
5 PCR with a subset of the patients and then
6 did TAm-Seq on the others.
7 Q. Let's go back to Page 1207 of
8 Dawson. It is going to be in the Discussion
9 section on the right-hand column.
10 A. Okay.
11 Q. Before I get into Page 1207, your
12 last answer said that they had done a comparison
13 of digital PCR with a subset of patients, and
14 then they did TAm-Seq on others.
15 And so, a person of skill in the art
16 following Dawson would want to perform only the
17 TAm-Seq, because Dawson teaches that the digital
18 PCR accuracy is expensive and rate limiting.
19 Right?
20 MR. KRAUSE: Objection to form.
21 THE WITNESS: So, Dawson is
22 proposing TAm-Seq as an assay that she

1 believes has certain advantages over digital
2 PCR.
3 On Page 1202, she writes, "In a
4 subset of plasma samples in which circulating
5 tumor DNA was analyzed by both techniques,
6 quantification of mutant allele fraction by
7 means of either TAm-Seq or digital PCR showed
8 excellent agreement." Right.
9 So, she is proposing TAm-Seq as an
10 alternative to digital PCR, and arguing for
11 advantages.
12 But, and some of those advantages, I
13 believe on 1207 she offers, might have to do
14 with the cost or at least the cost of the
15 assay.
16 But, in terms of accuracy which I
17 believe was part of your question, what they
18 are saying -- or what she is saying is that
19 the two assays actually had excellent
20 agreement.
21 BY MR. LUMAN:
22 Q. Okay. And one of the reasons that

TAm-Seq has some advantages over the digital PCR technique is that you would not have to sequence the tumor before conducting the TAm-Seq assay. Right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I don't believe that is true, right. The TAm-Seq was carried out with the plasma samples using the same targets that were used for digital PCR.

Otherwise, one wouldn't be able to do a comparison between them, right.

So, the same targets were used in two different assays. That is how you can compare them.

Where did they find the targets? Well, they selected TP53 and PIK3CA. And they selected a variable set of alleles based on their whole genome sequencing analysis and that is what they used.

So, they were looking with both assays at the same targets.

BY MR. LUMAN:

Q. So, what I would like to do now is turn in your declaration, Exhibit 1020, which is the declaration for the '783 patent.

A. Okay.

Q. Would you please turn with me to Paragraph 223.

A. All right.

Q. And this is a portion of your declaration from Paragraph 223 to 226 that addresses Claim 22. Right?

A. I'm trying to see what context I am addressing Claim 2.

It may have been in the section where I argue that Ley anticipates the claims of the two -- or '783 patent.

Or it may be in a section which -- in Ground 2, I present an argument that the '783 patent is obvious over Ley in view of the knowledge of a person skilled in the art.

And I believe that is the section we are looking at. So, it is Ley with a combination of what a person of skill in the art would

1 understand.
2 Q. And you see that Claim 22 is,
3 "Wherein the personalized probe set comprises
4 hybrid capture probes"?
5 A. Yes, I see that.
6 Q. I see in Paragraph 224, you cite the
7 Mertes reference, Exhibit 1006. Do you see that?
8 A. Yes, I do.
9 (Exhibit 1006 marked for
10 identification.)
11 MR. LUMAN: If you can make
12 Exhibit 1006 available to Dr. Quackenbush,
13 please.
14 THE VIDEOGRAPHER: So, I don't have
15 1006. It wasn't uploaded.
16 MR. LUMAN: Okay, I will upload it.
17 Okay. It has been uploaded.
18 THE VIDEOGRAPHER: Making it
19 available for the witness.
20 THE WITNESS: All right. It is
21 open.
22 BY MR. LUMAN:

Q. And on Page 375, there is a header, Enrichment Techniques.

Do you see that?

A. Yes, I do.

Q. And then Roman Numeral i has Hybrid capture.

A. Yes, I see that.

Q. It refers to nucleic acid strands. I will let you read the rest of it. I'm going to ask you about the nucleic acid strands.

Can you let me know when you have read the hybrid capture material?

A. All right. So, I have read Romanette i on Page 375 of Mertes.

Q. And where it talks about nucleic acid strands, can those nucleic acid strands that perform the hybrid capture be DNA strands or RNA strands or both DNA and RNA strands?

A. So, if we are using oligonucleotide probes to capture nucleic acid from a typical biological sample, they could represent either DNA or RNA, because both will form complementary

base pairs with a complementary target.

Q. If you could turn to Table 1 of Mertes which is on Page 377.

Can you let me know when you arrive there?

A. 377, you said?

Q. Yes.

A. I have that, yes.

Q. Do you see the row under Hybrid capture that is In solution?

A. If you don't mind, I'm going to rotate this page. All right. So, I have it rotated now.

Q. And then under the Vendor column, there is Agilent SureSelect.

Do you see that?

A. I see that, yes.

Q. Do you know if the Agilent SureSelect probes are DNA probes or RNA probes?

A. Are you asking if they are targeted towards capturing RNA or DNA? Or are you asking if they are made from RNA or DNA?

Q. I was asking if they were made from DNA or RNA?

A. So, I believe that the Agilent SureSelect probes are made from DNA rather than RNA. DNA tends to be more stable than RNA.

And, in fact, if we go back to the hybrid capture probes, the, the nucleic acid strands are hybridized to specifically prepare DNA fragments.

So, to the best of my knowledge and understanding -- or recollection, the Agilent SureSelect product was a set of DNA based probes.

Q. How about the other ones listed there like FlexGen, Roche NimbleGen.

Do you know if the other ones listed there are, if the probes are made of DNA or RNA?

A. I suspect they are all DNA, although I don't know for sure.

I seem to recall Roche NimbleGen being DNA probes. And it largely reflects the fact that DNA synthesis is very easy to carry out and the DNA probes are stable.

Q. So, if we go back to your declaration, in Paragraph 224.

Do you have an opinion on whether the DNA hybrid capture probes disclosed by Mertes are sufficient to render obvious Claim 22 which recites the hybrid capture probes?

A. So, Claim 1 recites the use of personalized probe sets without specifying what type of probe sets those might represent.

Claim 1 is a dependent claim. And my understanding is that claim -- sorry, Claim 22 is the dependent claim.

That Claim 22 now is limiting the space of personalized probe sets to be probe sets that consist of hybrid capture probes.

And so, I point to Mertes as an example that where Table 1 describes the currently employed enrichment techniques, and it says all major target enrichment techniques show relative pros and cons, so what Mertes is doing is providing an analysis about relative strengths and weaknesses of these.

I also earlier in this document cite to a paper by Mamanova showing overlapping areas of application for these.

And what I write is, "As explained in Section 5.C.3 above, PCR and hybrid capture were used on a relatively interchangeable basis in many experimental protocols and could also be used together as complements to one another."

And, then I point to the Mertes Table 1, "Accordingly a person of ordinary skill in the art would have found it obvious to create hybrid capture probes targeting the same sequences as Ley because doing so would have involved only the predictable usage of techniques known in the art to be interchangeably useful for the same purpose."

And, then point out on the next page that not only were there commercially available sets of hybrid capture probes, but I believe Agilent SureSelect offered a service that allowed people to specifically request probe design so they could ask for probes targeting specific

regions and receive those.

And I believe I quote Mertes on that as well.

Q. And so it is your opinion that the Mertes reference to the Agilent SureSelect probes would meet the hybrid capture probes of Claim 22?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I'm not offering an infringement argument. I am offering an obviousness argument here. That Ley discloses the use of PCR primers. And that it would have been obvious to one of skill in the art that one could use other capture methodologies.

In fact, the Mertes reference lays out the use of both solid and solution-based hybridization techniques, molecular inversion probes as the type of capture technique, multiple types of PCR, and then microdroplet technologies like the rain dance technology.

So, you know, one of ordinary skill in the art reading a reference like Mertes

would have known that Claim 22 would be obvious after reading Ley, that one could simply substitute a different capture technique, you know, that would still include both fixed and variable targets within the genome.

BY MR. LUMAN:

Q. And the specific type of capture technique required by Claim 22 is hybrid capture probes. You would agree with that, right?

A. So, Claim 22 says, "The method of Claim 1, wherein said personalized probe set comprises hybrid capture probes."

So, the hybrid capture probes would consist of a set that would target both fixed and variable elements in the genome.

Q. And what from the prior art Mertes reference would you cite to for meeting the hybrid capture probes limitation of Claim 22?

What part of -- I mean, what part of Table 1 meets that limitation?

MR. KRAUSE: Objection to form.

1 THE WITNESS: So, I cited to Table 1
2 as a way of demonstrating that a person of
3 ordinary skill in the art reading Mertes, or
4 just based on their own knowledge, would know
5 that there were various techniques that could
6 be used to enrich particular regions of the
7 genome.
8 And I pointed to Table 1 as an
9 example that really provides a survey. And
10 then Mertes, Mertes estimation of the various
11 strengths and weaknesses of each of these.
12 I could have pointed to other
13 portions of this document.
14 For example, if you look at
15 Figure 4, there are a set of results from
16 sequencing and analyzing different regions of
17 interest in the genome, where regions were
18 captured using different technologies.
19 And what they are showing is these
20 technologies largely provide similar results
21 in terms of the regions that they are able to
22 capture.

1 So, really I am pointing to Mertes
2 just to illustrate the fact that, you know, a
3 person of ordinary skill in the art reading
4 Ley would understand that PCR -- that the PCR
5 that Ley used could be substituted by another
6 technique like capture probes.
7 So, the -- as I wrote. "A person of
8 ordinary skill in the art would have found it
9 obvious to use hybrid capture probes
10 targeting the same sequence -- sequences."
11 BY MR. LUMAN:
12 Q. So, let's look -- I mean because you
13 pointed to Table 1 -- we can come back to
14 Figure 4 in a minute. Let's look at Table 1.
15 A. All right.
16 MR. LUMAN: And can we have
17 Exhibit 1006, Page 377 with Table 1 brought
18 up on the screen, please. Thank you.
19 BY MR. LUMAN:
20 Q. And so under the column Enrichment
21 Technique, where it says, "Hybrid capture with
22 solid support."

1 Would any of the solid support
2 things listed there under Vendor meet the hybrid
3 capture probe recited by Claim 22?
4 A. So, I am not making an infringement
5 argument here. So, I don't know what you mean by
6 meet the limitation in the context of the
7 question you are asking.
8 What I am using this table to do is
9 simply to illustrate that one reading Ley would
10 understand that -- a person of ordinary skill in
11 the art reading Ley would understand that there
12 are a variety of different technologies that
13 could be used to target different regions of the
14 genome.
15 And what the Mertes reference
16 clearly points out is that it was known in the
17 art that these could be substituted for each
18 other in a variety of different ways.
19 Q. Right. But I mean if a person of
20 ordinary skill in the art turned to Mertes
21 Table 1 and selected the molecular inversion
22 probes to replace with Ley's PCR primers, that

still wouldn't meet the limitation from Claim 22 about requiring hybrid capture probes and it wouldn't render the claim obvious.

You would agree with that, right?

MR. KRAUSE: Objection to the form.

THE WITNESS: So, I don't think I would make an argument that hybrid capture probes -- excuse me. That, I believe you said molecular inversion probes, that MIPs probes would render Claim 22 obvious, right.

In the claim language itself, it uses the term, probe set. And as I point out in Paragraph 225 of my declaration, the '783 patent specification confirms that those skilled in the art considered these techniques to be interchangeable as of the priority date.

In defining the terms, probe, nucleic acid probe, capture probe and bait, the '783 patent explains, and I cite from a portion of Column 29, Rows 4 to 21.

And I will just quote from the end

of this, "Probes can be amplification-based or capture hybridization-based. Non-limiting examples of probes include molecular inversion probes, amplification probes, biotinylated affinity probes or any probe comprising a detectable label."

So, the argument I'm making is that one reads Ley and one sees PCR.

But Mertes, and even the written description in the patent, say that PCR, right, PCR probes, amplification-based probes can be interchanged with capture hybridization probes, right.

So, one skilled in the art would know that one could take Ley and simply use another probe type.

If we are talking specifically about Claim 22, that would be substituting capture probes for Ley's PCR probes.

BY MR. LUMAN:

Q. And the capture probes that are being substituted are hybrid capture probes.

Right?

A. So, one would know, as the '783 patent tells us, probes can be amplification-based or capture hybridization-based.

So, hybrid capture probes, yes.

Q. In Paragraph 225 that you have cited, a portion of the specification of the '783 patent, did that portion of the specification inform your understanding of what Claim 22's hybrid capture probes refers to?

MR. KRAUSE: Objection to form.

THE WITNESS: So I'm not sure I understand the question you are asking me.

Claim 1, right, and Claim 22 is a dependent claim.

Claim 1, limiting ourself to the probe set, says, "Wherein said personalized probe set comprises nucleic acid probe molecules having an oligonucleotide directed genomic content." Right.

So, we have a personalized probe set

that consists of nucleic acid probe molecules.

And Ley -- and so the argument I make here is that Ley uses PCR based probes, right. And Claim 1 requires probes that target fixed and variable regions.

Ley uses fixed probe sets that refer to fixed and variable regions.

The written description in the patent in Column 29 teaches us that probes can have a variety of different forms. They can be amplification based, which would indicate PCR, or capture hybridization based.

So, as a person of ordinary skill in the art reading that, as a person of ordinary skill in the art reading Mertes and looking at the regions I cite -- and in this section I also refer back to an argument laid out in Section 5.C.3 where I believe I cite to Mamanova.

All of those would indicate that these techniques could be interchanged. They

do have relative strengths and weaknesses.

But that if I read a paper describing like Ley, the use of PCR to capture amplified particular regions, as a person skilled in the art I would know that I could also use hybridization capture probes.

BY MR. LUMAN:

Q. Can we turn in Mertes, I would like to go to Page 378.

A. All right.

Q. And do you see the heading Enrichment by Hybrid Capture?

A. Sorry. I accidently clicked one of the references and jumped to the references.

So, 378. Yes, I see that.

Q. Okay. It is the -- do you see the second sentence under that heading says, "The hybrid capture principle is based upon hybridization of a selection library of the very many fragments of DNA or RNA"? Do you see that?

A. Yes, I do.

Q. Is this saying that the hybrid

capture probes can be made of both DNA or RNA?

A. So, yes, one could potentially, if you read this, make a hybrid capture array using what are often referred to as baits.

Baits that consist of RNA or DNA, as they say here, "representing the target region against a shotgun library of DNA fragments from the genome."

So, one could potentially use RNA or DNA and that is what Mertes is telling you.

Q. Would a person of ordinary skill in the art have preferred DNA over RNA capture probes?

MR. KRAUSE: Objection to form.

THE WITNESS: So, it would depend on a person's particular goal in doing the experiment and the particular protocol that they were looking to use.

For example, one might devise a protocol that used RNA probes. And then, depending on their application, used an enzyme called RNase H to digest the RNA away,

1 right.
2 So, all this is saying is that there
3 is a long period of microarray research. And
4 because DNA and RNA obey the same base
5 pairing rules, one could potentially
6 substitute RNA or DNA for the hybrid capture
7 probes, the baits.
8 BY MR. LUMAN:
9 Q. In Mertes, would you turn to
10 Page 376 with me.
11 A. All right. I am there.
12 Q. And I am looking at the right-hand
13 column. It says, "All three major targeted
14 enrichment techniques." Do you see that
15 sentence?
16 A. I see that, yes.
17 Q. I think I might be in the wrong
18 paragraph. Just give me a second.
19 A. All right.
20 Q. Okay. Pardon me. I was -- I would
21 like to go to Page 379 instead. Thank you for
22 your patience.

A. You are welcome.

Q. And I am under the heading called Enrichment by PCR.

Do you see that on the right column?

A. One page off. Sorry. All right, I have found it.

Q. And I am looking at the second paragraph there. The first sentence of that second paragraph says, "The main downside is that the method doesn't scale easily in any format."

Do you see that?

A. I see where it says that, yes.

Q. Why is it that PCR doesn't scale easily in any format?

A. So, I think Mertes explains some of his justification for this. And I believe he is referring to singleplex PCR, because he says in the very next sentence, "To use this method effectively any significant extent of parallelizing singleplex or multiplex PCR would be -- would need to be supported by the use of automated robotics."

1 And then talks about some additional
2 potential challenges he sees.
3 But then on Page 380, he goes on to
4 say, "To increase the throughput of PCR by
5 keeping the number of PCR reactions as low as
6 possible, there is the alternative of multiplex
7 PCR."
8 And he points to Figure 1.3b.
9 "Given careful primer design and reaction
10 optimization, several dozen primer pairs can be
11 used together effectively in a multiplexing
12 reaction." Right.
13 And then he goes on to talk about
14 the software that enables that to happen. And
15 then "An alternative method is the commercially
16 available -- is commercially available from
17 Fluidigm that uses the microfluidics PCR chip to
18 conduct several thousand singleplex PCR reactions
19 in parallel."
20 So, my best read of this, given the
21 caveats he provides is that Mertes here is laying
22 out the idea of doing one PCR action in one tube

and simply saying that, yeah, that is hard to scale if you want to look at hundreds of targets.

But there are alternative PCR-based techniques that one could use. And I believe those are the types of techniques that Ley uses, multiplex PCR.

Q. And how about Forshew? Is Forshew's TAm-Seq a multiplex PCR?

A. I would have to look back at the Forshew reference.

But I believe in Figure 1, Forshew lays out -- I don't know.

I would have to go back -- I would actually have to go back and look at what Forshew describes.

I think Forshew used a small enough number of targets that he was able to accomplish them with singleplex PCR.

But, sitting here right now, I don't recall.

Q. You can go ahead and take a look at Exhibit 1030, if that would help you answer the

1 question.
2 A. So, Forshew actually describes a
3 mixture of PCR techniques. And you can find this
4 on Page 2 of the Forshew reference in Figure 1,
5 sub-Figure B.
6 So, it is, "Work flow overview.
7 Multiple regions were amplified in parallel. An
8 initial preamplification step was performed for
9 15 cycles using a pool of the target-specific
10 primer pairs to preserve representation of all
11 alleles in the template material.
12 "The schematic diagram shows DNA
13 molecules that carry mutations (red stars) being
14 amplified along wild-type molecules. Regions of
15 interest in the preamplified material were then
16 selectively amplified in individual (singleplex)
17 PCR, thus excluding nonspecific products.
18 "Finally sequencing adapters and
19 sample-specific barcodes were attached to the
20 harvested amplicons in a further PCR."
21 So, Forshew is describing multiple
22 different PCR steps, a preamplification, a

singleplex PCR in the preamplified products, and a -- then additional amplification, he refers to as a bar-coding PCR, in which he attaches sequencing adapters and sample-specific barcodes.

So, it is a mix.

Q. Does the preamplification part of multiplex PCR section of the TAm-Seq act the same?

A. Well, the fact that they tell us that the preamplification step was performed for 15 cycles using the pool of the target-specific primer pairs, tells me it was a multiplex PCR -- a multiplex PCR step in the assay.

Q. How about the barcoding PCR step, is that one multiplexed or singleplexed?

A. I -- it doesn't disclose it here in the figure legend. I would have to look in more detail probably at the supplementary protocol that is provided.

MR. LUMAN: Noting that, I am seeing that the Realtime. And there is a little bit of use of the word pull, P-U-L-L.

BY MR. LUMAN:

Q. And, Dr. Quackenbush, you meant pool, P-O-O-L?

A. Pool, yes. 15 cycles using a pool, P-O-O-L, of the target-specific primer pairs.

Q. Thank you.

A. I can't see that, so --

Q. Yes, I wanted to correct it while we are doing it now.

So, I would like to turn in your declaration, the Exhibit 1020, and let's turn to Paragraph 125.

Would you please turn there with me?

A. All right. I am there.

Q. And I am looking right above it. There is Limitation 1d. The claim language is repeated in bold.

Do you see that?

A. Yes, I do.

Q. And I want to look at the last bit of Limitation 1d. And it says, "Which inform a therapy choice or a change in the therapy of the

subject."

A. All right. I see where it says that.

Q. And then I am going to look at Paragraph 127. And Paragraph 127 in your report has an explanation of why you believe Ley informs a therapy choice or a change in therapy for the subject. Right?

A. Let me find that. All right. I have that.

Q. All right. So, who in Ley's experiment is making -- is informing the therapy choice or change for the subject?

Is it a physician? Is it the laboratory researchers? Is it the patient itself?

MR. KRAUSE: Objection to form.

THE WITNESS: So Claim 1d says, "Generating a report identifying," Number 1, "a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at

1 least a subset of (c) and (ii) genetic
2 variants which inform a therapy choice or
3 change in therapy for the subject."
4 In my report -- in my declaration, I
5 actually point out that in the supplementary
6 information there is actually a detailed
7 clinical record referring to this patient, "a
8 detailed case report that provides
9 information about a number of various
10 mutations," and now I am in Paragraph 128 of
11 my declaration, "that had been detected in
12 the patient's cancer genome.
13 "The germline and somatic variance,"
14 excuse me, "detected in the patient are
15 linked by Ley to the diagnosis of AML."
16 Right.
17 And the supplementary information in
18 Paragraph 129, "Ley also presents the
19 clinical and therapeutic implication of
20 mutations to the gene SCL29A1."
21 Now I am quoting, "SCL" -- oops --
22 "15A1 is a transmembrane peptide transporter

that is highly related," excuse me, "to SLC11A1 and SLC19A1 and SLC29A1, all of which are implicated in the transport of small molecules and drugs to cancer cells."

And it goes on to talk about the potential therapeutic implications. And one skilled -- and talks about particularly chemotherapy with cytovene and it has been associated with cyto -- excuse me, cytarabine resistance in human leukemia.

So, the presence of mutation in SLC29A would inform an oncologist that the use of this drug was contraindicated.

And then I go on to talk -- or it goes on to talk about the FLT3 and NMP1 mutations, and it talks about the therapeutic implications of those.

So, the sequencing is -- over time is providing information about the molecular state of the disease in this individual which would then be, and I believe -- so, this is actually a very interesting study.

The individual who was sequenced here was actually a colleague of the group at Washington University that performed this analysis.

That individual had been diagnosed with AML. It had been found -- that disease had been found with refractory therapy and that is why they undertook this particular analysis.

So, the analysis that was done and the case report that was written, I believe, came from a collaborative effort among the laboratory, computational and physician scientists who were involved in the paper.

BY MR. LUMAN:

Q. So, the --

A. And that is what resulted in the case report.

Q. So, the therapy choice or a change in therapy for the subject was made by a collaborative effort amongst the laboratory computational team and the physician scientists;

is that right?

MR. KRAUSE: Objection to the form.

THE WITNESS: So, that is not what I said. The claim simply requires generating a report which would inform a therapy choice or change in therapy, right.

So, the set of mutations, based on our understanding of what those mutations do, could inform a therapy choice, right.

So, any result from any assay like this is going to provide guidance. Ultimately the choice of therapy is going to be made by the patient and their physician.

But, that is an informed decision. And in this case it would be an informed decision based on the results of the sequencing assay that Ley carries out, right.

What Ley is providing is information to inform that therapy choice, and it is provided in the form of the case report that is in the supplement.

BY MR. LUMAN:

Q. And so, Ley would be the laboratory computational team that is generating the report that would inform the therapy choice.

Do I have that right?

MR. KRAUSE: Objection to form.

THE WITNESS: I don't know Ley's particular background, right.

It is the assay that produces the data, right.

The data has to be interpreted. And in this case I'm not sure if it was a computational analysis or individuals reviewing the literature and coming up with the potential therapeutic interventions.

In 2012, my colleague, Mick Correll, and I founded a company called GenoSpace. And we were providing software tools for the molecular -- for the molecular diagnostics industry.

The software tools we provided took mutational data and integrated that with what was known in the literature, largely

1 condensed through guidance that comes from
2 the National Cooperative Cancer Network,
3 NCCN.
4 And providing, based on the
5 mutational data, potential therapeutic
6 interventions, all right. Therapeutic
7 significance.
8 So, some mutations might indicate
9 the use of therapies. Other mutations might
10 contraindicate the use of therapies.
11 So, that kind of data informs the
12 decision that one would make.
13 And so, the case report here is
14 providing mutations with some interpretation
15 to inform the ultimate decision that is made.
16 But I don't have insight into who
17 drafted this report or how all of the pieces
18 were put together.
19 But, the example I am giving you
20 from the company we founded is just one
21 example of how that might be put into place.
22 BY MR. LUMAN:

Q. And in Paragraph 127 of your report where you -- it is the last sentence, where there is a therapy choice or change. And you give the example of switching away from the conventional therapy or resuming therapy upon relapse.

What was the change in therapy that was done in Ley for the specific patient?

MR. KRAUSE: Objection to form.

THE WITNESS: So, the claim language simply says, "Generating a report which inform a therapy choice or change in therapy in the subject."

A therapy choice can be no change in therapy, right. A therapy choice could be an alternative approach, right.

And so I don't recall in the case report, and I don't have it in front of me, whether a particular change in therapy was made.

But, clearly a choice in therapy was made. And that choice, given the data that was available, likely was informed by the

presence or -- by the presence or absence of particular mutations.

For example, in Paragraph 130, I wrote, "One skilled in the art would recognize that the characteristics of the disease and the patient's mutational," it should -- there is a missing word. It should be profile or state -- "in the FLT3 and NMP1 genes would contraindicate the use of allogenic stem cell transplant for this patient."

And then I cite to a reference, Davies, which talks about the particular mutation status of these two genes, right.

So, in -- the information here provides information that informs the choice. That choice could be a particular therapeutic avenue or the continuation of the same therapeutic avenue. They are both choices.

MR. LUMAN: How long have we been going since the last break?

THE VIDEOGRAPHER: So we have been

on one hour and 4 minutes.

MR. LUMAN: Let's take a short break.

THE WITNESS: Fine with me.

MR. KRAUSE: Sure.

THE VIDEOGRAPHER: The time is 4:11 p.m. Off the record.

(Recess taken -- 4:11 p.m.)

(After recess -- 4:24 p.m.)

THE VIDEOGRAPHER: The time is 4:24 p.m. Back on the record.

BY MR. LUMAN:

Q. Dr. Quackenbush, I would like to look in Exhibit 1061. That is your declaration for the '611 patent. Could you look in that declaration at Paragraph 207, please.

A. Sure. All right, I am there.

Q. And in Paragraph 207, you are setting forth an opinion on the -- on Newman's personalized selector containing the variable sequences that would meet Limitation 1a -- that can't be right.

1 That would be for Claim 5. Right?
2 MR. KRAUSE: Objection to form.
3 THE WITNESS: Okay, hold on. Let me
4 call up the '611 patent.
5 BY MR. LUMAN:
6 Q. All right, let me ask a different
7 question.
8 In Paragraph 207, you are relying on
9 the personalized selector from Newman to meet the
10 variable sequences for Claim 5 of the
11 '611 patent. Right?
12 A. So, in this section of my
13 declaration, I am providing an analysis of
14 Newman, describing how it anticipates a number of
15 claims in the '611 patent.
16 In the section you are referring to,
17 I am explicitly discussing dependent Claim 5,
18 which is the method of Claim 1.
19 And in the paragraph that you were
20 referring to I write, "As discussed for Claim 1,
21 Newman describes a plurality of nucleic acid
22 probe molecules."

And it goes on from there.

Q. Right. And the personalized selector from Newman, that is the 157 kilobase selector that we talked about earlier today, in the Online Method section of Newman?

A. Sorry. That was a while ago.

Q. Newman is Exhibit 1043.

A. Yes, I have it. Thank you.

All right. I'm sorry. Would you please re-ask your question?

Q. So, the personalized selector that you are referencing in Paragraph 207 of your declaration, is the 157 kilobase personalized selector that Newman discloses on the last page of its Online section. Correct?

A. So, in Paragraph 207, yes. The personalized selector for the glioblastoma analysis -- excuse me, contained variable sequences based on the sequencing result, which I mapped back to Step 1a.

And then, in Paragraph 208, also talk about the non-small cell lung carcinoma

1 selector which contains eight mutations per
2 patient, but then also describes the use of
3 probes designed for clinically relevant regions
4 that include actionable fusions, for example,
5 known fusions in sets of genes.
6 Q. So, you just pointed to the NSCLC
7 selector.
8 Now, the, Newman's personalized
9 selector, that was 157 kilobases, is not the same
10 as the NSCL selector that has the eight mutations
11 per NSCLC patient. Right?
12 A. So, the non-small cell lung
13 carcinoma, the NSCLC selector, is distinct from
14 the glioblastoma selector.
15 The glioblastoma selector, on this
16 last page of the document that we have discussed,
17 they said, "We designed 157 kilobase personalized
18 selector to cover these mutations," the 1,500, I
19 believe, mutations in the glioblastoma,
20 "employing the same biotinylated oligonucleotide
21 synthesis process is designed for -- as described
22 for the non-small cell lung carcinoma selector as

1 designed above."
2 So, they use the same basic
3 principles. Only for the non-small cell lung
4 carcinoma selector, I believe they targeted only
5 279 mutations.
6 So, it would be about one-fifth the
7 size of the genomic region represented here for
8 the glioblastoma.
9 Q. I would like to go back to
10 Exhibit 1020. That is your declaration in the
11 IPR on the -- let me get it right.
12 A. '783.
13 Q. Thank you. '783 patent. And would
14 you turn to the last page with me.
15 A. Yes.
16 Q. And that is your signature on the
17 last page?
18 A. Yes, it is.
19 Q. Are you aware of any changes that
20 you would like to make to the declaration?
21 A. I can't recall if it was this one or
22 the previous one where they -- I think there was

some missing words. But, sitting here right now, I can't think of anything that I would want to change.

Q. Can you turn to Paragraph 48 with me.

A. Sure. All right.

Q. So, in Paragraph 48, the second sentence says, "No two people (apart from identical twins) have identical DNA sequences throughout the entirety of their genomes."

Do you see that?

A. Yes, I do.

Q. Isn't it true that even identical twins do not have identical genes throughout their entire genome?

A. So, at some point they do, right. So, identical twins arise when a fertilized ovum begins to divide and splits and then separates.

Over the course of one's lifetime one picks up somatic mutations.

So, we all diverge from each other a tiny amount. But identical twins have

functionally identical genomes. There are -- you are right. There are small differences.

Q. So, it is not literally true that identical twins have identical DNA sequences throughout their entirety of their genomes, right?

MR. KRAUSE: Objection, asked and answered.

THE WITNESS: So, at the moment the blastocysts splits, they would, right.

Later on in their life they might not. They might have a you few small differences.

But those differences between the identical twins are going to be far smaller than the differences between any two other individuals.

So, maybe I could modify this by saying nearly identical DNA sequences as adults through the entirety of their genomes.

BY MR. LUMAN:

Q. Turn to Paragraph 109.

A. Sure.

Just to give you some scale, too. The difference between any two of us is about one base out of 1,000.

So, with the 6 billion-based genome, the difference between you and me is about 6 million genetic variants.

Between identical twins, it is going to be far less than one base out of 1,000, but I couldn't tell you the scale.

Q. So, even if, even if one base in a thousand, that is not identical.

A. That is you and me. For identical twins, it is going to be far smaller than that.

Q. Oh, right. I'm saying even for identical twins, they do not have identical DNA sequences throughout the entirety of their genomes, at least from the point that they are born, correct?

MR. KRAUSE: Objection, form.

THE WITNESS: So, identical twins are going to have nearly identical genomes; I

can't quantify the exact level of difference that would occur between identical twins. I just don't know.

But in many genetic tests, for example, in forensic genetics, one of the confounding factors that can occur in forensic DNA testing is a failure to identify differences between identical twins simply because the rate at which the genomes differ is vanishingly small.

BY MR. LUMAN:

Q. Do you see Paragraph 109?

A. Yes, I do.

Q. And, I'm looking -- it is actually the last sentence. Let's see. It says -- the last sentence, "In Ley, the probe set would thus necessarily include PCR primers that hybridize to the ten non-synonymous variable mutations."

Do you see that?

A. Yes, I do.

Q. Now, PCR primers, they don't actually hybridize to the mutations. They would

hybridize upstream or downstream from the mutations, right?

A. So, you can characterize this in a variety of different ways, right.

What I am referring to here is the fact that the loci themselves, the regions of DNA contain those mutations. Right.

So, those PCR primers would hybridize to the loci, the mutated loci, right. So, the non-synonymous mutations are in the loci themselves.

And that is what I was referring to here.

Q. So, if we wanted to write the sentence in a way that we have removed any ambiguity, you would need to specify that it is the PCR primer's hybridizing to the loci where the mutations of the ten non-synonymous mutations; is that right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, you could write this in a variety of different ways.

I think it is fairly clear. The probe set, right, actually hybridized to the loci that contained the mutations. It is not one other the other. But they are hybridizing to that mutation.

If you wanted to talk about insertions or deletions or translocations, the hybridization would naturally, with the two probes, that probe would actually span the, the mutated region.

Even with a point mutation, the probes span the mutated region.

So, in Ley, Ley was looking at non-synonymous mutations. And the PCR primers hybridized to those mutations in the sense that they hybridized in regions that allowed them to be assayed by sequencing.

BY MR. LUMAN:

Q. Now, the specific mutation for CDH24, that is a Y590X mutation, right?

A. I would have to look in Ley. I don't recall sitting here right now.

MR. LUMAN: Can we make Ley available to Dr. Quackenbush? It is Exhibit 1012.

(Exhibit 1012 marked for identification.)

THE WITNESS: All right. It is up.

BY MR. LUMAN:

Q. Yes, and I was looking in Table 2 on Page 69. Do you see that?

A. Hold on. I have to get it downloaded here. I've got a bunch of documents opened. It didn't download for some reason. Hold on.

There we go. Okay, so we are looking at which table?

Q. Table 2 on Page 69. And the specific mutation in CDH24 was a Y590X mutation, right?

A. That is how it is characterized, yes.

Q. It is not an insertion or deletion?

A. So, it is a point mutation. It is

1 characterized as a nonsense mutation. It occurs
2 at position 590 in the protein sequence. And I
3 believe I recall Y is lysine and X, I believe, is
4 a stop codon.
5 So, it is a point mutation that
6 tells the protein synthesis machinery to stop
7 making a protein and results in a truncated form.
8 Q. And when Ley's PCR primers
9 hybridize, they don't hybridize to the Y5NDX
10 mutation, do they?
11 A. They actually do, right. They
12 hybridize to the gene that contains that
13 mutation. So, the gene is mutated and they are
14 hybridizing to that gene or the region of that
15 gene.
16 So, they don't -- they don't bind to
17 the location of the point mutation but they are
18 still binding to the mutated gene.
19 Q. And so when you wrote in
20 Paragraph 109 that the PCR primers hybridize to
21 the ten non-synonymous variable mutations, you
22 really meant that they hybridized to the gene,

not to the mutation itself.

MR. KRAUSE: Objection.

THE WITNESS: The gene is mutated. They hybridize to the gene itself.

BY MR. LUMAN:

Q. Can you turn to Paragraph 124 with me, please.

A. Sure. All right, I am there.

Q. I'm going to -- it is in Paragraph 124, it spans the page. So on Page 69 I'm going to look at a sentence about halfway down Page 69. There is a sentence about halfway down that says, "While Ley does not provide the primer sequences."

Do you see that one?

A. Yes, I do.

Q. So, because Ley didn't provide the primer sequences, we don't know the exact primers that Ley used for her experiment. Right?

A. I believe it is Timothy Ley, so I think it is his experiment. And yes, we don't know the exact primers that Ley used.

Q. And if, if Ley designed primers for -- I'm looking at the table. You've got the table on Page 69.

A. Uh-huh.

Q. The CDH24 gene and it is 3,529 base pairs long. Do you see that?

A. Yes, I do.

Q. And so, if a person of skill in the art were going to design PCR primers, they could design a primer that hybridizes to many different locations throughout that 3,529 base pairs of the CDH24 gene. Right?

MR. KRAUSE: Objection, calls for speculation.

THE WITNESS: So, what Ley is doing is Ley is identifying mutations that occur in particular genes.

Ley then designs primers that hybridize to the mutation in the sense that they hybridize to the gene that is mutated.

Almost certainly they hybridize to a particular exon. So, we talked about the

structured genes before. Genes contain introns and exons.

The lengths that I provide here are really to show that the total length of sequence covered spanned by the probes that Ley uses is far less than 175,000 base pairs.

So what I did in providing the analysis in this table is actually looked at, you know, what you might call a worst-case scenario.

Where for each one of the genes I looked in GenBank, the public repository of gene sequences, and I got the entire coding length of the sequence.

Now that is certainly not what Ley used. But if Ley had for some reason decided to span the entire gene, then for each one of the ten genes or 12 genes that Ley uses, I summed up the length of all of those genes and showed it was 45,000 bases in length.

But one would target the regions following Ley. The regions of those genes

which contain mutations, it would be far less than the 45,000 base pairs that are represented in the entire length of those genes.

BY MR. LUMAN:

Q. And you said that it is certainly not what Ley used with respect to a -- what is shown in the table on Page 69.

How do you know that for certainty?

A. I would have to go back and read the protocol.

But Ley uses a technique that is often referred to, I believe, I believe he uses a technique called next generation sequencing. In fact, yes, he uses the Illumina sequencer, the Illumina Celexa technology he refers to it.

So, he is using a sequencing platform that, at the time produced, I think we were talking about 100 to 150 base pair reads, if I recall. We have discussed so many references today.

And so sequencing the entire length

of each gene, number one would be very time and -- well, very resource intensive, including time.

But also, wouldn't necessarily make sense, right.

What Ley did is, Ley did whole genome sequencing initially to identify mutations, and then Ley wanted to monitor those mutations.

The most rational way to monitor those mutations would be to specifically target those mutations in the gene. And, therefore, it would be very -- it would be hard to imagine a scenario in which one would try to amplify the entire gene or sequence the entire gene.

So, I can read through this and look in greater detail to try to find more evidence of that. But what I am presenting in that table is really kind of a worst-case scenario if Ley for some reason had decided to write a sequence, the entirety of each of these genes.

Q. But, I mean, Ley could have

1 sequenced the entirety of these genes with PCR
2 primers, right?
3 MR. KRAUSE: Objection to form.
4 THE WITNESS: Ley could have done a
5 lot of things. What is important is what Ley
6 did. And what Ley did was Ley analyzed the
7 entire genome using whole genome sequencing,
8 identified by comparing tumor and matched
9 normal, identified so -- I believe in Ley it
10 was the AML sample and a skin biopsy.
11 And then identified particular
12 regions that appeared to be mutated, designed
13 PCR probes to target those mutations and
14 hybridize to them so they could be sequenced.
15 And selectively amplified, then
16 sequenced. And then followed those -- looked
17 at those in multiple different samples.
18 So, you know, the exact details of
19 what he did, I don't recall sitting here
20 today. It is probably in the Online Methods,
21 the supplemental methods. And the PCR
22 primers may well be there. I simply don't

1 recall.
2 BY MR. LUMAN:
3 Q. Do you have Ley yet? Have we given
4 you a copy of that?
5 A. Yes, I have a copy of Ley.
6 Q. Okay. So, you have that available
7 to you?
8 A. Yes.
9 Q. And, this is important for the case
10 so I want to know your answer on whether or not
11 we can tell if Ley sequenced the entirety of
12 those 45,254 base pairs that you have put in
13 Paragraph 124 or if we know for certain that they
14 did not do that.
15 What is your answer on that?
16 Let me ask the question. Do you
17 know for certain whether or not Ley sequenced all
18 45,254 bases that are shown in Paragraph 124 of
19 your declaration?
20 MR. KRAUSE: Objection to form.
21 THE WITNESS: So, I believe that is
22 in the supplementary information on page --

which I don't have access to sitting here today -- on Page 71 of Ley.

What Ley tells us in the methods summary is, and I think I just spoke earlier, Ley actually used a combination of two different next generation sequencing technologies.

So, Ley did whole genome sequencing for the tumor genome in skin using the Illumina Celexa platform. Then used the decision tree which is presented in one of the figures to identify single nucleotide variants.

And then designed PCR primers to select those variants. And then validated those variants using conventional Sanger sequencing.

And then further analyzed PCR generated amplicons from primary genomic DNA on the Roche 454 sequencer.

So, he actually used three sequencing platforms to complete this work.

In the methods summary that is provided, there is no information about the total -- about his primer design.

I am assuming that is in the supplemental information. But it wasn't germane to the argument that I presented, so I didn't review that in depth.

MR. LUMAN: Could we make Exhibit 1042 available to Dr. Quackenbush. That is the -- it should be the Ley supplemental material.

(Exhibit 1042 marked for identification.)

BY MR. LUMAN:

Q. Dr. Quackenbush, can you let me know when you've got it?

A. So, I have that here. Yes.

Q. Okay. So, now you have Ley and the Ley supplemental material.

And, with that in hand, can you tell me for certainty whether Ley actually sequenced the 45,254 base pairs that you have listed in

1 Paragraph 124 of your declaration?
2 A. So, could you repeat the question,
3 please?
4 Q. Yes. Can you tell me for certainty
5 whether Ley actually sequenced the 45,254 base
6 pairs that you have listed in the table in
7 Paragraph 124 of your declaration?
8 A. So, I can tell you he absolutely did
9 not. And that evidence is -- the confirmation of
10 that is provided on Page 8 of 32. So, I don't
11 know if there is a particular page number, but
12 PDF Page 8.
13 It says, "Confirmation of Somatic
14 Mutations By 454 Sequencing. Amplicons
15 containing exons with relevant putative mutations
16 were generated from non-amplified genomic DNA
17 from the primary and relapse tumor samples, and
18 the skin biopsy obtained at initial banking (when
19 the patient was overtly leukemic)."
20 So, the amplicons containing the
21 relevant mutations were sequenced, right.
22 Each one of the genes that Ley

analyzed were listed in one of the tables you referred me to. Each one of them had a single mutation, right. And I believe that is correct.

So, if that is correct, then what this supplemental method is telling me is that Ley sequenced only the exons containing the relevant putative mutations.

And so rather than the entire worst-case scenario of 45,000 base pairs, Ley sequenced the far smaller region of the genome -- of, of -- small -- a small -- I can't say it now.

A far smaller region of the genome that was represented by those exons.

Q. Now, in the table on Page 69 and over on to Page 70 of your declaration, you have only included the length for the exon.

But the DNA that Ley is accessing, if he had designed PCR primers for the entire gene, it would include the introns as well. Right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, that is not what

1 Ley tells us he was interested in, right.
2 Ley was interested in tumor-specific
3 somatic mutations that alter the protein
4 coating genes, right.
5 For the purposes of this initial
6 study Ley writes, "We restricted our
7 downstream analysis to the coding sequences
8 of the annotated genes." Okay.
9 "We found only eight heterozygous
10 non-synonymous SNVs," single nucleotide
11 variants, "in the genomes." Right.
12 So, they analyzed the protein
13 coating sequences. Those are where they
14 found the mutations.
15 In the table that we discussed
16 earlier that shows the mutations, each one of
17 those is a protein coating mutation, right.
18 So, Ley is limiting his analysis to
19 the protein coating sequences which is what
20 is typically done, because those are the
21 mutations that we have the best -- and
22 especially in 2000 and, I believe '08, when

1 Ley did this work. Those are the types of
2 mutations about which we can best interpret
3 the potential biological results.
4 So, one could hypothetically do lots
5 of things. Ley tells us that he focused on
6 the, on the protein coating sequences, the
7 exons.
8 And in fact, if we look at table --
9 or look at the supplemental information in
10 the Confirmation section, it is only the
11 amplicons containing exons with relevant
12 putative mutations that were sequenced.
13 So, while Ley could have done a lot
14 of things, what Ley did was sequence a subset
15 of that 45,000 bases in a small subset.
16 BY MR. LUMAN:
17 Q. And so looking at Paragraph 124 of
18 your declaration, you have assumed -- I'm sorry.
19 You have deduced an upper bound on the sequence
20 coverage Ley uses by looking at just the exons.
21 But, the -- I mean if Ley were to
22 design primer sequences to the DNA available to

him, it would have had to -- if it were going to cover the whole gene it would cover the introns and the exons. Isn't that true?

MR. KRAUSE: Objection to form.

THE WITNESS: Ley tells us in multiple places in the article that the emphasis was on protein coating sequences, right.

In fact, if you look at Table 20 -- or not Table 20, the table that you were referring to in my report where I estimate the worst-case scenario, those are the coating sequence lengths. And those are annotated in GenBank.

So, I didn't make those up. That is what was there.

So, Ley's emphasis was protein coating sequences because those are the mutations that we understand, right. Those are the mutations -- as of 2008, I'm not sure if there were targetable therapies available.

But those are the mutations where we

have clinical information that guides treatment and therapy downstream.

So, it makes sense that that is what Ley would target. It doesn't make sense that Ley would then sequence the intervening sequences which aren't protein coating, right.

Tells us explicitly he did an analysis of protein coating sequence.

BY MR. LUMAN:

Q. So, let's talk about the PCR primers that Ley could have used.

Ley could have used PCR primers that would hybridize about 15 bases upstream or downstream of the mutation. Is that right?

MR. KRAUSE: Objection. Calls for speculation.

MR. LUMAN: What do you mean it calls for speculation?

MR. KRAUSE: You are asking what Ley could have used.

BY MR. LUMAN:

Q. Oh, all right. Let's ask what Ley did use.

Dr. Quackenbush, did Ley use PCR primers that hybridize 15 nucleotides upstream of the mutations?

A. So, Ley doesn't provide information about the actual primers that he used.

In the section on coating somatic mutations confirming -- excuse me -- on Confirmation of Somatic Mutations By 454 Sequencing, Ley tells us that amplicons containing exons with relevant putative mutations were generated from non-amplified genomic DNA, where the primary relapse tumor samples and the skin biopsy obtained at initial banking was performed.

454 sequencing of these amplicons was performed as previously described.

And there is a reference to Reference Number 5. And right before all of the tables -- sorry. Now I am on the massive pages.

So, Ley cites to a 2007 paper by

1 Thomas, et al., High-throughput Oncogene Mutation
2 Profiling in Human Cancer, that appeared in
3 Nature Genetics.
4 So, the sequencing and primer design
5 protocols may occur there, but what Ley tells us
6 is that Ley targeted the exons.
7 And again, while Ley could have done
8 many things, my best read of this is that this
9 was exonic sequencing, not sequencing of the
10 introns.
11 Q. So, do you know if Ley used PCR
12 primers that hybridize 80 bases upstream to the
13 mutations?
14 A. So, again, Ley doesn't describe here
15 the primer design methodology that was used.
16 But amplicons containing exons with
17 relevant putative mutations were generated and
18 sequenced.
19 Q. Do you know what length of PCR
20 primer Ley used, like was it 20 more, 50 more?
21 A. Again, that is not disclosed. I
22 could make guesses, but they would only be

1 guesses. I am assuming the PCR primers varied in
2 length depending on the calculated melting
3 temperature.
4 Q. You don't know the GC content for
5 the primers that Ley used to amplify the
6 mutations in his paper; is that right?
7 A. You are asking me many questions
8 about the primers. Ley doesn't disclose it.
9 There may be additional information that is
10 available. I don't see it immediately.
11 But whether or not Ley discloses
12 those, the total sequence that was generated was
13 far less -- it covered a region of the genome far
14 less than 45,000 base pairs.
15 And Ley clearly lays out a protocol
16 that renders the entirety of Claim 1 of the '783
17 patent obvious -- anticipates the entirety of
18 Claim 1 of the '783 patent.
19 Q. Ley doesn't provide information
20 about the melting temperature for the PCR primers
21 that were used in his experiment, does he?
22 A. No, but I don't see how that is

relevant. And actually he probably designed for annealing temperatures, not melting temperatures, but --

Q. And you don't know the annealing temperatures that Ley used for the PCR primers; is that right?

A. In this particular reference, Ley does not disclose the PCR protocol that was used, at least I can't find it. There may be additional material, but I don't have that available.

So, to the best of my knowledge, Ley doesn't disclose the parameters used for the PCR primer design.

Q. And because Ley doesn't disclose the parameters, the person of skill in the art doesn't know what concentration of primers Ley used in his PCR experiments. Right?

MR. KRAUSE: Objection to form.

THE WITNESS: So, a person -- go ahead, Andrew.

MR. KRAUSE: No. That is noted on

the record.

THE WITNESS: All right. So, a person of ordinary skill in the art reading this reference would understand very simply how to take DNA fragments, how -- sorry -- to take exons within the genome with a particular target mutation and design PCR primers to enrich or amplify those mutational targets.

One example is the program Primer3, which is probably the most widely used program.

If I had to make an uninformed guess, my guess would be that Ley used Primer3 and provided the coordinate of the mutation within Primer3 so that the PCR primers would bracket it and hybridize the mutation, and allow it to be amplified and sequenced.

So, one skilled in the art would understand very easily how to do this kind of analysis. The input for a program like

1 Primer3 would be the standard PCR conditions
2 one would use.
3 So, one could adjust the buffers and
4 other things appropriately. And there are
5 almost certainly other references available
6 from -- that are cited here. And if one
7 really needed the information, one could
8 reach out to Ley and request that
9 information.
10 BY MR. LUMAN:
11 Q. Do you know how many cycles of PCR
12 Ley performed to generate his amplicons?
13 A. I don't believe that is recited, but
14 a person of ordinary skill in the art would
15 understand how to design primers and conduct PCR
16 to target particular mutations.
17 Q. And that person of skill in the art
18 designing primers would have a range of primers
19 that they could select from in order to
20 accomplish what Ley was doing, right?
21 MR. KRAUSE: Objection to the form.
22 THE WITNESS: Again, a person of

ordinary skill in the art would design primers that were optimized to the laboratory conditions they were using.

They typically allow a program like Primer3 to design those primers and select them.

BY MR. LUMAN:

Q. There isn't a single set of PCR primers that are required to amplify mutations that Ley is trying to amplify. Correct?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I don't know what you mean by that. Ley clearly used a specific set of PCR primers.

The fact that Ley doesn't disclose those PCR primers in the document that was published in no way renders Ley unworkable.

One of ordinary skill in the art would have understood how to conduct PCR. PCR by this time was -- PCR was invented, I think in the '70's, so it is more than 30 years old.

So, you know, this -- the failure to disclose the primer sequences or the PCR conditions doesn't in any way mean that Ley did not anticipate the claims of the '783 or '611 patents.

BY MR. LUMAN:

Q. Do you know if Ley used the standard PCR amplification protocol or a nonstandard PCR primer amplification protocol?

A. Again, to the best of my knowledge, Ley doesn't provide, in the documents I have available, detailed descriptions of the PCR protocol used.

But a person of ordinary skill in the art would understand how to perform PCR and to target a small set of mutations in the genome; those mutations being mutations in exons.

And the failure to provide that in no way renders Ley incapable of anticipating the claims of the 781 -- or '783 or '611 patents.

MR. KRAUSE: We have been going a little over an hour. Is now a good stopping

point?

MR. LUMAN: How about 15 more minutes. Would that be okay?

MR. KRAUSE: If we could just take five. I need the restroom.

MR. LUMAN: Okay. We can take a break.

THE VIDEOGRAPHER: All right, the time is 5:18 p.m. Off the record.

(Recess taken -- 5:18 p.m.)

(After recess -- 5:25 p.m.)

THE VIDEOGRAPHER: The time is 5:25 p.m. Back on the record.

BY MR. LUMAN:

Q. Dr. Quackenbush, can you look at the table in Paragraph 124 of your declaration that spans paragraph -- Pages 69 to 70?

A. All right. I have it open.

Q. And you hadn't included any of the intron sequence in the lengths that you calculated for using the table that spans Paragraph 69 and 70. Right?

A. There was no reason to do that. Ley told us that Ley -- that the analysis they were performing was an analysis of coding sequences.

Q. If a person of skill in --

A. I'm sorry. And in fact, in the supplemental materials we were told that only the exons containing mutations were analyzed in the subsequent steps.

Q. And so if a person of skill in the art wanted to ensure that they got the entirety of the exon sequence, wouldn't they want to design PCR primers that flank out into the noncoding regions to make sure that they have at least multiple reads from the very beginning of the exon to the very end of the exon?

MR. KRAUSE: Objection to form.

THE WITNESS: First, if one were to target mutations one may not need the entirety of the exon.

Second, one could easily design PCR primers or could potentially design PCR primers depending on the application that

1 started at the exon boundaries and pointed
2 in. And then depending on the sequencing
3 protocol used, still be guaranteed to
4 sequence each and every base of the exon.
5 So, there are a number of different
6 protocols that one could use. One could
7 hypothetically do a lot of different things.
8 But the important thing is that Ley,
9 in, with the selected set of primers and the
10 downstream analysis, only targeted a small
11 fraction of this 45,000 base pair region of
12 the genome.
13 BY MR. LUMAN:
14 Q. So, we know that Ley was designing
15 amplicons for use on the 5 -- the 454 Roche
16 sequencer, right?
17 A. I believe the amplicons were
18 analyzed using both Sanger sequencing on an ABI
19 capillary sequencer, and then later on the 454
20 sequencer.
21 Q. Are you aware of anything unique
22 about generating amplicons for use on the ABI

capillary sequencer that would differ from generating amplicons for the 454 sequencer?

A. It would depend on your particular application how you might tailor your design or how you might harmonize the design to simplify the workflow.

Essentially both are DNA sequencers and they will sequence DNA. And PCRs are designed to amplify target regions. In the case of Ley, those are amplicons containing exons with relevant mutations.

Q. And so specifically for Ley, are you aware of anything unique that Ley had to take into account to generate amplicons for use on both the API -- ABI capillary sequencer and the 545 sequencer -- I'm sorry, the 454 sequencer?

A. So, you know, Ley doesn't disclose his primer design protocol. Ley does tell us the amplicons targeted exons.

I can tell you that as of the early 1990's, when I was at the Salk Institute, I was using automated programs to design PCR primers

for thousands of targeted regions in the genome and amplifying them using standard conditions.

So, although that is not provided -- and then sequencing some of the PCR products.

So, although that is not provided here, one skilled in the art would understand how to do that. One could also ask Ley for the protocol.

Q. Would Ley need to have used some promoter specific primers to be compatible with the 454 sequencing?

A. So, the library preparation that would occur would be library preparation for 454 sequencing. That was distinct from library preparation for Illumina sequencing.

Both methods were well known in the art as of 2000 -- I believe this is 2008. Both Illumina and 454 provided commercially available sequencers.

So, the protocols for taking PCR amplicons and sequencing them would have been well known.

Q. So, although the protocols were well known, was there something specific that Ley would have had to use to be promoter specific in its primers in order for the amplicons to be compatible with the 5 -- the 454 sequencer?

A. So, promoters usually refer to genes and regions of genes where transcription factors bind.

Most of these sequencing technologies, and I'm far more familiar with the Illumina sequencer, they use oligonucleotides, they refer to as P5 and P7, to bind in the flow cell.

The 454 sequencer used similar sequences. I believe the first step was emulsion PCR. I don't recall the details of 454.

But again, the library preparation chemistry was specific to the platform.

But one could start sequencing with PCR amplicons and take the same PCR amplicons and use them in 454 sequencing, Illumina sequencing or Sanger sequencing on the applied biosystems

instrument.

Q. Do you know if Ley used any type of nested PCR in order to generate the amplicons?

A. Again, Ley doesn't disclose the PCR protocol that was used. So, sitting here today, I can't tell you what method Ley might have used.

But methods for amplifying regions of the genome and sequencing them were well known in the art.

Q. Is it possible that Ley used nested PCR primers to generate its amplicons?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I can't speculate on what Ley did or did not do. I can tell you that Ley sequenced amplicons containing exons with the relevant putative mutations as -- and tracked those across multiple samples from the same individual.

BY MR. LUMAN:

Q. Could Ley have used -- do you know if Ley used semi-random primers in order to generate the amplicons that he used for

1 sequencing?
2 A. Again, Ley does not disclose, in the
3 documents I have in front of me, the actual PCR
4 protocols or sequencing protocols that were used.
5 But protocols to carry out this kind
6 of analysis were well known in the art.
7 So, Ley may have used a variety
8 of -- could have used any of a variety of
9 different techniques, but I can't speculate on
10 which ones were actually used.
11 Q. Are semi-random primers one of the
12 techniques that Ley might have used?
13 MR. KRAUSE: Objection to form.
14 THE WITNESS: I would have a hard
15 time rationalizing why Ley might have used
16 those.
17 The most logical thing for Ley to
18 have done would be to look at the target
19 exons that contained the putative mutations
20 and design primers that were specific to
21 those exons.
22 So, while Ley could have done all

1 kinds of crazy things, the most logical and
2 rational would be to simply design primers
3 specific to those exons.
4 BY MR. LUMAN:
5 Q. Could Ley have used random PCR
6 primers to generate the amplicons that were used
7 to sequence in the 454 sequencer?
8 A. Given that Ley was targeting
9 specific exons and wanted to selectively amplify
10 those, the use of random primers wouldn't be
11 possible. The use of semi-random primers,
12 depending on how you define that, would likely
13 not be possible.
14 What Ley describes is the targeted
15 sequencing of specific exons containing
16 mutations. Therefore, my understanding of what
17 Ley did is that Ley almost certainly designed
18 specific PCR primers to target the mutations that
19 he was interested in following across multiple
20 samples.
21 Q. The 454 sequencer has a different
22 read length that is possible than Illumina's

1 sequencers, correct?
2 A. All of these sequencing technologies
3 had different read lengths. As of the
4 publication date of Ley, which was 2008, I don't
5 recall what the relevant sequence read lengths
6 were.
7 Q. And that is also true of the Sanger
8 sequencing, that would have a different read
9 length that is possible to use than the 454
10 sequencer. Right?
11 A. So, Sanger sequencing, as of the
12 time when the draft genome was completed in 2001,
13 could read sequence fragments as long as 1,000
14 bases or more in length.
15 Typically, though, you could -- or
16 one could use, depending on application, use
17 Sanger sequencing to read far smaller fragments.
18 So, many of the fragments that I was
19 using and analyzing with Sanger sequencing were
20 only a few hundred base pairs in length.
21 I have analyzed smaller fragments.
22 I have also analyzed larger fragments.

1 As of 2008, I can't tell you what
2 the read lengths were on the 454 or the, the
3 Illumina sequencers.
4 I believe, if I recall, Ley actually
5 discloses in the method summary that the average
6 read lengths for Sanger sequencing were 32 and 35
7 bases. And I don't recall if he provides any
8 information about the read lengths they obtained
9 from the 454 sequencers.
10 Q. And would a person of ordinary skill
11 in the art have had to factor in the read length
12 of the 454 sequencer and the Sanger sequencing
13 method that Ley used in -- when designing primers
14 to use in Ley's assay?
15 A. So, the Sanger sequencing would
16 largely be irrelevant because the sequence read
17 lengths were far larger than the small regions of
18 the exons that would be targeted by the PCR
19 primers.
20 One consideration in designing those
21 primers might be the 454 sequence read lengths.
22 But I don't recall how long the

1 sequence read lengths were for that platform
2 in 2008.
3 Q. Is it possible that Ley used
4 hybridization capture probes to enrich the CDH24
5 gene and then use PCR primers afterwards?
6 MR. KRAUSE: Objection.
7 THE WITNESS: Ley could have -- go
8 ahead, Andrew. Oh, I thought you were
9 speaking.
10 So, Ley could have used all sorts of
11 different things. Ley doesn't tell us that
12 he did that.
13 Ley discusses the use of PCR to
14 amplify target regions. So, I will refer you
15 back to the supplementary information on
16 Page 8.
17 "Amplicons containing exons with
18 relevant putative mutations were generated
19 from non-amplified genomic DNA from the
20 primary and relapse tumor samples, and the
21 skin biopsy."
22 So, what Ley is disclosing is that

1 Ley did PCR from the non-amplified genomic
2 DNA.
3 BY MR. LUMAN:
4 Q. And Ley doesn't specify whether or
5 not any type of DNA processing took place before
6 the PCR amplicons were generated, right?
7 A. So, I don't know what you mean by
8 DNA processing. DNA would have to be extracted
9 from the primary and relapse tumor samples and
10 from the skin biopsy before PCR.
11 Although, one could also put cells
12 directly into PCR and do what is referred to as
13 Cell Pop PCR.
14 There is no reason to suspect that
15 that was done here because it is kind of a dirty
16 assay.
17 But we are told that the amplicons
18 were generated from non-amplified genomic DNA.
19 And what that indicates to a person of ordinary
20 skill in the art is that standard protocols were
21 used to extract genomic DNA.
22 This analysis was carried out at the

Wash U Genome Center where DNA extraction was a fairly common laboratory protocol, and one that a person of ordinary skill in the art would understand how to do.

Q. In the process of DNA extraction, would that include shearing the DNA?

A. It would depend. So, typically shearing isn't part of the extraction protocol. In many applications DNA could be sheared.

Again, one skilled in the art could easily design a protocol to take non-amplified genomic DNA and generate amplicons and sequence them.

Q. How about the use of restriction enzymes.

Is it possible that the DNA extraction process used at the Wash U Genome Center involved the use of restriction enzymes that would have spliced, for example, the CDH24 gene?

MR. KRAUSE: Objection to form.

THE WITNESS: So, I don't know what

1 you mean by spliced. Restriction enzymes cut
2 DNA.
3 If you want to splice pieces of DNA
4 together, you would have to do something --
5 you would have to do something much more
6 involved than simply using restriction
7 enzymes.
8 There is no reason to suspect that
9 restriction enzymes were used. It wouldn't
10 have been a standard library preparation
11 protocol. And in fact, we are told that the
12 amplicons containing exons were generated
13 from non-amplified genomic DNA. It doesn't
14 say the DNA was restricted.
15 Therefore, one skilled in the art
16 would understand that restriction enzymes
17 were not used in any processing of the DNA
18 that happened between DNA extraction and PCR
19 amplification.
20 BY MR. LUMAN:
21 Q. Are you aware of any other ways that
22 Ley could have generated amplicons to use in

1 the 454 sequencer that don't involve using PCR
2 primers?
3 MR. KRAUSE: Objection to form.
4 THE WITNESS: I don't know what use
5 it is to speculate about different things Ley
6 could have done.
7 Ley tells us that -- let's see. On
8 Page 69 of Ley, Ley says, "By sequencing
9 polymerase chain reaction PCR generated
10 amplicons from the tumor and skin samples,
11 and also from the relapse samples obtained
12 11 months after original presentation, we
13 determined that 152 of the variants were
14 false positives." Right. That is just one
15 example.
16 So, what Ley did was PCR. That is
17 what Ley told us that he did. Ley could have
18 potentially done a lot of different things,
19 but what Ley did is what Ley did.
20 And what Ley lays out in this 2008
21 article fully anticipates Claim 1 of both
22 the '781 and '611 patent.

And I believe I present arguments to that effect in both of my reports.

BY MR. LUMAN:

Q. Dr. Quackenbush, in preparing for today's deposition, did you review any documents?

A. Yes, I did.

Q. Which documents did you review?

A. So, those I recall reviewing were both of my declarations which we have been discussing today, both the '783 and '611 patents.

Ley, Forshew, Dawson, Newman and potentially some others.

Those are the ones that I recall sitting here today, but those are the ones that we have also discussed.

Ah, Mertes, Mamanova. I think those were the primary ones I reviewed. There may have been others.

Q. Did you review the Board's institution decision for the two IPRs that this deposition is about?

A. I recall reading them some time ago,

but I didn't explicitly review them for my testimony today.

Q. Did you do any independent research to prepare for today's deposition?

A. No, I did not.

Q. About how many hours did you spend preparing for today's deposition?

A. So, I couldn't tell you precisely. I did meet with Andrew and Amir yesterday for -- I think I we started at 11 and went until 4, so five hours.

And I believe I met with them the day before for three or four hours. And then I spent additional time reviewing the documents.

Q. And when you met with Andrew and Amir, was anybody else present?

A. No, no one else was present.

Q. Did you meet in person or by remote video conference?

A. We met by video conference.

Q. Okay. Let's see. Other than meeting yesterday and the day before, did you

meet with anybody else to prepare for today's deposition at any other time?

A. I did not meet with anyone else. I may -- I don't recall. I may have had a conversation with either one of the two gentlemen, but it would have been a short conversation probably largely around arranging times to meet by Zoom.

MR. LUMAN: Would it be all right if we take a short break for about five, 10 minutes?

MR. KRAUSE: Sure.

THE VIDEOGRAPHER: All right. The time is 5:49 p.m. Off the record.

(Recess taken -- 5:49 p.m.)

(After recess -- 5:55 p.m.)

THE VIDEOGRAPHER: The time is 5:55 p.m. Back on the record.

BY MR. LUMAN:

Q. Dr. Quackenbush, where are you located right now?

A. I am sitting in my wife's home

office at 86 Walpole Street in Dover, Massachusetts.

Q. Is anyone else in the room with you?

A. No. No one else is in the room with me.

Q. And has anyone joined you in the room during today's deposition?

A. No, I have left the room and talked to my wife, but other than that there is no one at home.

Q. Do you have any physical documents in the room with you?

A. No. I have a pad of paper that I have written a few notes, really page numbers or column numbers that I wanted to refer back to.

Other than that, I have nothing.

Q. And that is true for the entire deposition, you didn't have any other physical documents with you. Is that right?

A. I had no other physical documents, no.

Q. And other than the electronic

1 documents that were put into our Box share file,
2 did you have any other electronic documents
3 available to you today?
4 A. I had documents on my computer. I
5 didn't open any of them. I opened the documents
6 that you provided.
7 Q. And did you have any form of
8 communication with your attorneys during today's
9 deposition such as e-mail communications, chat
10 line, text message, phone calls, anything like
11 that?
12 A. No.
13 MR. LUMAN: I have no further
14 questions.
15 MR. KRAUSE: And Dr. Quackenbush, we
16 have no questions for you. So, thank you for
17 your time today.
18 THE WITNESS: All right. Thank you
19 very much.
20 And Henry, and Lori, thank you for
21 your time today.
22 THE VIDEOGRAPHER: Thank you. I'm

1 going to get us off the record. This marks
2 the end of today's deposition. The time
3 is 5:57 p.m.
4 (Whereupon, signature not having been waived,
5 the deposition suspended at 5:57 p.m. EST)
6 * * *
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CERTIFICATE OF NOTARY

I, LORI J. GOODIN, RPR, CLR, CRR, CA CSR # 13959 the Notary for this deposition, do hereby certify that the witness whose testimony appears in the foregoing deposition was sworn by me; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, or financially or otherwise interested in the outcome of this action.

Lori J. Goodin

LORI J. GOODIN, RPR, CLR, CRR
Notary Public in and for:

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Notary Commission Number: GG987804
My Commission expires: May 12, 2024
STATE OF CALIFORNIA, CA CSR# 13959
My Commission expires: February 22, 2024
STATE OF MARYLAND, COUNTY OF ANNE ARUNDEL
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DISTRICT OF COLUMBIA, WASHINGTON DC
My Commission expires: June 1, 2026
STATE OF DELAWARE: COUNTY OF KENT
My Commission expires: September 9, 2025
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1 John Quackenbush, Ph.D., c/o
IRELL & MANELLA LLP
2 1800 Avenue of the Stars, Suite 900
Los Angeles, California 90067
3
Case: Foresight Diagnostics Inc. v. Personalis, Inc.
4 Date of deposition: October 20, 2023
Deponent: John Quackenbush, Ph.D.
5
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7 The deponent may come to this office to sign the transcript,
8 a copy may be purchased for the witness to review and sign,
9 or the deponent and/or counsel may waive the option of
10 signing. Please advise us of the option selected.
11 Please forward the errata sheet and the original signed
12 signature page to counsel noticing the deposition, noting the
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15 not hesitate to call our office at (202)-232-0646.
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Deposition Date: October 20, 2023

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