

In the Matter Of:

Foresight Diagnostics Inc. vs

Personalis

JOHN QUACKENBUSH

September 21, 2023



VOLUME 1
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

Case IPR2023-00224
Patent 11,384,394

and

Case IPR2023-00317
Patent 11,408,033

VIDEOTAPED DEPOSITION of JOHN QUACKENBUSH, PH.D.

Thursday, September 21, 2023

9:31 a.m.

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Boston, Massachusetts

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Also Present:

Bob Giannini, Videographer

Josh Clarke, Lexitas monitor

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** Documents quoted on the record are
transcribed as read **

1 P R O C E E D I N G S

2 THE VIDEOGRAPHER: Good morning. We are
3 on the record. This is the videographer speaking,
4 Bob Giannini. I am with court reporter Michelle
5 Keegan with Lexitas Legal.

6 Today's date is September 21st, 2023. The
7 time is 9:31 a.m. Eastern Time. We are here at
8 Weil, Gotshal & Manges located in Boston,
9 Massachusetts, to take the video deposition of
10 Dr. John Quackenbush in the matter of Natera,
11 Inc., versus NeoGenomics Laboratories, Inc. [sic]

12 Will counsel please introduce themselves
13 for the record.

14 MR. WALTER: Derek Walter, Weil, Gotshal &
15 Manges, for patent owner Personalis.

16 MR. LUMAN: My name is Dave Luman. I'm
17 from the law firm of Knobbe Martens.

18 THE WITNESS: Sorry, you got the matter
19 wrong.

20 MR. KRAUSE: And this is Andrew Krause
21 from Irell & Manella LLP. With me is co-counsel
22 Amir Naini, from Naini P.C., representing

1 Foresight Diagnostics.

2 The matter in this is an IPR proceeding
3 between petitioner Foresight Diagnostics Inc. and
4 patent owner Personalis, Inc.

5 MR. WALTER: That's right.

6 JOHN QUACKENBUSH, PH.D.,
7 having been satisfactorily identified and duly
8 sworn by the Notary Public, was examined and
9 testified as follows:

10 EXAMINATION BY COUNSEL FOR
11 PATENT OWNER PERSONALIS, INC.

12 BY MR. WALTER:

13 Q. Good morning. Could you state your name
14 and address for the record.

15 A. Yes. My name is John Quackenbush. I live
16 at 86 Walpole street, W-A-L-P-O-L-E, in Dover,
17 Massachusetts.

18 Q. All right. You've been through many
19 depositions before so I'm only going to give you
20 one reminder, which is to try and make sure that
21 you don't speak over my questions and that you
22 wait for me to finish my question before you begin

1 your answer. Do you understand that?

2 A. Yes, I do.

3 Q. What did you do to prepare for your
4 deposition today?

5 A. So there are -- the deposition is about
6 two of the IPRs that were instituted. I read the
7 declarations that I submitted in those two IPR
8 matters. I read some of the supporting
9 documentation and references that were cited. I
10 also spent time meeting with counsel here
11 yesterday and then some additional time reviewing.

12 Q. You said you met with counsel yesterday.
13 How much time did you spend meeting with counsel
14 yesterday?

15 A. We started about 9:00 o'clock and I
16 believe we ended around 5:00. So eight hours.

17 Q. And the counsel you met with were
18 Mr. Naini and Mr. Krause?

19 A. Yes.

20 Q. Did anybody else participate in the
21 meeting?

22 A. No.

1 Q. Did you review the patents that are at
2 issue in the two IPRs we're here to discuss today?

3 A. Yes. The '394 and '033, I believe.

4 Q. Did you review the institution decisions
5 that were at issue in this case?

6 A. Yesterday, no. Specifically, no. I may
7 have looked at them sometime over the last few
8 weeks.

9 Q. At some point in time you had reviewed the
10 institution decisions. Is that accurate?

11 A. I believe I may have seen some of it. If
12 I did, it would have been cited in the materials
13 cited in my declarations.

14 Q. Do you know when the institution decisions
15 came out in this case?

16 A. Sitting here today, I do not know.

17 Q. Do you know if it was before or after your
18 declaration?

19 A. Those institution decisions? Yes, I did
20 review them. And yes, I believe they were after
21 my declaration.

22 Q. Did you review the institution decisions

1 in preparation for your deposition today?

2 A. So I don't know what you mean by "review."

3 I read them over and looked them over, but I

4 didn't study them in great detail.

5 Q. And that was in preparation for your

6 deposition today?

7 A. Yes.

8 Q. You're aware that Personalis submitted a

9 declaration from Henry Furneaux in support of

10 their preliminary response?

11 A. Yes. I believe that is true.

12 Q. Have you reviewed that declaration?

13 A. I've looked that over as well, yes.

14 Q. And you reviewed that in preparation for

15 your deposition today?

16 A. In part, yes.

17 Q. And have you reviewed the claims of the

18 patents in suit in preparation for your deposition

19 today?

20 A. I absolutely have reviewed the claims.

21 Yes. And those are a large part of what's

22 included in my declaration, so in the patent

1 itself and in the context of the declaration.

2 Q. Okay. Now, with regard to your
3 declarations, there's two declarations you
4 prepared, one for the '394 patent and one for the
5 '033 patent. Correct?

6 A. Yes, that's correct.

7 Q. Is there anything that you'd like to
8 change about those declarations?

9 A. Sitting here at this moment, I can't think
10 of anything. I didn't notice any typographical
11 errors or other errors or omissions that I can
12 recall.

13 Q. There's nothing as a matter of substance
14 you would wish to change about your reports?

15 A. Nothing that I can think of. No.

16 Q. Is there anything that you omitted from
17 your reports as a matter of substance that you
18 wish to have included?

19 A. I believe the documents stand on their
20 own, and I don't have anything further to add at
21 this point.

22 Q. Now, there were certain prior art

1 references you relied upon in connection with your
2 declarations. Did you participate in the search
3 to identify those references?

4 A. Yes, I did.

5 One of the things I often do when asked to
6 consider a patent is to look at some of the
7 references that are cited in those patents. I
8 also, given the fact that preparing a declaration
9 such as those through the IPR matters involves
10 looking back in time, I often do PubMed searches
11 to look at the relevant literature, filtering on
12 publication date to get a sense of what was
13 available at the time.

14 Q. Do you recall how much time you spent in
15 connection with the prior art search?

16 A. Sitting here today, I couldn't tell you.
17 No. That was -- I forget when we submitted these
18 declarations, but it was some time ago. And I
19 don't recall how much time I spent searching the
20 literature.

21 Q. With regard to the references that you
22 rely upon in your declarations, do you remember

1 which ones you identified in connection with your
2 search?

3 A. Specifically, no. Again, this was --
4 those declarations were submitted I think almost a
5 year ago. And I don't recall how much time I
6 spent or which particular references I identified
7 in the search.

8 Some of them I remember seeing years ago
9 when they were first published.

10 Q. With regard to the Leary reference that
11 you rely upon, do you know if you identified that
12 reference or if that was identified by counsel?

13 A. Sitting here today, I couldn't tell you.
14 Sitting here today, I couldn't tell you if they
15 were also cited, whether that was also cited in
16 the patents or not.

17 Q. Okay.

18 A. Actually, the Leary -- well, I don't know
19 who produced it in this matter. I believe the
20 last author in the Leary reference is Victor
21 Velachescu.

22 Victor is someone I've known for many

1 years, and he's someone who is really innovative
2 in the field of cancer diagnostics. So I recall
3 seeing that around the time it was first
4 published, but I don't recall if I identified it
5 specifically in the context of this matter.

6 Q. How about with regard to the Chan
7 reference? Do you know who identified that?

8 A. Again, sitting here today, I couldn't tell
9 you. I couldn't tell you.

10 Q. What about the Ley reference that you rely
11 upon? Same thing?

12 A. Again, sitting here today, I couldn't tell
13 you whether that was one I found or one of the
14 ones which the attorneys found and asked for my
15 opinion about.

16 Q. What about the Wagle reference?

17 A. Again, sitting here today, I couldn't tell
18 you. It was more than a year ago.

19 Q. How about the Forshew reference? Do you
20 know who identified that? Was that yourself or
21 was that counsel?

22 A. Again, sitting here today, I couldn't tell

1 you. I believe that's another paper I remember
2 reading or seeing about the time it was published.
3 But in the context of this matter, I couldn't tell
4 you who first identified it and brought it to our
5 discussions.

6 Q. Why is it that you have a recollection of
7 having read the Forsheew paper at the time it was
8 published?

9 A. So I don't know if I saw it at exactly the
10 time it was published. So in -- so the relevant
11 date for these patents is 2012. About that time I
12 was at the Dana-Farber Cancer Institute.

13 At Dana-Farber we were in the midst of
14 launching a program called "Profile." That
15 Profile program involved enrolling essentially
16 every single patient who was admitted to
17 Dana-Farber, profiling their genome to look for
18 mutations, and building both a research database
19 and a tool to help assist clinicians in making
20 decisions about treatment.

21 Around the same time, my colleagues and I
22 spun out a precision medicine software company

1 called GenoSpace. That company, GenoSpace, was
2 building software tools for precision medicine.

3 Our first two clients were a company
4 called PathGroup, which was a company based in
5 Nashville, Tennessee, that did pathology. They
6 were trying to break into molecular pathology and
7 they were doing sequencing. And we, as one of our
8 first clients, provided their precision medicine
9 reports.

10 Our other large client was a company or --
11 not a company. It was the Multiple Myeloma
12 Research Foundation. They were starting a -- they
13 were starting a project called "Commpas." And
14 it's spelled like "compass" except with two Ms
15 because it was for multiple myeloma, so
16 C-O-M-M-P-A-S.

17 The goal of Commpas was to enroll a
18 thousand treatment-naïve patients and to sequence
19 their genomes every year, integrating that data
20 with clinical information about treatment to
21 understand the evolution, development, and
22 progression of disease, and to better understand

1 response to chemotherapy.

2 In the context of multiple myeloma, a lot
3 of the analyses involved translocations. In
4 myeloma, one of the primary translocations is a
5 translocation between chromosome 4 and
6 chromosome 14. So it's referred to as t(4;14).

7 And that's the -- I guess this is more
8 relevant for the -- I think it was the Velachescu
9 reference, looking for translocations. But that's
10 the kind of approach that used whole genome
11 sequencing with mate pairs to identify
12 translocations.

13 Q. Your understanding is that the Forshew
14 reference used whole genome sequencing with mate
15 pairs?

16 A. Again, I'd have to look at the references.
17 I don't recall the details, sitting here. I think
18 it was the first one that starts with an L.
19 Victor Velachescu was the author.

20 If you'd like, I describe all of these in
21 my declarations. And if you'd be willing to
22 provide the declarations, I'd be happy to clarify

1 my understanding.

2 Q. I was asking something different. I
3 wasn't asking about the Leary reference. I was
4 asking about the Forshaw reference.

5 And I wanted to know why it was that you
6 had a recollection of having read Forshaw at the
7 time it was published or shortly thereafter.

8 A. So if you show me the Forshaw reference,
9 I'd be happy to refresh my memory. I think they
10 were looking at sequencing -- my recollection may
11 be wrong because I don't have the reference in
12 front of me.

13 But I think they were analyzing DNA in
14 plasma. So cell-free DNA. It was at a time at
15 Dana-Farber where I also ran something called the
16 Center for Cancer Computational Biology.

17 So the CCCB, the Center for Cancer
18 Computational Biology, provided computational
19 biology support for investigators across the
20 Harvard system.

21 We had a collaborator, whose name I do not
22 recall, who was working in ovarian cancer. My

1 primary contact in ovarian cancer was Ursula
2 Matulonis.

3 At the time, we were very interested in
4 working on this project with her and trying to
5 look at circulating tumor cells.

6 There are a lot of difficulties with
7 looking at circulating tumor cells, so we were
8 also considering looking at cell-free DNA. And if
9 I have my recollection correct, I think I remember
10 seeing it in that context.

11 But again, now we're talking about
12 something that happened 14 -- 13, 14 years ago.
13 That's my best recollection. But again, I may be
14 incorrect on some of the details.

15 Q. All right. I want to follow up on the
16 GenoSpace issue, but first I need to go off the
17 record for just one minute.

18 THE VIDEOGRAPHER: The time is 9:45.
19 We're off the record.

20 (Recess, 9:45 a.m. to 9:48 a.m.)

21 THE VIDEOGRAPHER: Okay. The time is
22 9:48. We're back on the record.

1 (Previously marked Exhibit 1020)

2 Q. All right. I've handed you a document
3 that's been previously marked as Exhibit 1020 in
4 IPR2023-317.

5 Do you recognize this as your declaration
6 related to the '033 patent?

7 A. Yes, I do.

8 Q. All right. You mentioned GenoSpace in one
9 of your previous answers, and I believe you
10 discussed that in your declaration in Paragraph 6.
11 Do you see that?

12 A. Yes, I do.

13 Q. All right. And in the 2012 time frame, is
14 it accurate that your work related to
15 bioinformatics?

16 A. So it's sort of a vague question. Part of
17 the work I did involved what I would -- is
18 sometimes referred to as "bioinformatics,"
19 sometimes referred to as "computational biology."

20 And that's a part of what I did. So the
21 work I was doing at Dana-Farber starting in 2005
22 involved both a combination of computational

1 biology, bioinformatics, and cancer genomics.

2 So when I came to Dana-Farber, I was
3 appointed in what was then the department of
4 biostatistics. They changed the name to the
5 department of biostatistics and computational
6 biology.

7 I was the first -- and with an academic
8 appointment at the Harvard School of Public Health
9 and the department of biostatistics.

10 I was the first person recruited into my
11 department at Dana-Farber that had a wet lab. And
12 when I came, we were largely doing work using DNA
13 microarrays and gene expression analysis.

14 I quickly, moving with the field,
15 graduated toward using sequencing. I believe in
16 2007 -- I forget the foundation that provided the
17 funding, but I received a grant from a foundation
18 to buy the first Illumina sequencer at
19 Dana-Farber. And that was set up in my lab.

20 And again, I can't remember the foundation
21 name. All I remember is they presented me with a
22 big paper check at a fashion show in Boston.

1 And if you look at me, I'm not really a
2 fashion show guy, so it really stood out. But I
3 went to the fashion show. I got the check.

4 And then in 2009, as part of the ARRA,
5 American -- the stimulus bill, funding came for
6 biomedical research. And I applied for funding
7 that the NIH made available through the stimulus
8 program. And I actually got money to upgrade that
9 sequencer to an Illumina HiSeq machine.

10 So again, it was the first HiSeq
11 instrument that was available at Dana-Farber. And
12 we had that in late 2009.

13 And then over time, we had a variety of
14 other sequencing instruments. We had -- I forget
15 some of the names. There was a solid state
16 sequencer. I'll remember the name later. It's
17 not really germane to what we're talking about
18 here today.

19 And a few others that people gave us
20 because they couldn't figure out how to get them
21 to work, so we got them up and running.

22 And really my group was developing a

1 combination of laboratory and computational
2 techniques to take -- to collect genomic data in
3 health and disease and to understand a variety of
4 different genomic alterations that could be used
5 to better understand and treat diseases like
6 cancer.

7 So although a big component of my work was
8 computational, really the foundation of my work
9 over the years and what I teach my students even
10 today is that even if you're doing computational
11 studies, you need to be thoroughly grounded in the
12 laboratory technologies that are being used.

13 So part of the reason I reviewed the
14 literature is to improve my work in computational
15 analysis. But at the time, part of the reason I
16 was reviewing a lot of the literature really had
17 to do with our efforts to try to establish these
18 new sequencing technologies at Dana-Farber.

19 Q. All right. Going forward I'd ask that you
20 be a little bit more concise. I just wanted you
21 to confirm if your work related to bioinformatics.
22 I didn't ask for a complete work history.

1 Could you try to be a little bit more
2 concise going forward, please?

3 A. I will do my best.

4 Q. Thank you.

5 A. But as I said, my work related to
6 bioinformatics, but there were many other aspects
7 of it as well, and the question seemed limiting.
8 So I'll try to answer more concisely.

9 Q. The last answer you gave would be a good
10 way to handle that. Maybe point out that there
11 were other aspects as well but it did relate to
12 bioinformatics. Thank you.

13 Is it accurate, then, that in the 2012
14 time frame your work involved analysis of
15 next-generation sequencing data in connection with
16 cancer?

17 A. Yes. A big part of my work in 2012
18 involved the generation and analysis of
19 next-generation sequencing data in cancer and
20 other diseases.

21 Q. Now, did the business of GenoSpace relate
22 also to the analysis of next-generation sequencing

1 data?

2 A. So GenoSpace had two primary product
3 lines. So the short answer is yes. There were
4 two primary product lines.

5 One was an integrated analytical system
6 that was built around the idea of analyzing genome
7 sequence data in the context of clinical data.

8 So genome sequencing and other types of
9 genomic data, we did have clients who used it
10 absent genomic data, simply used it for its
11 clinical capabilities.

12 And then with PathGroup and the whole
13 product line we've built around reporting for
14 precision medicine applications, it involved
15 analysis of next-generation sequencing data and
16 putting genetic variants in the context of
17 actionable findings from professional societies in
18 the literature.

19 The dividing line between what we did and
20 the various companies did in terms of that
21 analysis had to meet the regulations of CLIA, CAP,
22 and their own individual workflows.

1 Q. GenoSpace and PathGroup were two separate
2 companies?

3 A. PathGroup was a pathology company based in
4 Nashville, Tennessee.

5 Q. And when was that founded?

6 A. I couldn't tell you. They were a client
7 of ours.

8 Q. Now, with respect --

9 A. Excuse me. They're actually the very
10 first client we had in that space. We had quite a
11 few others.

12 Q. Now, with respect to GenoSpace, what
13 services specifically did it offer in connection
14 with next-generation sequencing data?

15 A. So there were many services that were
16 provided. So we had a research portal. That
17 research portal was the basis for our contract
18 with the Multiple Myeloma Research Foundation.

19 I can't give you details as to the
20 underlying technology that we used or the approach
21 that we used, even though I'm no longer affiliated
22 with GenoSpace. As I said, we sold it in 2017.

1 But the idea was that we would build -- we
2 built a store that would collect clinical data on
3 the individual patients that were being profiled
4 in the system.

5 And we collected genomic data, and there
6 are many types of genomic data. One was whole
7 sequencing, one was DNA sequencing. Whatever type
8 of genomic data.

9 Our underlying philosophy was that all
10 these different sources of data were FACS, and we
11 created large FACS stores that were highly indexed
12 and easily searchable.

13 On top of that, we would impose very
14 flexible data models to allow them to be linked
15 together. And that would provide us with the
16 ability to do analysis in the context of research
17 or to provide clinical context about genetic
18 alterations, genomic alterations, and the
19 underlying drivers of those.

20 The roots of that actually went back to a
21 project that was funded by the Oracle Foundation
22 at Dana-Farber to build a large integrated

1 clinical and genomic data warehouse. But we ended
2 up spinning this out with a very different
3 technology stack and different approach.

4 In the context of PathGroup and our other
5 diagnostic testing laboratories, they were
6 performing genomic sequence analysis. Some were
7 using targeted sequencing. Some were using whole
8 genome sequencing approaches.

9 And the idea was that we would identify
10 with them, either by helping them craft their own
11 internal pipelines for CLIA, CAP reasons or
12 relying on whatever pipelines they built. We'd
13 often -- we'd collect primarily the mutational
14 reports, so which genes saw mutations. And we
15 provided linkages to clinical guidelines.

16 So these companies weren't really doing
17 research. They were performing a clinical
18 service. We were linking them primarily to
19 guidelines from NCCN, the National Cooperative
20 Cancer Network, that linked various mutations to
21 recommendations for or against the use of various
22 treatments.

1 And part of the limitation simply to look
2 at those clinically actionable variants was that
3 those were the ones that were reimbursable, that
4 these companies could get paid for testing.

5 So it really involved a large variety of
6 clinically-facing and research-facing analysis of
7 genomic data in the context of information about
8 the status of patient health.

9 Q. Now, these various services you described
10 in connection with next-generation sequencing
11 data, how come the clients of GenoSpace were
12 unable to provide these services on their own?
13 Why did they need a company like GenoSpace to do
14 that in 2012?

15 A. You'd have to ask them. They may have
16 found it more cost-effective to contract with us.

17 I think we built a pretty robust clinical
18 data model that sped a lot of their applications.
19 But why these companies contracted with us, you'd
20 have to really ask them for their motivation.

21 Q. Well, let me try to ask it a different
22 way, then.

1 Why did you believe that there would be a
2 need in the marketplace for the types of services
3 that GenoSpace offered in connection with
4 next-generation sequencing data in the 2012 time
5 frame when you started the company?

6 A. So we really started focusing on the
7 research side of the project and the program. And
8 as we looked into this, what we recognized was
9 that the scope and scale of doing this as an
10 enterprise solution was different than what most
11 people could do in their own individual
12 laboratories.

13 So there are many things that you could do
14 in analyzing genomic data, depending on who was a
15 member of your team. But actually building this
16 into a robust clinical solution that met the
17 guidelines not only for CLIA, CAP but also the
18 regulations for HIPAA, the Health Insurance
19 Portability and Protection Act, around
20 safeguarding patient privacy on a large scale was
21 a challenge.

22 For example, the Multiple Myeloma Research

1 Foundation I think had 11 clinical partners that
2 they were working with. The only thing that made
3 sense in the context of what they were doing was
4 building a cloud-based solution.

5 At the time, cloud-based computing was
6 something a lot of hospital organizations were
7 afraid of. And a big part of our secret sauce in
8 the context of creating a platform that
9 organizations like MMRF were willing to use was
10 the fact that we had a really robust data security
11 infrastructure that allowed them to export --

12 (Interruption)

13 A. -- that allowed them to export the data to
14 a cloud-based service.

15 So a lot of it was -- I think a lot of our
16 strength in selling the company as a resource came
17 from our advanced analytics and from our approach
18 to data security.

19 Q. Why was it that organizations and
20 individual laboratories, such as the Multiple
21 Myeloma Research Foundation, would require a
22 cloud-based solution for what they were doing?

1 MR. KRAUSE: Objection, lacks foundation.

2 A. So you could ask MMRF why they chose us.

3 I know they had worked with a couple other
4 companies that had failed to provide the kind of
5 service they needed.

6 We adopted a cloud-based solution largely
7 for economic reasons. As a start-up company
8 founded largely on credit cards, we were able to
9 buy access to secure Amazon servers that were
10 cost-effective, far less costly on a month-to-

11 Month basis than buying large servers and
12 setting them behind a firewall.

13 So if you look at MMRF, part of what they
14 were considering was building their own -- I
15 think, if I recall, was building their own
16 computational infrastructure and trying to
17 maintain it or working with somebody to provide
18 that kind of level of security and service.

19 So they could have potentially built it
20 in-house. But what they needed was a centralized
21 location that would meet all the security and
22 privacy regulations to allow them to collect this

1 kind of data.

2 And this was particularly important for
3 them, given the fact that I think they had
4 11 hospitals -- sorry. I think it was more than
5 15 hospitals they were drawing from. A large
6 number, more than ten. Let me just say more than
7 ten; they're drawing data from more than ten
8 partner hospitals.

9 Hospitals are very cautious about how they
10 share patient data. For very good reasons,
11 they're mandated to.

12 And so 2009 when we were starting the
13 company, there were some pretty serious concerns
14 about the use of cloud-based infrastructure. And
15 again, we had really solved that problem in a very
16 robust way. We had to have the whole -- the whole
17 technology stack we built had to be HIPAA audited.

18 And we invested a lot of time and money in
19 trying to deal with hosting patient data outside
20 individual hospital firewalls. And that was
21 something that I think at the time we were one of
22 the few companies uniquely capable of handling

1 that level of data security.

2 Q. One of the things you said was that the
3 only thing that made sense for MMRF in the context
4 of what they were doing was building a cloud-based
5 solution. Do you know why that was?

6 A. So that's my perspective. For us, it was
7 a very cost-effective solution. And that's one of
8 the things we represented to them was that a
9 cloud-based solution for dealing with a thousand
10 patients, sequencing their genomes every year --
11 so a genome -- whole-genome sequence at
12 significant depth -- and I forget what depth they
13 were looking at, but it's about 300 megabases. So
14 if you have a thousand -- sorry. Not
15 300 megabases. 300 megabytes of data, a thousand
16 patients. I'm not going to do the math. But it
17 was a lot of data, plus there was a significant
18 amount of clinical data on these patients, plus
19 there's RNA sequencing data.

20 So you can sort of look at the economics.
21 A big part of the reason a lot of hospitals and
22 other organizations today are moving to cloud

1 -based solutions is simply the economics of using
2 the cloud versus building an in-house data center.

3 And hospitals and organizations fall on
4 either side, depending on the purposes. But it
5 was a cost-effective solution and it was one in
6 which our data security protocols gave them a good
7 deal of confidence that we could manage the data
8 effectively.

9 So maybe I'm showing some of my bias
10 toward what we built because I'm very proud of
11 what we were able to accomplish.

12 But looking at the situation -- looking at
13 it at the time, too, we also thought about the
14 fact that if we had one central instance,
15 maintenance of that central instance for their
16 resource was far easier than using a distributed
17 solution.

18 So there are other potential technological
19 solutions that would have involved trying to reach
20 through firewalls at each of the large number of
21 hospitals they were working with on an ongoing
22 basis to try to contact data.

1 And even trying to update the software
2 systems to each one of those hospitals becomes a
3 real headache. Right?

4 Centralization provides a lot of
5 advantages. And a big part of the philosophy in
6 building the company was we were going to provide
7 a highly advanced technological solution at scale,
8 so dealing with thousands of patients, and to do
9 it in a way that was consistent with federal
10 regulations.

11 Q. Now, one of the things you mentioned in
12 your last answer was the volume of the data.

13 Why was the volume of data that came from
14 next-generation sequencing platforms in that time
15 frame a challenge for individual laboratories to
16 deal with on their own?

17 A. So it's not necessarily a challenge for
18 individual laboratories. Right?

19 At the Dana-Farber Cancer Institute, we
20 ran a sequencing facility, the CCCB, the Center
21 for Cancer Computational Biology. And we
22 regularly returned whole-genome sequence data to

1 laboratories.

2 With the MMRF, they were talking about a
3 thousand patients and sequencing their genomes
4 every year over at least ten years and combining
5 that with information extracted from clinical
6 records.

7 So it was a pretty substantial amount of
8 data. Right? So you know, today I could fit a
9 whole-genome sequence on a flash drive. It really
10 depends on the individual projects and what you're
11 doing.

12 And the MMRF project was an example of a
13 large number of patients over an extended period
14 of time with multiple types of genomic data and a
15 pretty substantial amount of clinical information.

16 We also built for them a patient portal
17 and we were collecting self-reported data on
18 patients we used to augment the data that was part
19 of the research study. It returned information
20 back to the individual patients.

21 This was something beyond just analyzing a
22 genome to look for individual mutations or to

1 track those mutations over time.

2 This was a very large, complex study that
3 required computational expertise that a charitable
4 organization like the MMRF at least were able to
5 convince them that we could provide a
6 cost-effective solution to them.

7 Q. Okay. Now, you mentioned that today you
8 can fit a whole genome on a flash drive. Was that
9 possible in 2012?

10 A. I have an 8-terabyte flash drive now. I
11 don't know what kind of drives were available in
12 2012. Some of it would depend on what data you
13 collected, how much data you collected.

14 I'm trying to think back to 2012 how we
15 returned data to individual laboratories. I think
16 we just kept them on an internal server at
17 Dana-Farber through the CCCB.

18 I think we just kept them on an internal
19 server and granted them access. I actually don't
20 recall the technological details.

21 Some of it depends on if you're dealing
22 with raw sequence reads. Some of it depends on

1 whether you're dealing with the math and assembled
2 sequence. There are various levels of sequence
3 data and information.

4 So I could definitely fit a whole genome
5 on my 8-terabyte external flash drive today.

6 Q. And you don't recall how the genomes that
7 you were generating at your core sequencing
8 facility in 2012 were provided to clients?

9 A. Most of them we kept, so we set up an
10 internal server at Dana-Farber. Most of them we
11 kept on that server.

12 Most of our clients weren't interested per
13 se in having access to the raw data. They
14 actually worked with us in large part because not
15 only could we generate the data, and because we
16 were generating it, we had extensive information
17 about the quality of the sequence data.

18 We could help them correct their
19 laboratory protocols by iterating back and forth
20 with them, looking at some of the diagnostics we
21 ran on their DNA when they provided it, and then
22 we could integrate that with downstream analysis

1 that was with suited for their particular
2 applications.

3 Again, we dealt with a wide range of
4 different clients with different levels of
5 expertise. Some wanted very extensive support.
6 Others wanted just minimal support in generating
7 the data because they felt they had the capability
8 of analyzing it.

9 Q. Were there any data analysis services that
10 GenoSpace was able to provide to individual
11 laboratories that individual laboratories couldn't
12 otherwise do on their own because of the volume of
13 data that would come off of a next-generation
14 sequencing instrument?

15 A. So GenoSpace -- maybe I'm mixing up the
16 CCCB where we were doing sequencing at Dana-Farber
17 and GenoSpace.

18 Q. My question was about GenoSpace, just to
19 be clear.

20 A. Okay. So my last answer was really
21 dealing with a lot of things we were doing at
22 CCCB, which is what I thought you were asking us

1 about. Because there, we generated sequence data.

2 At GenoSpace, we weren't generating
3 sequence data.

4 So would you please repeat the question?

5 Q. Were there any data analysis services that
6 GenoSpace was able to provide to individual
7 laboratories with regard to next-generation
8 sequencing data that individual laboratories
9 couldn't otherwise do on their own because of the
10 volume of data that would come off the
11 next-generation sequencing instruments?

12 A. So again, we dealt with a wide range of
13 clients that had a diversity of backgrounds and
14 experience. There are many laboratories today
15 that generate next-generation sequencing data and
16 rely on others to analyze them.

17 Every laboratory is different. There are
18 many laboratories that have the ability to be able
19 to analyze large-scale data sets. Others don't.

20 Earlier we were talking about references.
21 Someone like Victor Velachescu, he clearly had the
22 capability and ability in his laboratory at Johns

1 Hopkins to analyze massive data sets. Other
2 investigators didn't.

3 If I look at our clients at GenoSpace, we
4 had individual -- we started with diagnostic
5 testing companies.

6 PathGroup was one example on the clinical
7 reporting side. They were a group largely focused
8 on -- they at least started with doing
9 traditional -- I hate the word "traditional," but
10 sort of standard immunohistochemistry analysis and
11 testing individual markers on tumors. And they
12 were moving toward handling genome sequence data.

13 They actually built a genome sequencing
14 facility in-house and they managed a lot of that
15 data on their own. But the aspects of generating
16 a clinical report was something that we managed to
17 streamline and make very cost-effective for them.

18 Could they have done it in-house?
19 Potentially, yes. They chose to work with us
20 because they found us to be a reliable and
21 cost-effective solution. At least that's my
22 assumption.

1 Many of the other diagnostic testing
2 companies we worked with generated next-generation
3 sequencing data at scale but found it advantageous
4 to partner with us.

5 With the MMRF and our other clients for
6 the research portal, I simply believe they found
7 it cost-effective to work with us.

8 What analyses they did in-house, I
9 couldn't tell you. Whether or not they actually
10 did sequencing in-house or simply provided us with
11 sequence data, I couldn't tell you.

12 So we dealt with a wide range of different
13 laboratories with different capabilities. And
14 their individual choices for the kind of analyses
15 they did is something I can't really speculate
16 about.

17 MR. WALTER: Let's go off the record for a
18 second.

19 THE VIDEOGRAPHER: The time is 10:18. We
20 are off the record.

21 (Off the record, 10:18 a.m. to 10:20 a.m.)

22 THE VIDEOGRAPHER: The time is 10:20.

1 We're back on the record.

2 BY MR. WALTER:

3 Q. One of the references you rely upon in
4 these IPR proceedings is the Chan reference. Do
5 you recall that reference?

6 A. Yes, I do, vaguely. I'm somebody who is
7 very visual, so I'd probably want to take a look
8 at it. That's how I tend to remember things. I'm
9 sometimes bad with names but much better with a
10 visual representation of the paper.

11 Q. Do you recall generally what the Chan
12 reference was about?

13 A. So the Chan reference in academic
14 research, academic science, we tend often to think
15 of papers in the context of the last author rather
16 than the first author.

17 This paper is from a group led by -- I
18 believe his name is Dr. Dennis Lo at the
19 University of Hong Kong.

20 Lo is someone who did work in cell-free
21 DNA. And I don't recall all the details of the
22 paper, but I do recall that they did perform an

1 analysis of cell-free DNA.

2 And Chan notes that tumor-derived DNA in
3 plasma of cancer patients is something their
4 technology would work for.

5 And they also described the use of
6 solution phase hybridization-based capture probes.
7 So those were two of the reasons why I included
8 the Chan reference in my analysis.

9 (Previously marked Exhibit 1008)

10 Q. All right. I've handed you the Chan
11 reference, which I believe is marked as
12 Exhibit 1008 in both of the IPRs that are at issue
13 today.

14 In the Chan reference, do you know if it
15 disclosed any experiments where there was
16 sequencing of DNA from a cancer patient over
17 multiple time points?

18 A. So I don't believe -- earlier I said I
19 thought Chan may have used DNA from other sources.
20 In fact, the analysis presented in Chan I believe
21 now simply looks at tumor-derived DNA in the
22 plasma of cancer patients.

1 I do not believe that Chan in and of
2 itself provides analysis over time of samples from
3 individual cancer patients.

4 But that's why I relied on Chan and Wagle
5 together in my obviousness analysis that's
6 presented I believe in Ground 3 of my report for
7 the '033 patent.

8 Q. Do you know if Chan discloses PCR assays
9 directed to polymorphisms identified by
10 whole-genome sequencing?

11 A. So to make sure I answer concisely, would
12 you please repeat the question?

13 Q. Do you know if Chan discloses PCR assays
14 directed to polymorphisms identified by
15 whole-genome sequencing?

16 A. To the best of my knowledge and
17 recollection sitting here today and reviewing the
18 paper briefly, I don't believe that Chan actually
19 discloses PCR assays.

20 Chan does disclose the use of whole-genome
21 sequencing and analysis to identify single
22 nucleotide variants, one type of polymorphism

1 that's relevant for understanding cancers.

2 But again, a big part of my analysis and
3 looking at obviousness for the '033 patent was
4 looking at Wagle in light of Chan.

5 Q. Do you know if Chan discloses capture
6 probe assays directed to polymorphisms identified
7 by whole-genome sequencing?

8 A. Would you repeat the question, please?

9 Q. Do you know if Chan discloses capture
10 probe assays directed to polymorphism identified
11 by whole-genome sequencing?

12 A. So sitting here today, to the best of my
13 recollection and looking back at my report, I
14 believe that Chan actually does disclose such
15 analysis and does present the analysis in the
16 context of monitoring tumors over time.

17 So I'll refer you to Paragraph 196 of my
18 report.

19 "Using DNA analyzed from tumor samples and
20 from plasma taken at multiple time points,
21 including before and after surgery to resect the
22 tumor, Chan observed that its approach 'would

1 allow genomic alterations harbored by tumor cells
2 within a patient to be scanned at different levels
3 of resolution ranging from a global view of cancer
4 associated copy number aberrations to point
5 mutations carried by different clones of tumor
6 cells.'

7 "Chan concluded that the methods would
8 'allow quantitative and'" -- sorry --
9 "'qualitative and quantitative aspects of such
10 aberrations to be followed serially as evidenced
11 by correlation between the fractional tumor DNA
12 concentration measured and the size of the tumor.'

13 "Thus, Chan tracks mutations of interest
14 over time in order to monitor a patient's cancer."

15 So I believe Chan used capture probes in
16 this analysis, hybridization capture probes,
17 rather than PCR-based capture probes in his
18 analysis.

19 Q. Can you point me to anywhere in the actual
20 paper where there's disclosure of capture probes
21 being used?

22 A. So although Chan doesn't explicitly

1 describe the use of capture probes for monitoring
2 tumors, Chan actually discloses that the use of
3 such approaches was very well known in the art.

4 And I'll point to Paragraph 213 in my
5 report where I actually summarize what appears in
6 Chan toward the end of the paper on page 223. And
7 I won't read the entire quote.

8 But it reads, "Given that plasma DNA in
9 cancer patients consists of a mixture of tumor and
10 nontumor DNA with the former being present at a
11 minority population in many patients, one needs to
12 perform relatively deep sequencing to obtain the
13 necessary analytical power.

14 "Thus, as currently implemented, the
15 shotgun sequencing approach, whole-genome
16 sequencing, we have described is relatively
17 expensive compared with many targeted approaches."

18 And he cites to Reference Number 8, which
19 is the Forshew paper. So clearly he is aware of
20 Forshew and Forshew's work with targeted
21 approaches.

22 With the continuing and thus far rapid

1 reduction in sequencing cost, it is not expected
2 to be much of an obstacle in the near future. One
3 can also envision the possibility of using shotgun
4 sequencing of a plasma sample upon presentation of
5 a cancer patient, mining the shotgun sequencing
6 data of plasma DNA for copy number aberrations in
7 SNVs, and then specifically targeting such
8 sequences for serial monitoring processes.

9 In this regard, he suggests solid phase
10 hybridization-based capture approaches have
11 already been successfully used to enrich plasma
12 DNA for noninvasive prenatal diagnosis, and cites
13 to two references. Those references are Number 34
14 and 35, the Liao reference and a reference from
15 Lam.

16 And hence, we see that the targeted and
17 shotgun approaches can be used in combination for
18 cancer detection and monitoring.

19 So although Chan himself doesn't
20 explicitly use capture probe to do the future
21 monitoring, Chan recognizes that it's a viable
22 approach based on everything that appears in the

1 literature.

2 Q. Another thing Chan doesn't explicitly do
3 is monitor genetic aberrations serially over time.
4 Correct?

5 A. So in some sense Chan does because what
6 Chan is doing is looking at primary tumors and
7 then also tumor DNA in blood.

8 Chan also provides, I believe, an analysis
9 of tumor size and presence of mutations. However,
10 based on his citation of the Forshaw reference, it
11 would have been obvious to anyone that one could
12 easily perform such monitoring over time.

13 And one skilled in the art would obviously
14 understand that if one could perform an assay on
15 an individual today, they could perform the same
16 assay tomorrow or two weeks from now.

17 (Previously marked Exhibit 1001)

18 Q. I'm handing you a document that's been
19 marked as Exhibit 1001 in the IPR related to the
20 '394 patent. It is the '394 patent itself.

21 You're aware that the claims of the '394
22 patent require a first and second nucleic acid

1 sample?

2 A. Could you repeat the question, please?

3 Q. You're aware that the claims of the '394
4 patent require a first and second nucleic acid
5 sample?

6 A. So I believe "require" is a term of art in
7 patent litigation, and so I don't know that the
8 extent of what "require" means.

9 But Claim 1 of the '394 patent, which is
10 different than the one we were just discussing,
11 which is the '033 patent, involves a first
12 sequencing assay on a first nucleic acid sample, a
13 second sequencing assay on a second -- on a second
14 nucleic acid sample, and a third sequencing assay
15 on an additional subset of nucleic acids from an
16 additional nucleic acid sample.

17 Q. Do you contend with respect to the '394
18 patent that Chan discloses the claimed first and
19 second nucleic acid samples?

20 A. I'd like to refresh my memory, if I could
21 have my declaration in the '394 case.

22 Q. You're not able to say whether that was in

1 your declaration?

2 A. I don't believe this is a memory test.

3 You're asking me to provide testimony, and I want
4 to make sure my testimony is as accurate as
5 possible.

6 Q. I've given you your declaration. It's
7 Exhibit 1020 in the '394 IPR.

8 A. Can you repeat the question, please?

9 Q. Do you contend with respect to the '394
10 patent that Chan discloses the claimed first and
11 second nucleic acid samples?

12 A. So you are correct that I did cite to Chan
13 in my declaration for the '394 patent.

14 In fact, there are many examples in Chan
15 of Chan performing an analysis on multiple samples
16 derived from an individual.

17 I can point you to Figure 3 in Chan on
18 page 219 in which Chan has a little cartoon
19 indicating a woman who has both breast and ovarian
20 tumors and showing analyses of DNA samples derived
21 from four separate ovarian tumors.

22 So at the very least, Chan discloses that.

1 As we discussed earlier, Chan also
2 discloses the analysis of primary tumors and then
3 monitoring of DNA using cell-free DNA, which would
4 represent two independent biological samples.

5 Q. If there's anywhere in your declaration on
6 the '394 patent where you present opinions that
7 Chan discloses the claimed first and second
8 nucleic acid samples, please identify those
9 paragraphs now.

10 A. Would you repeat the question, please?

11 Q. If there's anywhere in your declaration on
12 the '394 patent where you present opinions that
13 Chan discloses the claimed first and second
14 nucleic acid samples, please identify those
15 paragraphs now.

16 I'm asking about the paragraphs in your
17 declaration.

18 A. Ah. Sorry. I misunderstood your
19 question. I thought you were asking about the
20 Chan reference itself.

21 So you'll recall, if you'd read my
22 declaration, that I used Chan in Ground 3. I use

1 Leary in view of Chan and Liao and the knowledge
2 of a person of knowledge of skill in the art to
3 present my argument about obviousness.

4 Although I'm not a patent attorney or
5 licensed patent agent, I understand that
6 obviousness does not require that each and every
7 element of a claimed invention has to be disclosed
8 in every reference that's cited.

9 Leary clearly describes the analysis of
10 serial samples from tumor patients and Leary
11 clearly on its own at least renders the '394
12 patent obvious.

13 I chose Chan in part because of the use of
14 capture probes. And Chan, being a person of skill
15 in the art at the time of the alleged invention,
16 concludes that these methods would allow
17 quantitative and qualitative aspects of
18 aberrations to be followed serially, as evidenced
19 by the correlation between the fractional tumor
20 DNA concentration measured and the size of the
21 tumor.

22 So this is paragraph -- I apologize. It

1 will take me a second to find it -- 227 of the
2 report.

3 And so while Chan doesn't explicitly, to
4 the best of my recollection, perform these assays,
5 Chan understood that if you could perform an assay
6 today on an individual, you could perform a second
7 assay on that individual tomorrow or six months
8 from now and gain additional information.

9 Q. So is it accurate, then, that with regard
10 to the Chan reference you do not rely upon that
11 for the first and second nucleic acid sample? You
12 rely upon Leary for that. Is that right?

13 MR. KRAUSE: Objection to form.

14 A. So I'm not sure -- again, I know "rely
15 upon" is a legal term of art.

16 Q. I want to stop there. It's not. It's
17 just plain English. I know you've invoked that a
18 couple times, "rely upon" or "require." That's
19 just plain English. That's not a legal term of
20 art. I just want to correct that misconception
21 right now.

22 A. So would you please define what you mean

1 explicitly by "rely upon."

2 Q. You're not able to understand what I mean
3 when I say you rely upon something?

4 A. I would like to know -- I would like to
5 better understand your question so I can answer it
6 more completely.

7 So do you mean rely solely upon? Do you
8 mean use as part of my analysis?

9 Could you please define the scope of your
10 question.

11 Q. All right. Before we get into that, I
12 just want to be clear for the record, you've been
13 an expert in patent cases more than a dozen times.
14 Right?

15 A. That's probably true. Yes.

16 Q. And you've been asked probably many times
17 whether you rely upon something in your reports.
18 Right?

19 A. And I've often queried what the question
20 means.

21 Q. All right. I'm not sure that's a fair
22 query, but we'll go ahead and indulge you on it.

1 "Rely upon" means that you cite it in
2 support of your opinions. Do you understand that?

3 A. I'll use that as the definition. Yes.

4 Q. I didn't say "relied solely upon." I just
5 said "rely upon." Do you understand that?

6 A. I was just trying to get clarification
7 because I don't want my answers to be taken out of
8 context.

9 Q. There was no danger of that here.

10 A. Thank you for indulging me.

11 Q. What I asked was, with respect to the '394
12 patent, you don't rely upon Chan for the claimed
13 first and second nucleic acid samples? You rely
14 upon Leary for that. Is that right?

15 MR. KRAUSE: Object to the form. And the
16 declaration speaks for itself.

17 A. So again, if you'll read Paragraph 227,
18 Chan concluded that the methods would "allow
19 qualitative and quantitative aspects of such
20 aberrations to be followed serially as evidenced
21 by the correlations between the fractional tumor
22 DNA concentration measured and the size of the

1 tumor."

2 So the fact that Chan uses the phrase
3 "serially" indicates that he at least contemplated
4 the use of multiple samples.

5 In preparing this declaration, I tried to
6 be as concise as I could and didn't call out every
7 single element. I looked at Leary in light of
8 Chan -- excuse me -- in view of Chan, Liao, and
9 the knowledge of a person of ordinary skill in the
10 art.

11 And so while I may not have explicitly
12 called out the use of multiple samples in Chan, my
13 analysis of Chan is consistent with Chan's use of
14 multiple samples.

15 MR. KRAUSE: We've been going for an hour
16 and a half. Is now a good time to take a break?

17 MR. WALTER: Sure. We can take a break.

18 THE VIDEOGRAPHER: The time is
19 11:00 o'clock. We're off the record.

20 (Recess, 11:00 a.m. to 11:09 a.m.)

21 THE VIDEOGRAPHER: The time is 11:09.
22 We're back on the record.

1 BY MR. WALTER:

2 Q. Let's take a look at the Chan reference
3 and let's look at page 212, the first paragraph in
4 the left-hand column.

5 It reads, "Owing to their targeted nature,
6 the approaches outlined above can provide only a
7 partial glimpse of the tumor genome in the plasma
8 of cancer patients." Do you see that?

9 A. I see where it says that. Yes.

10 Q. And you understand that when it refers to
11 "the approaches outlined above," it is referring
12 to the approaches that are identified in the
13 preceding paragraph?

14 A. Could you repeat the question, please?

15 Q. You understood that when Chan refers to
16 "the approaches outlined above," on page 212, he's
17 referring to the approaches that are cited in the
18 preceding paragraph?

19 A. Yes, Chan is referring to the studies
20 cited in the preceding paragraph. He's talking
21 about some of the targeted nature of the analyses
22 that are done.

1 But in fact, he cites specifically to
2 Leary, which is Reference 13, which is one of the
3 references that I've used in my obviousness
4 analysis, and points out that one could use
5 massively parallel sequencing on tumor samples to
6 first identify specific genomic rearrangements
7 that can then be subsequently detected in plasma.

8 So the limitation there, at least, in the
9 context of Chan talking about the advantages of a
10 nontargeted or shotgun approach, are really
11 referring to the second step in the analysis, not
12 the primary identification of alterations.

13 Q. And Chan states that those approaches
14 provide only a partial glimpse of the tumor genome
15 in the cancer patients. Correct?

16 A. You recited the text correctly.

17 But again, you have to read this in
18 context. Chan then goes on to say, "For a
19 genomewide view of the tumor genome in
20 circulation, a nontargeted random or shotgun
21 sequencing approach would be desirable."

22 So again, he's talking about the second

1 stages of analysis that after, as Leary does in
2 Reference 13, different genomic alterations are
3 identified by massively parallel sequencing, which
4 is often used synonymously with whole-genome
5 sequencing or next-generation sequencing, at least
6 as of 2012, that Chan here specifically is
7 referring to the followup steps where one rather
8 than using a targeted approach might see some
9 benefits from using whole-genome sequencing.

10 And as you recall, Chan also in the
11 conclusion later on talks about some of the
12 advantages of using targeted approaches and
13 analyzing circulating DNA.

14 Q. You contend that in this paragraph on the
15 top page of Paragraph 212 Chan is advocating the
16 use of a nontargeted or shotgun sequencing
17 approach for what you describe as the followup
18 analysis. Right?

19 A. I think that's a fair characterization.

20 Again, if you read the paragraph above
21 that Chan is referring to, Chan specifically calls
22 out Leary, which is Reference 13, and McBride,

1 which is, I believe, another one of the references
2 I've cited.

3 And at this moment, I don't recall all the
4 details of McBride. But Chan himself wrote, "One
5 approach is to use massively parallel sequencing
6 on tumor samples to first identify specific
7 genomic rearrangements that can subsequently be
8 detected in plasma."

9 So in advocating for the use of
10 whole-genome shotgun sequencing or next-generation
11 sequencing or massively parallel sequencing, when
12 Chan says, "For a genomewide view of the tumor
13 genome in circulation, a nontargeted random or
14 shotgun sequencing approach would be desirable."

15 So reading it in light of someone using a
16 shotgun nontargeted whole-genome next-generation
17 sequencing approach and then subsequent analysis,
18 I can only infer that Chan was referring to the
19 subsequent analyses, which if we review either
20 Leary or McBride is carried out using capture
21 probes, in the case of Leary, PCR probes directed
22 towards specific alterations.

1 Q. And when you say "subsequent analyses,"
2 what are you referring to?

3 A. I'm referring to what Chan is referring to
4 where Chan says one approach is to use MPS,
5 massively parallel sequencing, on tumor samples to
6 first identify genomic rearrangements that can
7 subsequently be detected in plasma.

8 So I'd be happy to review the Leary
9 reference in detail. Leary renders the claims
10 obvious because Leary describes the analysis -- an
11 analysis based initially on whole-genome
12 sequencing and then the use of capture probes in
13 the form of PCR primers designed specifically to
14 target regions that are followed up in subsequent
15 analyses.

16 Q. And your contention is that in
17 Paragraph 212 -- excuse me.

18 Your contention is that in the paragraph
19 at the top of the left-hand column of page 212,
20 Chan is advocating the use of a nontargeted random
21 or shotgun approach for those subsequent analyses.
22 Is that right?

1 A. That's the simplest reading of it. If
2 Leary and McBride are using -- and I'll use the
3 shorthand -- shotgun approach in the context of
4 this answer, if Chan and -- sorry.

5 If McBride and Leary are using a shotgun
6 approach followed by targeted analysis, then if
7 Chan is going to argue for an approach that might
8 differ from what they ultimately use, given the
9 fact that he's advocating the use of a shotgun
10 approach, it doesn't make logical sense that he
11 would be arguing to replace the shotgun approach
12 with a shotgun approach. It's really the
13 subsequent targeted analysis.

14 So that's the best way I can interpret it.
15 And it's hard for me to see a different
16 interpretation.

17 Q. Okay.

18 (Previously marked Exhibit 1012)

19 Q. All right. I've handed you a document
20 that's been previously marked as Exhibit 1012.
21 It's Exhibit 12, I believe, of both IPRs. This is
22 the Ley reference that you rely upon?

1 A. Yes, this is the Ley reference.

2 Q. You understand this reference discloses
3 shotgun sequencing of an AML tumor and the match
4 normal from a patient?

5 A. So I don't recall Ley referring to this
6 approach of shotgun sequencing. The term "shotgun
7 sequencing" has taken various shades of definition
8 over time. I believe Ley refers to this as
9 whole-genome sequencing or massively parallel
10 sequencing.

11 But yes, they analyze an AML, acute
12 myeloid leukemia, genome and its match normal
13 counterpart obtained from the same patient's skin.

14 Q. And the sequence reads are aligned with
15 the reference genome?

16 A. So on page 71 of the paper, there's a
17 method summary. Like many papers published for
18 the past, I don't know, 10 or 15 years, a lot of
19 the methods are included online, so there's only a
20 brief summary of the methods presented here. And
21 I don't have access, sitting here right now, to
22 the online supplement with the methods.

1 But Ley does state that the analyzed reads
2 were aligned to the human referenced genome NCI
3 build Number 36 using a tool called MAQ.

4 Q. And that's done to identify mutations that
5 are causing the cancer. Correct?

6 A. So I would say that is almost correct.
7 It's hard to know exactly what's causative in many
8 cases with cancers.

9 So there was an analysis that was
10 performed with a tumor sample and a match normal
11 sample. Those were analyzed at presentation and
12 at relapse because this patient happened to
13 relapse.

14 And in comparing the tumor sample with the
15 match normal sample, they tell us that they
16 identified mutations in ten genes with acquired
17 mutations. So these appeared in the tumor.

18 Two were previously described mutations
19 that are thought to contribute to tumor
20 progression, so they may be causative.

21 And eight were new mutations present in
22 virtually all tumor cells at both presentation and

1 relapse, so over time, but the function of those
2 is not yet known.

3 So I don't believe they reached a firm
4 conclusion as to the fact that these were
5 causative, but two at least are suspected.

6 And this would provide some evidence that
7 all ten may play a causative role in the disease
8 development and progression.

9 Q. Now, you mentioned that relapsed tumors
10 were sequenced in Ley. Correct?

11 A. That's what it states. It says, "Eight
12 were new mutations present in virtually all tumor
13 cells and present at relapse."

14 Q. Now, since they're sequencing DNA from the
15 tumor, they know that there's going to be
16 mutations that are potentially associated with
17 cancer in the sequence data. Correct?

18 A. Sorry. Would you repeat the question,
19 please?

20 Q. Now, in Ley when they're sequencing DNA
21 from the relapse tumor, the tumor, so they know
22 that there's going to be mutations that are

1 potentially associated with cancer in the sequence
2 data from the tumor. Correct?

3 A. So my recollection of Ley is that Ley in
4 the relapse sample analyzed targeted regions that
5 were found in the primary sample. I may not be
6 remembering that correctly, but I believe that is
7 correct.

8 It's not necessarily known whether all
9 these mutations are causative. And that's stated
10 multiple times in the paper.

11 If you look at the bottom of page 68 in
12 Figure 2, there's actually a pretty extensive map
13 of the analysis they did in comparing the
14 individual's inherited -- what we call the
15 germline genome, which hopefully is what they
16 inherited from their parents and is represented in
17 the skin, versus the tumor genome.

18 In this case, it's leukemia. And so the
19 tumor itself is really the sequencing and analysis
20 of white blood cells, which are easy to sample and
21 sequence.

22 This is a patient -- I recall this paper

1 very clearly. I know most of -- many of the
2 authors very well. I remember this paper very
3 clearly. This is an individual who had been given
4 therapy and relapsed.

5 There was no immediate cause for that
6 relapse known, if I recall. And so this was an
7 attempt to use genome sequencing to try to get
8 additional information.

9 As I mentioned earlier, those ten variants
10 they found were not the only variants they found,
11 but they were, I believe, coding variants in genes
12 that disrupted the code of the genes, altered the
13 code of the genes.

14 And the analysis at least indicated that
15 these continued, suggesting that the relapse was
16 most likely a relapse of the same tumor, not a new
17 tumor, new disease.

18 Q. What was the purpose for sequencing the
19 relapse tumor samples in the Ley reference?

20 Let me try to ask the question a different
21 way.

22 A. Sure.

1 Q. In Ley, did they sequence the relapse
2 tumor for the purpose of checking to see if the
3 cancer had returned or were they sequencing the
4 relapse tumor to try to identify the mutations
5 that were causing the cancer?

6 MR. KRAUSE: Objection to form.

7 A. So I don't think either of those answers
8 make -- either of those options make logical
9 sense. Given the fact that it was a relapse, they
10 knew the tumor -- the cancer had returned.

11 So the person had been treated and the
12 tumor had returned. Even the authors themselves
13 don't associate causality of those mutations with
14 the development and progression of disease.

15 They clearly state in the abstract that
16 two had been previously described and were thought
17 to contribute to tumor progression. So they may
18 not be initiating events that caused the tumor but
19 contributed to its development and progression.

20 Eight are of unknown -- what does it say?
21 The function of which is not yet known. So this
22 was in part an investigative study to try to

1 understand -- to try to understand more about the
2 patient's disease.

3 I can't speak to their motivations. I
4 don't recall it being laid out. But I know one of
5 the things -- I recall that one of the things that
6 they were trying to do is simply to try to
7 identify potential therapeutic targets that might
8 be found in sequencing the genome.

9 Part of the analysis in looking at a
10 relapse sample that one of skill in the art would
11 perform as of 2008 would be to try to understand
12 whether or not this was the same tumor that had
13 actually recurred or whether it was a tumor that
14 had arisen spontaneously, so a second tumor.

15 Q. Do you know why in the Ley reference -- I
16 think you suggested this. The Ley reference
17 doesn't lay out what the purpose was behind
18 sequencing the relapse tumor sample. Correct?

19 A. So to the best of my recollection, I don't
20 believe that Ley specifically discloses a
21 particular reason for sequencing the relapse
22 samples.

1 It's one of those things that a person of
2 ordinary skill in the art would do, in particular
3 if one were analyzing the genome of an individual
4 whose tumor had recurred.

5 Because one of the obvious questions to
6 ask would be, is this the same tumor, that it
7 somehow escaped therapy or became resistant to
8 therapy, and to really understand the nature of
9 the disease.

10 So both from a research perspective and a
11 clinical perspective, it's sort of an obvious
12 thing to do. It clearly demonstrates an analysis
13 of whole-genome sequence across multiple time
14 points. It also allowed them to look at various
15 types of mutations and characterize those at
16 different time points.

17 Q. Your understanding is that the sequencing
18 of the relapse tumor that took place was a
19 whole-genome sequencing experiment? And I ask
20 that because you stated that it discloses
21 whole-genome sequence across multiple time points.

22 A. I may have misspoken.

1 I actually believe that the original
2 sequencing was whole-genome sequencing and that
3 subsequent sequencing was targeted, although I'd
4 have to really go back and look. And I probably
5 want to see the online supplement to make sure.

6 But I believe that the relapse samples
7 were targeted.

8 Q. You'd have to go back and look at the
9 online data to be sure. Is that right?

10 A. You're asking me very specific questions
11 about the methods. The methods are typically
12 included in an online supplement.

13 Sitting here right now, from my review of
14 the paper, to the best of my knowledge, the
15 analysis that was done was done in a targeted
16 fashion on the relapse samples. But I could be
17 mistaken.

18 Q. Now, you rely upon the Ley reference in
19 Ground 2 of your obviousness combination.
20 Correct? And that's for the '394 patent.

21 A. Sorry. Would you repeat the question,
22 please?

1 Q. You rely upon the Ley reference in
2 Ground 2 of your obviousness combination for the
3 '394 patent. Correct?

4 A. So I cite to, in Ground 2, Leary in view
5 of Ley and the knowledge of a person of ordinary
6 skill in the art.

7 In rereading this specifically in 214 --
8 in response to your previous question,
9 Paragraph 214, I do point out that Ley performed a
10 targeted resequencing on mutations that comprise
11 SNPs and indels that were present in the patient's
12 tumor sample, and then go on to talk about the use
13 of other databases and resources to identify other
14 variants to monitor.

15 Q. All right. For what claim elements do you
16 rely upon Ley in your obviousness combination with
17 respect to Claim 1 of the '394 patent?

18 A. So in Paragraph 212, I state -- in
19 Ground 1, I explain that Leary satisfies Claim
20 Step 1.(c)2 which requires "said capture probes
21 hybridize to one or more polymorphisms which are
22 based on or extracted from one or more databases

1 of polymorphisms, observed in a population of one
2 or more samples, or a combination thereof," by
3 designing PCR primer capture probes that hybridize
4 to polymorphisms.

5 Leary in view of Ley, continuing in
6 Paragraph 213, further renders obvious alternative
7 embodiments within the scope of Claim Step 1.(c),
8 including selecting different types of
9 polymorphisms such as SNPs and indels as well as
10 polymorphisms based on -- sorry -- quote, based on
11 one -- based on or extracted from one or more
12 databases of polymorphisms, whether alone or in
13 combination with the polymorphisms Leary
14 identified in their samples.

15 And so, as I pointed out in Ley, there's
16 actually a pretty extensive analysis of the work
17 that they did to select their subset of variants,
18 including an analysis of various databases which
19 were available at the time.

20 Q. All right. So let's do it this way, now
21 that you've had a chance to review that. Let's
22 look at Claim 1 of the '394 patent. And let's go

1 to Step 1.(c). Actually, let's start with
2 Step 1.(a).

3 Do you rely upon the Ley reference for
4 Step 1.(a) in your obviousness combination?

5 A. So my understanding of "obviousness" is
6 that each and every element of each individual
7 claim does not have to appear in any particular
8 reference.

9 I haven't performed an independent
10 analysis of Ley in light of the disclosure of
11 essentially all of Claim 1 in Leary.

12 I really rely on Ley for the reasons that
13 I stated here. But if we look at Claim Element
14 1.(a), sitting here today, I can tell you that in
15 Claim 1.(a) they clearly describe -- sorry -- Ley
16 clearly describes generating a first subset of
17 nucleic acid molecules from a first nucleic acid
18 sample obtained from an individual.

19 Q. Okay. Is there anywhere in your
20 declaration where you cite disclosure in Ley as
21 satisfying Claim Element 1.(a) of the '394 patent?

22 A. So as I said earlier, I didn't perform

1 that analysis. That analysis isn't necessary,
2 based on my understanding.

3 My understanding of Leary was pretty
4 extensive, as reported in my disclosure. And as I
5 stated in Paragraph 212, 213, 214, I'm simply
6 using Ley as a way to demonstrate that one of
7 ordinary skill in the art would understand that
8 the types of mutations, for example, that Leary
9 describes, translocations, aren't limiting in any
10 way and that others working in the field at the
11 time would understand that all sorts of mutations,
12 including single nucleotide variants, insertions,
13 deletions, and polymorphisms derived from other
14 databases, could easily be analyzed.

15 Q. Let's go to Step 1.(b). And I just want
16 you to answer if you have anywhere in your report
17 where you rely on Step 1.(b). we'll get to what
18 you think you relied upon specifically later, I
19 believe.

20 Is there anywhere in your report where you
21 rely upon Ley as disclosing the claim elements set
22 forth in Step 1.(b) of Claim 1 of the '394 patent?

1 A. So to the extent which you're asking me
2 about demonstrating each and every element of
3 Claim 1 is represented in Ley, again, I'll state I
4 don't believe that it's required that I
5 demonstrate that in this obviousness argument that
6 I present.

7 But I'll refer you to Paragraph 215, where
8 I quote Ley saying, "We restricted our downstream
9 analysis to the coding sequences of annotated
10 genes. We also detected previously described,
11 recurrent somatic mutations in FLT3 and NPM1
12 genes."

13 So the analysis that's referred to here is
14 the analysis of whole-genome shotgun sequencing.

15 They couldn't have performed that analysis
16 if they didn't conduct a first sequencing assay on
17 said first subset of nucleic acids to yield a
18 first result comprising a first nucleic acid
19 sequence therein -- wherein said first sequencing
20 assay comprises whole-genome sequencing.

21 Q. Paragraph 214 is where you provide support
22 for how you believe Ley discloses portions of

1 Step 1.(c) of Claim 1 of the '394 patent.

2 Correct?

3 A. So Paragraph 214 described performing
4 targeted resequencing.

5 But in Paragraph 215, it talks about where
6 those variants were found. And one of ordinary
7 skill in the art reading this would understand
8 reading Ley in context that if they were
9 restricting their analysis to coding sequences and
10 annotated genes that they had found in their
11 sequencing, that that would also capture elements
12 of Claim 1.(b).

13 But again, I don't think it's required
14 that I map Ley -- each and every step in Ley to
15 the claimed invention in the patent. I'm simply
16 using Ley to augment what's presented in Leary.
17 And I provided a very extensive analysis of Leary,
18 which renders Claim 1 on its face obvious.

19 Q. Okay. So what specifically do you rely
20 upon Ley for? How do you contend Ley is needed to
21 augment Leary?

22 MR. KRAUSE: Object to the form.

1 A. So Ground 2 of the analysis that I present
2 in my expert report regarding -- my declaration
3 regarding the '394 patent lays out an analysis of
4 Claim 1 and Claims 4 and 5, I believe. Yup,
5 Claim 1 and Claims 4 and 5, between page 101 and
6 page 105.

7 I don't believe that Ley is necessary to
8 render the claims of the '394 patent obvious. I
9 believe that I provide a pretty conclusive
10 analysis that Leary on its own renders the entire
11 patent or all the claims that I cite as obvious.

12 I also recognize that arguments may be
13 made that because Leary focuses on translocations,
14 it wouldn't be obvious to one skilled in the art
15 to extend it, for example, to other types of
16 mutations.

17 So I'm simply using Ley to point out what
18 anyone of ordinary skill in the art would have
19 known as of 2013, that Ley shows that very similar
20 approaches -- whole-genome sequencing,
21 next-generation sequencing, massively parallel
22 sequencing -- can be used to identify a variety of

1 different mutational types.

2 Those can be used in targeted subsequent
3 assays, so primary tumor and in this case
4 recurrence, that those mutations can be tracked
5 over time.

6 And in Claims 4 and 5, the claim of
7 method 1, wherein said one or more polymorphisms
8 are a set of genes with known biomedical
9 interpretable variants.

10 Ley provides an analysis that shows that
11 many of these variants are interpretable and are
12 known in the literature and in public databases.

13 And then Claim 5, the method of Claim 4,
14 wherein said set of genes with known biomedically
15 interpretable variants comprise one or more genes
16 or variants associated with cancer.

17 And again, Ley clearly lays out that some
18 of these genes had previously been associated with
19 cancer.

20 So to the extent that any of that happens
21 to be missing in Leary -- and I don't believe it
22 does -- I provide an additional analysis that

1 could be interpreted in the context of one of --
2 in the -- could be interpreted by a person of
3 ordinary skill in the art.

4 Q. You understand Claim 1 of the '394 patent
5 requires the use of capture probes?

6 A. So yes, claim -- well, Claim 1.(c) recites
7 the use of an analysis using a plurality of
8 capture probes. And I won't read -- well,
9 "wherein said plurality of capture probes
10 hybridize to one or more polymorphisms," which are
11 present on or extracted from one or more databases
12 of polymorphisms.

13 Q. You don't rely upon the Ley references
14 disclosing that capture probe claim element you
15 just referred to. Correct?

16 A. So again, I've presented Leary in Ground 1
17 and provided a very extensive analysis of the
18 capture probe that Leary used.

19 I didn't believe it was necessary for me
20 to provide the same level of analysis of Ley,
21 although I can tell you that, in fact, Ley
22 describes the performance of targeted resequencing

1 on mutations comprising SNPs and indels that were
2 present in the genes of a patient's tumor sample.

3 That targeted resequencing, in fact, as I
4 point out in Paragraph 212, is accomplished by
5 designing PCR primer capture probes that hybridize
6 to these polymorphisms that were observed in a
7 population of at least one sample, the patient,
8 and also augmented by analysis of various cancer
9 databases.

10 Q. Now, one of the things you've referred to
11 in describing Ley a couple times is something
12 called "directed resequencing."

13 A. I believe that's correct. Yes. I think I
14 said "targeted resequencing," but I may have also
15 said "directed resequencing."

16 Q. Now, I want to go back to your previous
17 answer. You pointed to Paragraph 212 as
18 constituting a disclosure of Ley doing targeted
19 resequencing. That's what you stated in your
20 previous answer. Correct?

21 MR. KRAUSE: Objection to form,
22 mischaracterizes his testimony.

1 A. So I may have misread Paragraph 212.

2 Sorry. It's hard to read because the binder clip
3 is bending the page and this is a pretty thick
4 report.

5 In Paragraph 212, I open by saying in
6 Ground 1, I explained that Leary satisfies Claim
7 Step 1.(c)2, which requires said capture probes
8 hybridized to one or more polymorphisms, which are
9 based on or extracted from one or more databases
10 of polymorphisms observed in a population of one
11 or more samples or combination thereof.

12 In Paragraph 212, I supplement what my
13 argument is in Leary, in anticipation of potential
14 objections that Leary may only be analyzing
15 translocations, which was the real focus of the
16 analysis presented in Leary, to simply demonstrate
17 that one of ordinary skill in the art would
18 understand that an approach like that disclosed in
19 Leary is not limited simply to translocations,
20 that any kind of polymorphism could be analyzed.

21 Ley clearly describes that. And as I
22 mentioned earlier, Ley does do targeted

1 resequencing. And I believe that this was done by
2 PCR, although I could look back at the Ley paper
3 in detail.

4 Q. All right. To be clear, Paragraph 212 of
5 your report refers to Leary, not Ley. Correct?

6 A. Paragraph 212, I'm talking about the Leary
7 reference. Yes.

8 Q. Thank you. All right.

9 Now, have you ever heard the term
10 "directed resequencing"?

11 A. Almost certainly I have.

12 Q. Do you know what that refers to?

13 A. I would have to see it in context.

14 Q. In the context of what we're talking about
15 in this case, do you have an understanding of what
16 the term "directed resequencing" refers to?

17 A. If you could point me to a reference, I
18 would give you the answer in the context of that
19 reference.

20 Q. Do you know if you've discussed directed
21 resequencing in any of your declarations in this
22 case?

1 A. I very well may have. If you can point me
2 to those paragraphs and lines, I'd be happy to
3 provide some context for you.

4 Q. Okay. Does the term "directed
5 resequencing" have an understanding to the person
6 of ordinary skill in the art of the patents that
7 are at issue in this case?

8 A. So I don't believe the term "directed
9 resequencing" occurs in the claims, although I
10 could be mistaken. If you can point me to those,
11 I'd be happy to refresh my memory and discuss
12 them.

13 I also am not sure whether they appear in
14 the written descriptions of either of these
15 patents. One of ordinary skill in the art would
16 read the phrase "directed resequencing" in the
17 context of the manuscript in which -- or the
18 reference in which it was presented and understand
19 it and interpret it in that context.

20 Different authors may use it to represent
21 different things. As I believe I said earlier,
22 sometimes the use of language is precise in the

1 biomedical literature.

2 Q. What would you have understood the term
3 "directed resequencing" to mean in the
4 January 2013 time frame?

5 A. I would have to answer that question in
6 the context of any particular reference that I was
7 reading. And if I were writing about it and using
8 that term, I would also write and provide some
9 context, given the experiments that I was
10 conducting.

11 Q. All right. Let's take a look at
12 Paragraph 217 of your declaration, where you refer
13 to "directed resequencing."

14 What do you understand "directed
15 resequencing" to be referring to when you referred
16 to it in your declaration at Paragraph 217? And
17 this is your declaration on the '394 patent.

18 A. Sorry. In Paragraph 217, you said?

19 Q. Yes.

20 A. Where does "directed resequencing" occur?

21 Q. It's at the bottom of Paragraph 217. The
22 last few lines read, "Leary, polymorphisms that

1 were found in the coding sequences of annotated
2 genes, Exhibit 1012, Ley, 66, see also Id at 6670,
3 discussing desirability of directed resequencing."

4 MR. KRAUSE: 104.

5 A. So in quoting here, I believe I'm quoting
6 from Ley on page 66 and also page 70. I'm not
7 going to bother to scan through the dense text to
8 find those.

9 But in the context of Ley, if Ley is
10 referring to directed resequencing specifically,
11 you'll recall that what Ley did was a whole-genome
12 sequence analysis, actually two, using both --
13 using matched tumor and normal samples, Ley
14 identified a set of genetic variants that he and
15 his colleagues decided to analyze further in the
16 recurrent sample and also in other leukemia
17 samples.

18 And rather than performing whole-genome
19 sequencing, they designed PCR capture probes to
20 specifically capture those target regions and
21 sequence those in the subsequent analyses.

22 So I believe what Ley is discussing is the

1 relative advantages of doing targeted resequencing
2 or directed resequencing in those subsequent steps
3 in contrast to doing whole-genome sequencing
4 across all analyses that one performs.

5 Q. Okay. Now, would you say that the claims
6 of the '394 patent pertain to the directed
7 resequencing process as you just described it or
8 are they something different?

9 MR. KRAUSE: Object to the form.

10 A. So I'm not sure exactly what you're asking
11 me.

12 Claim 1 encompasses a number of different
13 steps. The first is generating a subset of
14 nucleic acid molecules from a first nucleic acid
15 sample and conducting a first sequencing assay on
16 the first subset of nucleic acid molecules to
17 yield a first result, comprising a first nucleic
18 acid sequence wherein first -- the first nucleic
19 acid sequencing assay comprises whole-genome
20 sequencing.

21 So there's a whole-genome sequencing
22 aspect of Claim 1. We've been stuck on

1 Claim 1.(c) for a period of time, so that involves
2 "generating a second set of nucleic acid molecules
3 from a second nucleic acid sample of said
4 individual by contacting said second nucleic acid
5 sample" . . . "with a plurality of capture probes,
6 wherein said plurality of capture probes hybridize
7 to one or more polymorphisms which are based on or
8 extracted from one or more databases of
9 polymorphisms, observed in a population of one or
10 more samples, or a combination thereof, wherein
11 said first sample or said second sample is
12 obtained from the subject at a first time point."

13 And then D, "conducting a second
14 sequencing assay."

15 So it goes on. There are additional steps
16 going through G.

17 Some element of that does include
18 capturing sequences and doing a second -- on a
19 second nucleic acid sample and performing a second
20 sequencing assay on those captured sequences.

21 And one could refer to that as "targeted
22 sequencing" or "directed resequencing" in contrast

1 to a whole-genome sequencing, which is described
2 in Claim 1.(b).

3 Q. All right. Let's go to Paragraph 152 of
4 your declaration.

5 A. All right. I have it.

6 Q. Here, you're showing data from the
7 National Institutes of Health regarding the cost
8 of sequencing. And you have a graph?

9 A. Yes, a graph appears on page 85.

10 Q. And you state on page 85 that by
11 January 2013 the cost of sequencing had been
12 reduced to \$0.06 per megabase. Do you see that?

13 A. I see where it says that. Yes.

14 Q. Based on that, what would the cost of
15 whole-genome sequencing be for a single individual
16 in January 2013?

17 And if you need to write down the
18 calculation, feel free to do that.

19 If you'd like to do that, I'll give you a
20 piece of paper and you can write it down and we'll
21 mark it as an exhibit.

22 A. So I'm not sure what goes into this

1 assumption of \$0.06 per megabase. I'd actually
2 want to go back and look at the NIH data.

3 I actually frequently lecture on the cost
4 of whole-genome sequencing or next-generation
5 sequencing. And one of the -- one of the things
6 that I do is I present a cost of sequencing a
7 genome. And again, there are a lot of assumptions
8 built into that.

9 It's based on the same data from the
10 NHGRI, which is available on a spreadsheet which
11 you can download and see exactly what their
12 calculation entails. And also what data goes into
13 that estimate I think is presented.

14 But the cost of whole-genome sequencing as
15 of 2009 estimated based on the NHGRI was \$100,000.

16 And I know that explicitly because when I
17 talk about this in my class or in lectures, I
18 often state that in 2009 if my wife or son had a
19 rare tumor I would have mortgaged the house and
20 sequenced their genome.

21 Today, the cost of sequencing has dropped
22 to about \$1,000. And again, there are a lot of

1 assumptions built into that.

2 The estimate as of 2013 would probably be
3 around \$10,000. If you want to give me a piece of
4 paper, I'm happy to try to sketch out a
5 calculation.

6 Q. Sure. That's what I'll do. You can use
7 that \$0.06 per megabyte number, you can sketch it
8 out, and we'll mark this as an additional exhibit.

9 A. It's \$0.06 per megabase, not being
10 megabyte.

11 Q. Megabase.

12 A. So a genome is 3 times 10 to the 9th
13 bases. So a megabase is 10 to the 6th bases. So
14 what we're talking about is three times 10 to the
15 3rd megabases. And the cost of this is 6 times 10
16 to the minus \$2 per megabase.

17 So a simple calculation would be 3 times
18 10 to the 3rd megabases times 6 times 10 to the
19 minus \$2 per megabase, which is going to be 18
20 times 10 to the 1st, which is going to be about
21 \$180, which seems relatively small.

22 And again, I'm not sure what assumptions

1 are built into this. But I would say that the
2 total cost is probably more than \$180. That may
3 be just the cost based on generating the raw
4 sequence data.

5 Again, I'm not sure what the assumptions
6 are. But the whole point of this graph is to
7 indicate that the cost would drop pretty
8 dramatically by 2013.

9 Q. Do you have any explanation for why the
10 calculation that you arrived at was \$180 but, you
11 know, based on your experience and your lecture
12 that you provide to students, in 2013 the actual
13 known cost was \$10,000?

14 A. Again, I'm not sure if it was \$10,000 in
15 2013. It may have been as low as \$1,000. I've
16 often used the example of being able to pay for a
17 genome with your -- with a credit card.

18 And at the time -- so between 2007 and
19 2013, 2014, the cost of sequencing a genome was
20 dropping by about 33 percent per quarter.

21 So again, I don't know what assumptions
22 went into this. It may be -- okay.

1 So, ah, I actually do know where some of
2 the source of error is or the source of
3 disagreement.

4 So this is actually -- I didn't -- I
5 estimated the cost of sequencing 3 billion bases
6 of DNA. This is cost per raw megabase of DNA
7 sequence.

8 So this is for a raw megabase. And the
9 discrepancy between \$180 for a raw megabase and
10 the actual cost of sequencing a genome would come
11 from the fact that in most applications one would
12 typically generate deeper sequence than onefold
13 coverage, although not necessarily in all
14 applications.

15 And I can point to many different examples
16 where one might want to sequence a genome at a
17 lower all-fold coverage at least in terms of
18 sequence coverage.

19 So I think Leary is a nice example of
20 sequence at about onefold in terms of sequencing
21 coverage but much greater clone coverage, directed
22 towards the discovery of translocations.

1 So the cost of sequencing is going to
2 depend on the purpose. And this is just an
3 estimate of \$180 for 3 billion bases of DNA. Raw
4 sequence. It's not finished genome sequence. And
5 that's the source of the discrepancy.

6 Q. All right. Very good.

7 So how many times do you typically need to
8 sequence to get the finished genome?

9 A. It depends on your application.

10 Q. For what people would call sequencing a
11 genome in 2013, how many times would you do it?

12 A. It depends on your application.

13 Q. Okay. What was the assumption underlying
14 the NIH data that you relied upon? Do you know?

15 A. This is actually just a cost per raw
16 megabase of DNA sequence. So I'm sure it's
17 factoring in reagents costs. There might be some
18 personnel costs factored in. I'm not sure.

19 Q. Would 10 X be appropriate? When I say
20 "10 X," I mean a 10 X sequencing. Would that be
21 appropriate?

22 A. You mean tenfold coverage?

1 Q. Yes.

2 A. Would that be appropriate for what?

3 Q. For sequencing an entire genome, a
4 whole-genome sequencing. Would someone say 10 X
5 would be sufficient for whole-genome sequencing?

6 MR. KRAUSE: Objection to form.

7 A. So it would depend on your application.
8 There are examples like Leary where the sequence
9 coverage was lower but the physical coverage of
10 the genome was much higher, I think about
11 eighteenfold at least.

12 It may have already ended by 2013, but
13 there were projects like the 1000 Genomes Project
14 that did low-pass sequencing over genomes to
15 identify polymorphisms, across the whole genome.

16 So the depth of coverage is going to
17 depend on your application.

18 What a person of ordinary skill in the art
19 would know was that one could simply adjust the
20 depth of coverage to arrive at a relative coverage
21 of the entire genome. And I'll put "entire" in
22 quotes.

1 And also a degree of accuracy. And all
2 that would simply require is sequencing more,
3 sequencing less. And again, it's going to depend
4 on your particular application.

5 MR. WALTER: Let's go ahead and mark that
6 document as Exhibit 2016. I selected a number,
7 and the court reporter can put a stamp on it.

8 (Exhibit 2016 marked for identification)

9 MR. NAINI: If you're at a point for a
10 bathroom break, that would be great.

11 MR. WALTER: Let's go ahead and mark that
12 exhibit and then we can take a break. We'll take
13 a lunch break now. We'll be back at 1:00 o'clock.

14 THE VIDEOGRAPHER: The time is 12:22.
15 We're off the record.

16 (Lunch recess, 12:22 p.m. to 1:05 p.m.)

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

2 (Previously marked Exhibit 1018)

3 THE VIDEOGRAPHER: The time is 1:05.

4 We're back on the record.

5 BY MR. WALTER:

6 Q. Dr. Quackenbush, I've handed you a
7 document that's been marked as Exhibit 1018. I
8 believe it's in both IPRs. Do you recognize this
9 document?

10 A. Yes. I believe this is actually part of
11 the spreadsheet that the NHGRI maintains on its
12 website that's tracked their genome sequencing
13 cost estimates over time.

14 Q. And if you look at the entry for
15 January 13th of the cost per genome, it's listed
16 as \$5,671. Do you see that?

17 A. Yeah, I see that entry here. Yes.

18 Q. And would you agree that, based on your
19 calculation of \$180 for a single run to the
20 genome, that \$5,671 figure is representing about
21 30 X sequence coverage?

22 MR. KRAUSE: Objection to form.

1 A. Yeah, that's probably a rough estimate.
2 Thirtyfold is going to be about \$5,400, which is
3 close to what they're providing as their estimate.

4 But again, this estimate is going to be
5 based on the assumptions of that particular use
6 case that one would develop for a genome. There's
7 going to be a range in cost depending on depth of
8 sequencing, as people sequence less than onefold
9 to sometimes more than a hundredfold.

10 So this is a cost that's based on a set of
11 assumptions.

12 Q. Now, is it your contention that in
13 January 2013 skilled artisans were engaged in the
14 practice of drawing blood samples from cancer
15 patients to analyze circulating tumor DNA in those
16 blood samples?

17 A. So I'm not sure how you're defining
18 "skilled artisans."

19 I will tell you that I believe some of the
20 references that we are discussing, for example the
21 Chan reference, which was published in 2013,
22 described the analysis of tumor-derived DNA from

1 plasma, which would indicate blood samples. Which
2 individuals may have drawn the blood, I can't tell
3 you.

4 Q. Do you know what the typical volume of a
5 blood draw was from a cancer patient if someone
6 was interested in collecting blood to sequence the
7 cell-free DNA in the blood of a cancer patient?

8 A. Again, I'm not -- I'm not a phlebotomist,
9 so I don't do blood draws myself.

10 From having blood drawn and other
11 information I've seen in various contexts, I
12 believe the standard blood tube is about 7 mls.
13 It's between 7 and 10 mls.

14 Q. And do you have an understanding of how
15 many nanograms of DNA one can expect -- strike
16 that. Let me ask the question a different way.

17 And do you have an understanding of how
18 many nanograms of cell-free DNA one can expect to
19 find in a typical 7-milliliter blood draw?

20 A. There are different types of DNA. There
21 is going to be cellular DNA, there is going to
22 cell-free DNA.

1 I don't believe I opined on that in the
2 context of my report. And so sitting here today,
3 I couldn't tell you what are the likely ranges of
4 cell-free DNA in a 7-ml blood tube.

5 Q. You don't have any estimate of whether
6 it's on the order of 10, 100 nanograms,
7 1,000 nanograms? You don't have any ballpark
8 figure?

9 MR. KRAUSE: Objection to form.

10 A. Again, I don't think I included that in
11 any of my reports. If you point me to that, I'd
12 be happy to refresh my memory. But sitting here
13 today, I wouldn't want to speculate.

14 Q. In the 2013 time frame, do you have any
15 understanding of how many nanograms of DNA were
16 typically subject to analysis when you're taking
17 cell-free DNA from the blood of a cancer patient
18 and you intend to sequence it?

19 MR. KRAUSE: Objection to form.

20 A. Would you repeat the question, please?

21 Q. In the 2013 time frame -- I'll ask the
22 question a slightly different way.

1 Do you have any understanding of how many
2 nanograms of DNA were typically subject to
3 analysis when taking cell-free DNA from the blood
4 of a cancer patient for sequencing in the
5 January 2013 time frame?

6 MR. KRAUSE: Same objection.

7 A. So I'm not sure what you mean by
8 "typically." There could be a wide range of
9 applications in which people could use different
10 quantities of cell-free DNA.

11 The only -- I don't believe I opined on
12 that in any of my declarations. I don't believe
13 there's any description of amounts of DNA that
14 appear in the '394, '033 patents.

15 The only reference I have in front of me
16 right now that discusses analysis I believe was of
17 cell-free DNA from blood plasma is the Chan
18 reference.

19 And although Chan discusses the amount of
20 genomic DNA that they analyzed, they don't provide
21 any information on the quantity of cell-free DNA,
22 other than to state that the DNA in plasma samples

1 were relatively small.

2 Q. Let's go to Paragraph 121 in your
3 declaration on the '394 patent. And in this
4 section, you're presenting opinions related to the
5 Leary reference.

6 As you can see, Step 1.(a) of Claim 1 of
7 the '394 patent requires a first nucleic acid
8 sample. Do you see that?

9 A. I see it says, "generating a first subset
10 of nucleic acid molecules from a first nucleic
11 acid sample obtained from said individual."

12 So yes.

13 Q. And in Leary, you contend that first
14 nucleic acid sample comes from a tumor. Correct?

15 A. So I don't have the Leary reference
16 sitting in front of me.

17 But in Paragraph 122, I quote from Leary,
18 describing what they call PARE, personalized
19 analysis of rearranged ends, which is shown in
20 Figure 1 of the paper.

21 And they say, "We initially analyzed four
22 tumor samples, two colon and two breast tumors,

1 and their match normal tissues using the sequencer
2 referred to as the Applied Biosystems SOLiD
3 System."

4 And it says, "Genomic DNA from each sample
5 was purified, sheared, and used to generate
6 libraries with mate-pair tags, approximately
7 1.4 kilobases apart."

8 Q. What do you contend is the first nucleic
9 acid sample in Leary?

10 A. So in this specific example that I'm
11 talking about, there are first nucleic acid
12 samples representing DNA extracted from the tumor.
13 So there are four separate samples they're
14 analyzing.

15 So in each one of the individuals, one of
16 the first samples is the tumor sample. They also
17 analyze the match normal sample, which was common
18 to provide a reference for identifying somatic
19 mutations specific to the tumor.

20 So in the broader context of looking for
21 mutations in a tumor and then subsequently
22 analyzing them using PCR capture probes, the first

1 sample would be the tumor sample from a particular
2 individual.

3 Q. And is it the tumor sample or the match
4 normal sample, or do you contend it can be either
5 one?

6 A. It would depend on your application. One
7 could find somatic mutations or germline mutations
8 that occurred in the individual patient by
9 comparing the normal sample back to a reference
10 genome, which I believe is part of the analysis
11 Leary carries out.

12 And again, I don't have the Leary paper
13 sitting in front of me.

14 But in the context of identifying
15 tumor-specific mutations and then analyzing those
16 tumor-specific mutations, if we were to map
17 Leary's claims to all of Claim 1 of the '394
18 patent, the best representative of that first
19 sample would be the tumor sample from the
20 individual.

21 Q. In your declaration, does it state
22 anywhere whether you're relying upon the tumor

1 sample or the match normal sample as satisfying
2 the first nucleic acid sample claim element?

3 A. So sitting here today, I'm not -- I don't
4 think I identified either one. I'm not sure that
5 it matters. But logically, given the fact that
6 Leary is really describing subsequent analysis of
7 tumor-specific mutations, it's logical that it
8 would be the tumor-specific sample.

9 The patent doesn't require -- in fact, the
10 patent itself doesn't require the use of tumor
11 samples, to the best of my recollection, in its
12 claims. There may be dependent claims other than
13 Claim 1 that does, but it simply requires the
14 first sample.

15 So in the context of mapping Leary back to
16 the claim -- the elements of Claim 1, I'm not sure
17 it matters. But again, the most logical would be
18 the tumor sample, given that that's primarily what
19 Leary uses in subsequent analyses, the mutations
20 that are specific to the tumor.

21 Q. Let's go to Paragraph 127. And this is
22 where you begin to opine on claim elements related

1 to a second subset of nucleic acids.

2 And you can see that this claim element
3 requires a second nucleic acid sample. Do you see
4 that?

5 A. The claim says generating a second subset
6 of nucleic acids from a second nucleic acid
7 sample. Yes, it says that.

8 Q. And if you take a look at Paragraph 131,
9 you point to the tumor DNA as being the second
10 nucleic acid sample. Correct?

11 A. Would you repeat the question, please?

12 Q. You point to the tumor DNA in Leary as
13 being the second nucleic acid sample that is
14 claimed in Claim 1 of the '394 patent. Correct?

15 A. So I don't have the Leary reference in
16 front of me. And I would appreciate having it so
17 I can answer the questions more fully.

18 But Leary does use tumor DNA as a second
19 source of DNA to generate a second subset of
20 nucleic acid molecules.

21 So the second sample he analyzes is also
22 tumor DNA. And what I lay out subsequently over

1 the next few pages is the analysis of that second
2 DNA sample.

3 One of ordinary skill in the art would
4 understand that the first DNA sample would have
5 been subject to laboratory protocols that would
6 have set it up to be used or prepared it to be
7 used in massively parallel whole-genome
8 sequencing, and that the targeted captured by
9 contacting the second nucleic acid sample with a
10 plurality of capture probes would use a different
11 aliquot, a different tube, a different DNA sample.

12 And one of ordinary skill in the art would
13 also understand it could be applied to other tumor
14 samples or other DNA samples from the same
15 individual.

16 Q. Is there anything else in Leary that you
17 contend corresponds to the claimed second nucleic
18 acid sample in Claim 1 of the '394 patent besides
19 the tumor DNA?

20 A. I don't have a copy of Leary in front of
21 me. If you'd be so kind as to provide it, I'd be
22 happy to read it over and see if there's something

1 else.

2 But the second DNA sample that I talk
3 about here is a tumor DNA sample.

4 Q. Okay. Now, do you contend that that
5 second DNA sample that is a tumor sample is
6 subject to the sequencing?

7 MR. KRAUSE: Objection to form.

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

9 Q. Do you contend that the second DNA sample
10 that is a tumor sample is subject to sequencing?

11 A. So maybe you're misreading the claims.
12 Claim Element 1.(c) doesn't talk about sequencing
13 a second tumor sample.

14 Claim Element 1.(d) says "conducting a
15 second sequencing assay on said second subset of
16 nucleic acid molecules to yield a second result
17 comprising a second nucleic acid sequence."

18 So the sequencing is conducted on a subset
19 of nucleic acid molecules. In Claim 1.(c),
20 Claim 1.(c) describes "generating a second subset
21 of nucleic acid molecules from a second nucleic
22 acid sample of said individual by

1 contacting" . . . it "with a plurality of capture
2 probes."

3 So starting on page 68 and going through
4 the end of page 75, I dissect and map elements of
5 Leary back to Claim Element 1.(c) that involves
6 using PCR capture probes to generate a second
7 subset of nucleic acid molecules.

8 And then starting on page 76 and going
9 through the middle of page 77, so about a page and
10 a half, I talk about Leary's sequencing analysis
11 of the second subset of nucleic acid molecules.

12 Q. All right. So you contend that the second
13 nucleic acid sample is subject to PCR?

14 MR. KRAUSE: Objection to form.

15 A. So if we read Claim Element 1.(c), Claim
16 Element 1.(c) says "generating a second subset of
17 nucleic acid molecules from a second nucleic acid
18 sample of said individual by contacting said
19 second nucleic acid sample with a plurality of
20 capture probes" and then discusses the capture
21 probes, "wherein" . . . they "hybridize to one or
22 more polymorphisms which are based on or extracted

1 from one or more databases of polymorphisms," and
2 one of those databases could include a database
3 that comes from the first individual.

4 So if you read Leary, what Leary does
5 after performing whole-genome sequencing is
6 identifies a set of putative break points for
7 translocations in the genome.

8 Again, I don't have the Leary reference
9 sitting in front of me, so I don't recall all the
10 different tumor samples that Leary analyzes. I
11 believe there were two breast and two colon that
12 we had talked about earlier, although I could be
13 mistaken.

14 But one of the things that happens
15 frequently in solid tumors is the genome gets
16 rearranged. There may be translocations. A
17 translocation occurs when a piece of one
18 chromosome breaks off and attaches to a broken-off
19 piece of another chromosome, so the chromosomal
20 segments are translocated or swapped between
21 chromosomes.

22 And so in his analysis -- and again, I

1 don't have the Leary reference in front of me
2 despite asking for it multiple times.

3 But Leary describes identifying those
4 break points, then designing PCR primers as
5 capture probes.

6 In Paragraph 131, Leary is designing use
7 of PCR primers spanning the putative break points
8 of the 42 identified rearrangements constitutes
9 the use of capture probes to generate a second
10 subset of DNA from the tumor sample, the PRC.

11 You talked about the second sample being
12 subjected to PCR. That PCR reaction which Leary
13 carries out uses capture probes to generate the
14 second subset, which is then subsequently
15 sequenced in Step 1.(d), which Leary describes and
16 I provide the evidence for that in more detail
17 starting on page 76.

18 Q. Now, in Paragraph 75 of your declaration,
19 you state that PCR results in the exponential
20 amplification of target DNA sequences. Is that
21 true?

22 A. So that's exactly what it says in the

1 first sentence of Paragraph 75.

2 There are many forms of PCR. The most
3 commonly used form of PCR or the most commonly
4 used forms are variations of Kary Mullis's
5 original PCR, which he patented in 1975.

6 And that original PCR method was designed
7 to exponentially amplify specific segments of DNA
8 with the goal of capturing them from the
9 background sample, in the sense that they're far
10 more prevalent than the original DNA from which
11 they were derived.

12 Q. All right. Now, with respect to the PCR
13 that is used in the Leary reference, how many
14 primers are used for each site, each polymorphic
15 loci?

16 A. I don't have the Leary reference sitting
17 in front of me. I believe for the fifth time I'll
18 ask you to provide the Leary reference.

19 I believe that -- well, actually, if you
20 look at my report on page 72, there are a list --
21 I can't count them all, but I believe these are
22 the 68 sites that Leary analyzes. And I

1 believe -- sorry.

2 On page 71, for confirmation we designed
3 primers . . .

4 Actually, page 71, or I quote on page 70,
5 "Leary designed primers to 42 of the paired-end
6 regions and used them for PCR spanning the
7 putative break points. 35 of these yielded PCR
8 products of the expected size in the tumor samples
9 but not in the normal samples. Sanger sequencing
10 of seven PCR products confirmed the rearrangements
11 in all cases tested."

12 So if there are PCR primers for 42 of
13 them, Leary designed 42 pairs of PCR capture
14 probes.

15 Q. And why was there a pair of primers for
16 each of the 42 loci?

17 A. So as a capture technology, PCR uses pairs
18 of capture probes, commonly referred to as
19 primers, to capture, amplify those individual
20 segments of DNA.

21 Q. And why is it that you use a pair of
22 primers to do the capture?

1 A. Would you like an explanation of PCR?

2 Q. If you can do so in a reasonably brief
3 fashion to convey why you use the pair to do the
4 capture in PCR.

5 A. So in its most common form, PCR is used to
6 amplify specific segments of DNA. And what those
7 PCR capture probes or primers do is they bracket
8 the region of DNA that one wants to capture from
9 the sample.

10 So the pair is a way of defining the
11 endpoints of the region one wants to capture.

12 Q. Now, in the PCR process, the capture
13 doesn't take place simply by virtue of the primer
14 hybridizing to the target DNA. Is that right?

15 MR. KRAUSE: Objection to form.

16 A. Would you repeat the question, please?

17 Q. In PCR, the capture doesn't take place
18 simply by virtue of the primer hybridizing to the
19 target DNA. Is that correct?

20 MR. KRAUSE: Same objection.

21 A. So I'm not sure where in the patent it's
22 explicitly stated that capture has to occur at the

1 point of hybridization. In fact, it would be hard
2 for me to think of any technology where capture
3 would simply occur the moment hybridization
4 occurred.

5 The patent itself in Column 31 provides a
6 definition of "Capture Probes." And it says, "The
7 methods disclosed" . . . "may comprise one or more
8 capture probes, a plurality of capture probes, or
9 one or more capture probe sets."

10 So in reading capture probe sets and then
11 further the characteristics of capture probes,
12 typically the capture probe comprises a nucleic
13 acid binding site.

14 So the patent explicitly in Column 31 and
15 the "Capture Probe" section tells us they can be
16 comprised of sets, which PCR primer pairs is what
17 capture probes are, and that capture probes have
18 nucleic acid binding sites. And PCR primers as
19 capture probes are designed to bind.

20 So the capture probes bind. And the DNA
21 one could say is captured through the binding of
22 those primers and the subsequent PCR reaction.

1 If one -- in the same way that if one used
2 hybridization capture probes, the simple act of
3 hybridizing wouldn't provide you a purified
4 sample. Those have to be extracted from solution
5 in some way.

6 So the capture probes are part of the
7 process of capturing DNA. They're not the process
8 itself.

9 Q. And in the PCR process that effectuates
10 the capture, what are the basic steps in that
11 subsequent PCR reaction to effectuate the capture?

12 MR. KRAUSE: Objection to form.

13 A. So in Leary -- now for I think the sixth
14 time I'll ask you to provide a copy of Leary so I
15 can look over Leary.

16 Leary in its "Method" section may provide
17 a detailed description of the PCR protocol that
18 they use. In general, PCR, like many -- like
19 every single molecular biology assay which one
20 would use -- which one of ordinary skill in the
21 art would use as of 2013 to capture DNA fragments,
22 involves multiple steps.

1 Typically for each target region, PCR
2 involves the denaturation of DNA. And that's
3 common for every capture technology I can think of
4 because you need single-stranded DNA with some
5 kind of probe to form a duplex where the probe can
6 bind to the DNA.

7 So as the patent tells us, we can have
8 probe sets. So for each target region, there's a
9 capture probe set. That capture probe set
10 hybridizes to the DNA.

11 One then lowers or one raises the
12 temperature to denature the DNA, adds capture
13 probes in great molar excess.

14 The capture probes anneal to the DNA as
15 temperature is lowered. Typically there is a DNA
16 polymerase. Sometimes those are added. Now we
17 use thermal-stable polymerases.

18 The DNA polymerases bind to the DNA. The
19 capture probes initiate copying of the DNA. And
20 the process is repeated multiple times, providing,
21 as we talked about earlier I think in
22 Paragraph 76, an exponential amplification of the

1 target capture region.

2 (Previously marked Exhibit 1002)

3 Q. I'm handing you Exhibit 1002, which is the
4 Leary reference that is from the '394 IPR.

5 A. Thank you.

6 Q. Take a look at Figure 1 of the Leary
7 reference. And there's a graph in the lower
8 right-hand corner of Figure 1.

9 Do you contend that Figure 1, that graph
10 in the lower right-hand corner, is a disclosure of
11 Step (e) of Claim 1 of the '394 patent?

12 A. So Claim 1.(e) says, "using said plurality
13 of capture probes to generate an additional subset
14 of nucleic acid" sequences "from an additional
15 nucleic acid sample isolated from an additional
16 sample obtained from said subject at an additional
17 time point different from said first time point."

18 So we start with the first time point and
19 we generate data. And then we generate data on an
20 additional time point.

21 So in Paragraph 144, the bottom right
22 panel of Figure 1, represented, shows -- it says

1 "below." It should say "above." It's actually
2 blown up below -- represented below shows the
3 creation of seven subsets of nucleic acid
4 molecules at different time points than the time
5 point at which the first subset is generated.

6 Specifically, the graph reports the amount
7 of tumor biomarkers, the polymorphic
8 rearrangements, in the plasma through the use of
9 PCR primer capture probes to detect nucleic acids
10 in each sample.

11 So the figure is showing an analysis of
12 the data that is generated at seven different time
13 points, each of which meets the requirement of
14 being, or would require generating an additional
15 subset of nucleic acid molecules from an
16 additional nucleic acid sample at a different time
17 point.

18 Q. Now, those samples that appear in the
19 graph in the lower right-hand corner of Figure 1,
20 do you know one way or the other whether they're
21 subject to sequencing?

22 A. So I believe that after Leary confirmed

1 his rearrangements by Sanger sequencing, which we
2 discussed -- I don't think it specifically
3 discussed Sanger sequencing.

4 But sequencing when we were discussing
5 claim element I think it was 1.(c), the analysis
6 of a second subset of nucleic acid molecules.
7 Sorry. 1.(d) was the sequencing. And Leary
8 sequences in 1.(d).

9 I don't believe Leary subsequently
10 sequenced the samples but relied on his validation
11 of the PCR products that were captured in
12 Claim 1.(d) and used the size of those samples.

13 However, one skilled in the art would
14 understand that if one could sequence samples in
15 the second stage, one could sequence them in the
16 third and subsequent stages.

17 Part of the reason I didn't argue for
18 anticipation was that Leary doesn't explicitly
19 describe sequencing those, although one skilled in
20 the art would see it's obvious and one could
21 sequence at Stage 2. One can do it at 3, 4, 5 to
22 7.

1 Q. And what was the purpose for which Leary
2 conducted Sanger sequencing at Stage 2?

3 MR. KRAUSE: Objection to form.

4 A. I would say the simplest answer would be
5 to determine the sequence of the capture probes,
6 the captured product.

7 Q. And why did Leary want to determine the
8 sequence of the captured product?

9 MR. KRAUSE: Objection to form.

10 A. One could speculate as to why Leary might
11 want to do that.

12 Q. Having reviewed Leary, do you have any
13 understanding of why Leary did the sequencing of
14 the captured PCR product in what you've referred
15 to as Stage 2, or do you not have any
16 understanding as to why?

17 MR. KRAUSE: Objection to form.

18 A. So I quote from Leary in Paragraph 130 of
19 my declaration on page 70. I believe it's on
20 page 6 of the Leary reference.

21 Primers were used for PCR on tumor and
22 match normal samples, as previously described. So

1 Leary is being rigorous. The candidate
2 rearrangement was confirmed if a PCR product of
3 the expected size was seen in the tumor but not in
4 the match normal sample.

5 Sanger sequencing of PCR product was used
6 to identify the sequence break points in each --
7 in a subset of cases.

8 So Leary is performing an analysis on the
9 PCR samples and determining the specific sequence
10 of the break point in each one of those subset of
11 samples.

12 Q. And do you know why Leary wanted to do
13 that?

14 MR. KRAUSE: Objection to form.

15 Q. Do you have any understanding as to what
16 the purpose of that was?

17 A. I'm not sure what you're asking me. Leary
18 wanted to, as he tells us, identify -- was used to
19 identify sequence break point in a subset of
20 samples.

21 Break points, as I told you earlier, are
22 common in rearrangements, sometimes in deletions

1 that occur. But break points occur in tumors
2 frequently when the genome breaks apart.

3 I believe most of what Leary was looking
4 for are translocations. And that's sort of
5 indicated in Figure 1 in Leary, showing two
6 different chromosomes fused together.

7 And Leary is performing an analysis to
8 identify the sequence break points in the regions
9 of the genome that he captured in Step 2.

10 Q. Now, was that sequence break point
11 identified in connection with the whole-genome
12 sequencing that you believe was done in Leary?

13 A. Sorry. I don't understand the question.

14 Q. The sequencing break point that you
15 contend Leary is attempting to identify when it
16 sequences a PCR product, was that identified in
17 connection with the whole-genome sequencing that
18 you contend Leary does?

19 MR. KRAUSE: Objection to form.

20 A. So I don't contend that Leary does
21 whole-genome sequencing. Leary does whole-genome
22 sequencing, and there are a number of

1 contemporaneous and subsequent references that
2 refer to Leary as whole-genome sequencing.

3 In fact, earlier we were talking about the
4 Ley reference where Ley specifically calls out the
5 use of massively parallel sequencing in Leary in a
6 first stage to identify tumor mutations.

7 So I'm not just asserting it. I provide
8 evidence to support that.

9 What Leary does is an analysis using
10 paired ends of DNA fragments. And the little
11 cartoon that's shown in Figure 1 of Leary shows
12 how -- that analysis of paired ends in a cartoon
13 form but sort of gives a high-level view of how
14 that analysis is carried out.

15 So if I have a DNA fragment and one end
16 maps to one chromosome and one end maps to another
17 chromosome, then what I'm going to see is that the
18 most logical conclusion is that somewhere in the
19 middle of these fragments is a break point.

20 So I can localize the region of that break
21 point. But as the cartoon also illustrates -- and
22 they only have two, but Leary discloses at least

1 eightfold sequence coverage.

2 So now we have 18 sets of fragments that
3 are likely to lie across the break point. That
4 allows you to dramatically narrow the region down
5 from 1.4 kilobases to something smaller.

6 I can't tell you, sitting here today,
7 whether any of the sequences actually landed in
8 the middle of the break point or not. But
9 identifying the specific base location of the
10 break point in most applications I can think of
11 wouldn't be essential.

12 The nice thing about the analysis that
13 Leary carries out is Leary identifies the break
14 points, designs PCR capture probes, and captures
15 those break points using hybridization, which
16 capture probes have to do to nucleic acid
17 sequences where there is some kind of variant, and
18 then generates a second set of nucleic acids,
19 sequences them, and confirms the break points that
20 were discovered and, in fact, finds additional
21 information about those break points, potentially
22 allowing them to map it down to the specific base

1 where the break occurs.

2 Q. Why can't you tell me, sitting here today,
3 whether any of the sequences from which you
4 contend this whole-genome sequencing in Leary
5 actually landed in the middle of the break point
6 or not?

7 MR. KRAUSE: Objection to form.

8 A. So in doing my analysis, I relied on what
9 Leary reported. I did not go back and see whether
10 or not these sequences had been submitted to
11 dbDaP. I did not make a research request to get
12 access to the sequences from dbDaP, which would
13 have required permissions that I would have to
14 justify based on a research need. And I would
15 then have to map these back to the genome to see
16 if I could identify the break points.

17 I don't believe Leary reports that. What
18 Leary reports doing is -- and this would require
19 things way beyond the scope of what I could do in
20 my role here today. And if I did, it would
21 probably violate a number of NIH rules.

22 So given what was reported, I rely on what

1 Leary told us, which is that Leary identified the
2 regions of the break points. Break points are
3 mutations.

4 Leary demonstrated that he could design
5 PCR capture probes and amplify those, sequence
6 them, and verify what he found.

7 So I rely on the veracity of Leary and his
8 coauthors in reporting data back in the journal
9 article that we're discussing.

10 Q. So you believe the sequence break points
11 were identified in what you contend is the
12 whole-genome sequencing and that they were later
13 verified by the sequencing of the PCR amplicons.
14 Is that correct?

15 MR. KRAUSE: Objection to form.

16 A. So again, you're using the word
17 "contending." Leary, according to contemporaneous
18 references, did whole-genome sequencing --

19 Q. Let me stop you right there. Recognize
20 that there's a dispute on this point. Okay? And
21 I've used the word "contend" so that I don't put
22 words in your mouth.

1 But what I would ask that you not do is
2 dispute that point and regurgitate your opinion on
3 that with every answer. Okay? I've been fair by
4 using the word "contend."

5 Just please answer my question without
6 redebating every time I use that word whether
7 there's whole-genome sequence or not. Can you do
8 that?

9 A. I won't cite contemporaneous references.

10 Q. Okay. So go ahead and answer my question
11 again.

12 You believe the sequence break points were
13 identified in Leary based on what you contend is
14 the whole-genome sequencing and that they were
15 later verified by the targeted sequencing of the
16 PCR amplicon. Is that correct?

17 MR. KRAUSE: Same objections.

18 A. So Leary performs whole-genome sequencing
19 using this mate-pair approach with an eighteen --
20 I think 18.6-fold clone coverage in the first
21 example that is presented in the paper.

22 That identifies translocations. Those

1 translocations reflect places where chromosomes
2 broke and fused together.

3 As of 2013 or even as of today, one will
4 find references to translocations that occur in
5 many different tumor types. And they're typically
6 referred to as translocations between two specific
7 chromosomes.

8 So earlier today, we discussed the
9 Multiple Myeloma Research Foundation's Compas
10 study. And in Compas -- sorry -- multiple
11 myeloma, one of the canonical mutations that
12 occurs early in myeloma is the translocation
13 between chromosome 4 and chromosome 14. It's
14 referred to as t(4;14). It's actually important
15 for clinical management of the disease.

16 The actual base pair or location in the
17 whole-genome sequence at which that translocation
18 occurs varies between individuals, but the t(4;14)
19 translocation is important for therapeutic and
20 disease management decisions.

21 So one skilled in the art would understand
22 that identifying a translocation wouldn't require

1 mapping it down to the individual base.

2 Leary was able to map this down well
3 enough that he could design PCR capture probes to
4 capture these and was able to map them down to --
5 if we look at Figure -- the figure that's
6 reproduced on Figure 74. It's the top of
7 Figure 2, Figure 2A in the Leary paper. To map it
8 down to a window of -- at least in the four
9 examples shown here of about a thousand bases or
10 so, maybe 1,000 to 1,600 bases.

11 And what Leary could say at that point is
12 a translocation occurred somewhere in that region.
13 That's enough to make a clinical decision. That's
14 enough to identify the specific mutation. It was
15 verified and further mapped after PCR capture and
16 subsequent sequencing.

17 MR. WALTER: Most of that was
18 nonresponsive. I would ask that you be more
19 concise and more direct in your answers.

20 MR. NAINI: I think that's your view.
21 I'll let the witness state whether he agrees with
22 that or not, but I don't want the record to be

1 misinterpreted as us agreeing with what you just
2 said.

3 Q. Now, Leary wasn't able to map the
4 translocation down to the individual base because
5 Leary didn't sequence all the bases. Right?

6 MR. KRAUSE: Objection to the form.

7 A. Leary actually mapped the translocation to
8 the individual base as clearly described -- well,
9 I don't know if he says the individual base.
10 Mapped it down to the individual base as clearly
11 described in my report when I discuss the Sanger
12 sequencing of the second set of PCR capture
13 probes.

14 Leary didn't need to map the translocation
15 down to the individual base to identify the
16 genomic alteration.

17 If we read the claim language, the claim
18 language itself says in Claim Element 1.(c),
19 "wherein said plurality of capture probes
20 hybridize to one or more polymorphisms which are
21 based on or extracted from one or more databases
22 of polymorphisms, observed in a population of one

1 or more samples, or a combination thereof,
2 wherein" . . . "first sample or said second sample
3 is obtained from said subject at a first time
4 point."

5 So there's no requirement in Claim 1 of
6 the '394 patent that requires that a polymorphism
7 be mapped to an individual base. All one has to
8 do is identify a polymorphism. And that's what
9 Leary did.

10 MR. WALTER: Okay. That also was
11 unfortunately nonresponsive.

12 MR. KRAUSE: You know how to ask a better
13 question, if you want to. He's giving the best
14 answers he can to your questions. If you'd just
15 let him answer and ask your next question.

16 MR. WALTER: I was asking about the
17 sequencing. He didn't say anything about the
18 sequencing in his answer.

19 A. Excuse me.

20 I'll amend my answer to say that Leary's
21 sequencing, that his whole-genome sequencing which
22 we map back to Step 1, allowed him to identify the

1 polymorphisms. And Claim 1 does not require
2 identification of polymorphisms to an individual
3 base.

4 Nowhere in Claim 1 does the term
5 "individual base" appear anywhere.

6 Q. Leary didn't sequence all the bases in his
7 whole-genome sequencing. Correct?

8 MR. KRAUSE: Objection to form.

9 A. It's virtually impossible to sequence all
10 the bases in any individual genome.

11 The first human genome was reported
12 completed as a draft sequence in 2001. In 2005,
13 the genome was declared finished. In 2006, it was
14 declared finished again. In 2022, it was declared
15 finished with the Y chromosome -- sorry -- the X
16 chromosome being finished. In 2023, it was
17 declared finished again with the Y chromosome
18 being finished, with the caveat that there's still
19 gaps in the sequence.

20 So sequencing any genome to completion is
21 next to impossible. I provided an analysis in my
22 declaration using the Lander-Waterman paper from

1 1998, I believe, that talks about the asymptotic
2 process of sequencing. And there's no requirement
3 that the whole-genome sequencing cover each and
4 every base.

5 Q. And in Leary, the sequencing that you
6 contend -- strike that.

7 In Leary, the sequencing that you contend
8 was whole-genome sequencing, it wasn't complete
9 enough to be able to map the translocations down
10 to individual bases. Correct?

11 MR. KRAUSE: Objection to form.

12 A. So I don't know if any of Leary's
13 sequences spanned individual break points. I
14 can't say that because I don't have the data and I
15 haven't done the analysis.

16 Whether or not -- all it requires -- all
17 the claim requires is whole-genome sequencing to
18 identify polymorphisms and subsequently analyze
19 those polymorphisms.

20 The analysis that Leary does identifies
21 those polymorphisms and subsequently analyzes
22 those polymorphisms. The claims don't require any

1 particular level of resolution.

2 And so the question you're asking, in my
3 view, isn't relevant to mapping the claims of
4 Leary back -- sorry -- the work performed and
5 described in Leary back to the claims of the '394
6 patent.

7 Leary sequenced -- and I believe
8 Dr. Furneaux also did this analysis -- sequenced
9 in his lowest coverage sample about 2.9 billion
10 bases of DNA, which is pretty close to the 3 or
11 3.1 billion bases of DNA we commonly think of as
12 comprising the human genome.

13 MR. WALTER: Again, a lot of that was
14 excess. My question was much more direct than
15 that.

16 MR. KRAUSE: We object to the colloquy.

17 MR. WALTER: That's fine. But, you know,
18 I have to make a record here. And while I'm at
19 it, there's been a lot of excess delay in the
20 answers based on simple questions he should be
21 aware of.

22 MR. KRAUSE: He's allowed to look at the

1 documents.

2 MR. WALTER: He's allowed, but not for
3 five, six, seven minutes at a time.

4 MR. KRAUSE: That's your view.

5 THE WITNESS: I've asked for documents and
6 you failed to provide them in the past, which
7 might have sped up some of my answers.

8 MR. NAINI: And I would be interested to
9 see if there are any answers you can identify that
10 are five or six or seven minutes long.

11 MR. WALTER: Okay.

12 MR. NAINI: Especially if they're coupled
13 with a question that's not open-ended or vague the
14 way they have been.

15 (Previously marked Exhibit 1006)

16 Q. I've handed you a document that's been
17 marked as Exhibit 1006. It's 1006 in both IPRs.
18 It's entitled "Targeted Enrichment of Genomic DNA
19 Regions for Next-Generation Sequencing."

20 Do you recognize this document,
21 Dr. Quackenbush?

22 A. Yes, I do recognize it. It's another

1 person I'm very familiar with, Anthony Brookes and
2 his group. Yes. It's one of the references I
3 believe I cited in my reports.

4 Q. Did you identify this reference for
5 inclusion in your report?

6 A. Sitting here today, I can't tell you if
7 this is one of the ones I found or not.

8 Q. And what did you rely upon this reference
9 for in your report? Do you recall?

10 A. I don't recall specifically where I cited
11 to Mertes. Without an electronic document to
12 search, I can't find it quickly.

13 So in light of your request that I not
14 search through the documents, if you can point me
15 to where I cite to Mertes, I'd be happy to discuss
16 it further.

17 Q. Do you have a general recollection of why
18 you relied upon Mertes?

19 A. So given your recent statements about
20 using time, I will ask you to point me to the
21 place in this document where I cite to Mertes.
22 Otherwise, to answer your question, I'm going to

1 spend time looking through the document to provide
2 you a full and complete answer.

3 Q. Okay. It's discussed rather extensively
4 in your declaration.

5 I do think it is the kind of thing you
6 ought to know without me having to point you to
7 it. But I'll do that now.

8 A. All right. That would be very helpful.
9 Thank you.

10 MR. WALTER: You're over there laughing.
11 This is something he cites multiple times in his
12 declaration.

13 MR. NAINI: Derek, if you're referring to
14 me, I was not laughing. There is no audio of me
15 laughing. I am surprised --

16 MR. WALTER: Okay. Well --

17 MR. NAINI: Let me finish, please. I let
18 you finish.

19 I'm surprised you said that after making
20 the assertion that you did to this witness in kind
21 of an antagonist manner. I would ask that you not
22 badger the witness.

1 Ask your questions. He'll answer them to
2 the best of his ability, as he has all day.

3 MR. WALTER: I disagree that he's done
4 that all day.

5 MR. NAINI: I understand you disagree, but
6 you're wrong.

7 MR. WALTER: I'm not wrong. I'm right. I
8 think if you're fair with yourself -- now you're
9 laughing.

10 MR. NAINI: I'm not laughing. I'm
11 breathing.

12 MR. WALTER: Okay. You're laughing.
13 You're over there snickering.

14 MR. NAINI: Derek, I'm not snickering.
15 You're glowering at me.

16 MR. WALTER: I am.

17 MR. NAINI: That's not nice.

18 MR. WALTER: It's not nice for you to
19 snicker at me.

20 MR. NAINI: I am not snickering and I have
21 not. I take this very seriously. I'm surprised
22 that you're doing this now.

1 MR. WALTER: Okay. Well, you shouldn't be
2 surprised because --

3 MR. NAINI: Maybe I shouldn't. Others
4 know you better than I.

5 BY MR. WALTER:

6 Q. All right. Let's take a look at
7 Paragraph 69.

8 A. Thank you. I actually found it in
9 Paragraph 69. The additional time I had was
10 useful.

11 Q. Have you reviewed Paragraph 69 of your
12 declaration? Do you recall the general reasons
13 for which you relied upon the Mertes reference in
14 your declaration?

15 A. So I've told you previously I'm more
16 visual in the way I remember things. And now
17 looking at the tables in Mertes, it's easy for me
18 to see I didn't include this.

19 I used actually two references, Mertes and
20 Mamanova. In an analysis, I did a variety of
21 different technologies that existed in the
22 relevant time frame of this patent. I believe the

1 Mertes reference is from 2011.

2 There's also a reference from Mamanova.

3 And both of these discuss different capture
4 strategies, including hybridization-based
5 strategies, PCR, other techniques, and talk about
6 some of the relative strengths and weaknesses of
7 each.

8 For example, Mertes says, and I quote from
9 this in Paragraph 69, the advantage of PCR and
10 circularization-based methods, i.e., MIPs,
11 molecular inversion probes, is they achieve very
12 high enrichment factors and few off-target reads
13 but only for small target regions. This is more
14 suited to clinical genetics where typically only a
15 few critical loci are needed or assessed.

16 So Mertes is describing different capture
17 technologies that include PCR and others.

18 Q. Is it fair that you view Mertes as a
19 reliable source for understanding what the skilled
20 artisan understood about hybrid capture and PCR in
21 the January 2013 time frame?

22 MR. KRAUSE: Objection to form.

1 A. Mertes is one piece of the puzzle.

2 Part of the reason I cite to Mertes and
3 Mamanova is they provide complementary sources of
4 information.

5 The biomedical literature is vast, tens of
6 thousands of papers published every year. I
7 pulled out two as representatives.

8 But I wouldn't want to rely on any
9 particular limitation laid out. I'm not using
10 these as primary references to argue or to present
11 the case for obviousness in the case of the '394
12 patent but rather really to provide background on
13 capture technology.

14 This is in the "Background" section of my
15 report.

16 Q. All right. I'm not suggesting anything of
17 the sort, that it's the sole piece of information
18 that you're relying upon and that there isn't
19 complementary sources of information.

20 But you will agree that the Mertes
21 reference that you relied upon in your declaration
22 is a reliable source for background regarding what

1 the skilled artisan would know about hybrid
2 capture and PCR in the January 2013 time frame.
3 Correct?

4 MR. KRAUSE: Objection to form.

5 A. Again, as I told you, the biomedical
6 literature is vast. When you say "rely upon," I
7 don't know the scope. We talked about "relied
8 upon" earlier, the scope of what you're trying to
9 include in that.

10 Mertes is one piece of the puzzle. The
11 fact that in the same "Background" section I cited
12 to both Mertes and Mamanova was an attempt to try
13 to illustrate that they provide complementary
14 views.

15 The important thing about Mertes is that
16 Mertes really underscores the fact that there's
17 many different capture technologies, some of which
18 includes hybrid capture, others of which include
19 PCR-based capture.

20 Q. Was there anything in Mertes that you
21 deemed inaccurate?

22 MR. KRAUSE: Objection to form.

1 A. Sitting here today, I couldn't tell you.
2 I'd be happy to read the Mertes reference in its
3 entirety and provide a more detailed answer, if
4 you'd like.

5 Q. Certainly if you found that there were --
6 at some point you did review the Mertes reference.
7 You read this reference. Right?

8 A. The last time I read it was probably a
9 year ago in preparing the declaration.

10 Q. And having reviewed it at that time in
11 connection with preparing your declaration, you
12 felt it was a reliable source to include in your
13 declaration. Correct?

14 MR. KRAUSE: Objection to form.

15 A. To the extent that I quoted from Mertes,
16 the sections that I quoted from I believe
17 illustrate important aspects of the state of the
18 field at the time.

19 Most importantly, in Table -- I think it's
20 Table 1. In Table 1 of Mertes, which is
21 reproduced on page 34 of my report, what Mertes
22 laid out is the fact that there were many

1 different what he refers to as target enrichment
2 technologies, what we today have been referring to
3 as capture technologies.

4 There were many different target
5 enrichment or capture technologies that existed.
6 Many of them were commercially available.

7 Whether or not I agree specifically with
8 Mertes on the relative strengths and weaknesses of
9 any or whether any would be suitable for any
10 particular application, I'm not willing to render
11 an opinion on without rereading Mertes.

12 But the fact that I cited to this and
13 showed this table in my declaration was really an
14 attempt to show that the use of capture
15 technologies was nothing innovative or inventive,
16 that there were commercially available platforms,
17 including platforms that one could easily
18 customize for any particular application.

19 Q. You've reviewed the table on Mertes --
20 which table is it?

21 A. Table 1.

22 Q. You reviewed Table 1?

1 A. I don't know what you mean by "reviewed."

2 I looked at Table 1. I just looked at it now.

3 Q. Having looked at Table 1, is there
4 anything in there that you deem would have been
5 inaccurate in the January 2013 time frame?

6 MR. KRAUSE: Objection to form.

7 A. So sitting here today, 10 years or
8 12 years after this paper was written, I will tell
9 you that this represents Mertes' informed opinion
10 of the various technologies that were available.

11 He states some pros and cons. If I
12 thought about them more deeply, I might quibble
13 with some. I'm not going to do that today without
14 thinking about it in much more detail.

15 He also provides limits on amounts of DNA
16 that one could use, the number of targets that one
17 might use. And again, I'm not going to provide an
18 opinion today about whether or not I think any of
19 those are accurate or inaccurate.

20 The most important element of this and the
21 reason I included it was the fact that there are
22 many, many -- as of 2013, there were many, many

1 different capture technologies that existed.

2 We mentioned Mamanova before. I like
3 Mamanova's graphic because it shows the overlap
4 between these different technologies and
5 Mamanova's interpretation of the relative
6 strengths and weaknesses.

7 So, you know, the important thing that
8 both of these provide I think is the idea that
9 there are a lot of overlapping application areas.
10 There are a lot of techniques that were known in
11 the art.

12 I'm not going to -- unless you want me to
13 really spend the time to do that, I'm not going to
14 dissect each and every element even of the table.

15 Q. Now, you said that the biological sciences
16 literature is vast.

17 How did the Mertes reference bubble up to
18 the top of that vast world of literature and
19 become one of the references you relied upon in
20 your report?

21 A. So you may be familiar that the NCBI, the
22 National Center for Biotechnology Information,

1 which is the center embedded in the National
2 Library of Medicine, which is one of the
3 institutes of the National Institutes of Health,
4 the NCBI maintains a large annotated database
5 called PubMed.

6 PubMed is the premier database in the
7 biomedical literature. Not all journals that are
8 written are indexed in PubMed.

9 So journals have to meet a certain set of
10 quality and other criteria to be indexed or
11 included. PubMed references are reviewed and
12 keywords are flagged and used to annotate each
13 individual reference.

14 If one goes to PubMed and does a search,
15 what one can do is search for specific terms. And
16 one can do straight searches and Boolean searches.
17 One can also easily filter the searches using
18 tools available at PubMed. So one of them is a
19 slider that allows you to slide and pick date
20 windows.

21 So if I were to search -- and I don't
22 recall the exact search terms which would return

1 Mertes.

2 But if Mertes was one of the references I
3 found, it would have been found by going to
4 PubMed, in this case searching for a specific set
5 of terms like "PCR" or "capture" or "enrichment"
6 with some other qualifiers, and then performing
7 additional filtering on the PubMed records to
8 identify them, scanning the abstracts, and
9 selecting those that seemed to be the most
10 relevant.

11 Q. You don't know any -- you don't have any
12 idea how Mertes was identified for use in your
13 declaration in this case. Right?

14 MR. KRAUSE: Objection to form, asked and
15 answered.

16 A. Sitting here more than a year after I
17 wrote my declaration, I can't tell you if this is
18 a reference that I found or this is a reference
19 that the attorneys found and provided it to me to
20 examine.

21 I will tell you that each and every
22 reference was a reference that I examined and felt

1 was suitable for use to illustrate various aspects
2 of the argument that I was presenting.

3 (Previously marked Exhibit 1007)

4 Q. And is the same thing true of
5 Exhibit 1007, which is the Mamanova reference that
6 I'm handing you?

7 MR. KRAUSE: Objection to form.

8 A. It is. So you're asking me about
9 qualifications too. And I think this is really
10 important.

11 So one of the things that one often looks
12 at when evaluating references -- and I talked
13 about the process of doing PubMed searches.

14 One of the things, you know, you often
15 rely on, too, is the standing of individual
16 authors in the field or the institution from which
17 they come.

18 So these are two nice examples. Anthony
19 Brookes is someone who is very involved in The
20 Human Genome Project and was really a leader. He
21 is at the University of Leicester in the U.K.

22 The Mamanova reference is actually from a

1 group that is based at the Wellcome Sanger
2 Institute, one of the institutes that was involved
3 in the initial sequencing of the genome.

4 I think Brookes was there at one point. I
5 don't recall exactly. But this is one from a
6 group at the Wellcome Sanger Institute in the U.K.

7 Q. Why did you mention the groups that these
8 publications came out of?

9 A. Well, you were asking about some of the
10 criteria that one uses to evaluate them. That's
11 not exclusive. That's not to say that every
12 reference that comes from a good institution can
13 be trusted completely, but it's one of the
14 criteria that you use in evaluating things, in the
15 same way that I would reject a reference from 2020
16 in looking at the time frame of 2012 to 2013.

17 Authors who have established their
18 credibility generally are authors that I tend to
19 look toward for various aspects of analyses.

20 Q. That's what I didn't understand. What
21 you're saying is that the authors and research
22 groups from which the Mamanova and Mertes papers

1 came out of are respected authors and respected
2 research groups. Is that what you're saying?

3 A. They're not perfect. But just looking at
4 the group, Jay Shendure is someone I have known
5 for many years. He's the next-to-last author
6 here.

7 These are people who at the time were
8 familiar with the relevant technologies. And so
9 in approaching their -- the references in
10 evaluating them -- let me put it this way.

11 If you were to go to a bookstore and buy a
12 book, you'd be more likely to buy a book from an
13 author who you've read before and whose work you
14 enjoy.

15 In evaluating scientific papers, I'm more
16 likely to pick up a paper from someone who I know
17 has an established record in the field.

18 It doesn't mean I believe everything they
19 write, but it's one of the pieces of evidence or
20 one of the pieces of information that you use in
21 evaluating any kind of reference.

22 Q. Would you agree that the Mertes and

1 Mamanova references together provide an
2 appropriate or would you say they provide an
3 inappropriate background explanation for
4 understanding target enrichment technologies in
5 these IPRs?

6 MR. KRAUSE: Objection to form.

7 A. So they provide -- again, they're pieces
8 of a puzzle. And you can ask about all sorts --
9 you're referring to target enrichment. In the
10 context of the IPRs, we can think of them as
11 capture technologies.

12 They provide pieces of evidence. What one
13 has to recognize is that any one of these
14 publications has to be interpreted in the light of
15 what a person of ordinary skill in the art would
16 understand and then project it on to the claims in
17 the patent in trying to analyze those claims.

18 These two references were really provided
19 to give a glimpse of the state of the art as of
20 2012, 2013, in capture probe technologies.

21 And part of the reason I like this
22 Mamanova reference so much -- again, I'm sort of a

1 visual person. There's Figure 2 that appears on
2 page 32 in my expert report or my declaration for
3 the '394.

4 And what it really shows is that there are
5 a lot of overlaps between these technologies in
6 terms of what Mamanova perceived as the best use
7 cases for each of these.

8 Q. And there's also regions where they don't
9 overlap. Correct?

10 MR. KRAUSE: Objection to form.

11 A. There always are. Because you can pick
12 out in Mamanova's diagram areas where, in her
13 opinion, the one technology might have an
14 advantage over another.

15 Q. Now, we've talked a lot about whole-genome
16 sequencing. When did you first become familiar
17 with whole-genome sequencing?

18 A. So it's hard to answer that question
19 because the term has taken on many different
20 flavors of meaning.

21 My first --

22 Q. Let me --

1 A. 1992 when I got my -- actually, before
2 that. 1990 when the genome project started.

3 Q. Let's do it this way.

4 (Previously marked Exhibit 11)

5 Q. I'm handing you a document, it's paper 11.
6 It's the decision instituting IPR for the '394
7 patent.

8 THE WITNESS: So, Derek, before we get
9 into this, we've been going for about an hour and
10 a half and I'm trying to be respectful of our
11 court reporter. Would now be a good time to take
12 a break?

13 MR. WALTER: Sure.

14 THE VIDEOGRAPHER: The time is 2:31.
15 We're off the record.

16 (Recess, 2:31 p.m. to 2:41 p.m.)

17 THE VIDEOGRAPHER: Okay. The time is
18 2:41. We're back on the record.

19 BY MR. WALTER:

20 Q. All right. I handed you the institution
21 decision in the '394 IPR. And I want you to turn
22 to page 22. And you can see there that the board

1 offered its construction for a whole-genome
2 sequencing in the last full paragraph.

3 Were you familiar with that construction?

4 A. Yes. I recognize this.

5 Q. Do you agree with this construction?

6 A. I'm not sure what you mean by "agree
7 with." This construction is consistent with the
8 analysis that I offered in my declaration.

9 Q. When I use the word "agree" -- I guess
10 I'll phrase it a different way.

11 Do you believe that this construction is
12 correct as a matter of substance and is how a
13 person of ordinary skill in the art would have
14 understood whole-genome sequencing in
15 January 2013?

16 MR. KRAUSE: Objection to form.

17 A. So as I said earlier, many of these terms
18 used in molecular biology change over time.
19 They're used in different ways by different
20 individuals in different contexts. If we apply
21 this in the context of the patents in question,
22 it's a reasonable analysis.

1 One of the things that's difficult to
2 interpret -- so if we look at it, a nontargeted
3 approach to sequencing. So if we look at what's
4 disclosed in Leary, Leary clearly uses a
5 nontargeted approach to sequencing all or almost
6 all of the genome. I don't know what all or
7 almost all represents fully.

8 And if I think about this in the
9 context -- I think what's really important about
10 the construction from the board is where they
11 continue in their decision in the same paragraph
12 to the next page where they refer to my discussion
13 that increasing coverage depth is something one
14 can do as required by an experiment.

15 So to approach all or almost all, whatever
16 we define that to be, if we don't need it at this
17 moment, all we have to do is sequence more. And
18 that was something that was clearly known in the
19 art.

20 So the depth of sequencing coverage to get
21 all or almost all is something which is fungible
22 in the context of the state of the art in 2013.

1 Q. Do you have any plans to revise your
2 opinions in view of the board's construction of
3 whole-genome sequencing?

4 A. I don't see there's any need to. If we
5 talk about Leary, Leary clearly carries out
6 whole-genome sequencing. One skilled in the art
7 would know that if one wanted greater sequencing
8 depth or wanted to discover, as you were alluding
9 to earlier, the individual base pair or
10 translocation occurred, all one would have to do
11 is run the sequencer with more DNA from the same
12 samples. Nothing that was beyond the capability
13 of any person working in the field at that time.

14 Q. Now, let's go back to when whole-genome
15 sequencing was something you first became familiar
16 with. I want to change my question a little bit.

17 When did you first become familiar with
18 whole-genome sequencing, as that term was defined
19 by the board?

20 MR. KRAUSE: Objection to form.

21 A. 1990. That was when The Human Genome
22 Project started with the goal of sequencing a

1 reference human genome.

2 Q. And when would you say whole-genome
3 sequencing as defined by the board was first
4 reported in the literature? Was that 1990 as
5 well?

6 A. So the first-draft genome sequence was
7 reported in 2001. You read reports of the
8 sequence being done earlier.

9 I'm not sure I should be mapping this back
10 to the literature. Really, the question is what
11 does this refer to within the context of the two
12 patents in question.

13 And I'll simply say that as presented
14 here, a whole-genome sequencing was an established
15 technique. Leary clearly carried it out. Forshe
16 carried it out. So whole-genome sequencing wasn't
17 invented by the patent owners of the -- either the
18 '033 or '394 patents.

19 Q. You said whole-genome sequencing was an
20 established technique. At what point in time
21 would you say it was an established technique?
22 What year would you say it became established?

1 MR. KRAUSE: Objection to form.

2 A. In what context?

3 Q. Any context.

4 A. So as a concept, prior to 1990 when people
5 conceived of sequencing the human genome, the goal
6 was to sequence the entire genome.

7 The publication in 2001 of a draft genome
8 actually simultaneous -- nearly simultaneous
9 papers in Science & Nature by Celera Genomics and
10 the public Human Genome Project represented a kind
11 of whole-genome sequence.

12 In about 2005, genomes were sequenced. In
13 about 2005, a company called 454 Genomics
14 introduced a sequencer. That sequencer was used
15 to sequence the genome of Jim Watson. So that was
16 a kind of whole-genome sequencing.

17 The depth of coverage and the technology
18 was very different than the first genome. There
19 were many other genomes that were sequenced with
20 different technologies.

21 Whole-genome sequencing is a concept that
22 has existed for a long time, and it's had a

1 variety of different definitions.

2 So I don't think I could put a date on it.

3 So I'm not sure how to apply this to the
4 literature.

5 If I applied this concept, though, to
6 analyzing the '394 and '033 patents, clearly in
7 the context of the '394 Leary is doing
8 whole-genome sequencing as a first step.

9 And as the patent board noted, if the
10 depth of sequencing isn't enough to meet a
11 particular -- someone's particular definition of
12 "almost all," all one would have to do is run the
13 sequencer again.

14 Q. At what point in time would you say
15 researchers were routinely performing whole-genome
16 sequencing, as that term has been defined by the
17 board before or after 2010?

18 MR. KRAUSE: Objection to form.

19 A. It would depend on your application and
20 what you mean. I don't know what "almost" means
21 and I also don't know what "routinely" means.

22 So I can tell you that in 2009 we started

1 a project to get genomic sequence data, maybe
2 earlier than that, at Dana-Farber on every patient
3 who walked through the door.

4 At some point, we moved away from targeted
5 techniques to whole-genome sequencing. It was a
6 cost consideration as much as anything else.

7 But even when we started this in 2009, we
8 clearly envisioned doing some kind of whole-genome
9 sequencing.

10 So it was used more frequently in the
11 analysis of samples in laboratory studies. Again,
12 if you go to NHGRI, you can -- the National Human
13 Genome Research Institute, you can probably find
14 graphics of the number of complete genomes over
15 time.

16 And by 2010, there were probably thousands
17 that had been announced.

18 But there's a broad range in the depth of
19 coverage too. There are projects like the 1000
20 Genomes Project that were looking for
21 polymorphisms that did what people referred to as
22 light sequencing.

1 There were other projects like Craig
2 Venter had his own genome sequence and did it to
3 great depth.

4 So it's hard to -- it's really hard to
5 say. It's not a question with an easy answer.

6 I think what's really relevant here is
7 whether or not there were other references that
8 were doing whole-genome sequence that rendered the
9 claims -- that anticipated rendering the claims
10 obvious. And I think I laid that out in my
11 declaration.

12 Q. You mentioned the 1000 Genomes Project.
13 Was that one that used whole-genome sequencing or
14 some form of targeted sequencing?

15 A. It was -- the 1000 Genomes Project was a
16 SNIP discovery project. So they were looking at
17 single nucleotide polymorphisms. The difference
18 between your genome and my genome is about one
19 base out of a thousand. Given the fact we have
20 two copies of our genome, there are 6 billion
21 bases, about 6 million differences between you and
22 me.

1 The 1000 Genomes Project was an attempt to
2 categorize those in populations from around the
3 world, recognizing that our genomes actually carry
4 a history of human migration and evolution in
5 them, and that in analyzing any kind of genomic
6 data you need a broad survey.

7 Q. Was the 1000 Genomes Project one that used
8 whole-genome sequencing or some form of targeted
9 sequencing?

10 A. Since it was a discovery project and we
11 wanted to find variation across populations, it
12 used a nontargeted approach to sequencing. And
13 that nontargeted approach would, I believe, meet
14 the board's definition of whole-genome sequencing
15 insomuch as one would understand what almost all
16 the genome means.

17 Q. Now, do you know one way or another
18 whether the term "whole-genome sequencing" was
19 being commonly used in the literature prior to
20 2010?

21 MR. KRAUSE: Objection to form.

22 A. I'm sure the term "whole-genome

1 sequencing" was used by many authors in many
2 different contexts prior to 2010. For example,
3 there are a number of contemporaneous references
4 that characterized Leary's approach as a
5 whole-genome sequencing approach.

6 Q. All right. Let's go to Paragraph 103 of
7 your declaration.

8 MR. NAINI: Of the '394 patent?

9 MR. WALTER: Yes, for the '394 patent.

10 Q. And do you see in that paragraph you refer
11 to a PCR primer capture probe? Do you see that?

12 A. Yes, I do.

13 Q. Okay. Is the term "PCR primer capture
14 probe" something that you see commonly used in the
15 literature?

16 A. So I don't believe the term "PCR capture
17 probe" occurs in the literature.

18 But again, I'm evaluating the references
19 that I cite in my declaration in the context of
20 what's disclosed in the two patents, the '033 and
21 '394.

22 One of the things I understand is that

1 patent owners can act as their own lexicographers
2 and define things.

3 And so in looking at Column 31, the
4 inventors or the claimed inventors of the '394
5 patent -- I believe it's also in the written
6 description of the '033 -- have a definition of
7 "capture probes." And the criteria are they can
8 have probe sets, like PCR primer pairs, and the
9 main criteria is they have nucleic acid binding
10 sites.

11 And so based on their definition, their
12 definition actually includes PCR primers.

13 So for clarity in my presentation to the
14 patent board, I use the term "capture probe,"
15 although as I said earlier I'm not sure that
16 that's a term that appears frequently in the
17 literature.

18 MR. WALTER: All right. A lot of that was
19 nonresponsive. So I didn't ask --

20 MR. KRAUSE: That was entirely responsive
21 to your question.

22 MR. WALTER: It wasn't.

1 MR. NAINI: We can agree to disagree.

2 Q. I was asking about PCR primer capture
3 probe, not PCR capture probe.

4 And I just want to know, have you ever
5 seen the term "PCR primer capture probe" used in
6 the literature?

7 MR. KRAUSE: Objection to form, asked and
8 answered.

9 A. So again, I'll point you to Column 31 of
10 the patent. The patent claims require capture
11 probes. The written description or specification
12 of the patent defines "capture probes." It
13 includes probe sets, and the criteria is they have
14 to have nucleic acid binding sites.

15 In reading this, it's clear that probe
16 sets which bind to nucleic acids include PCR
17 primers.

18 So for clarity in my presentation, I refer
19 to them as "PCR primer capture probes" in addition
20 to "capture probes" and also "PCR capture probes,"
21 I believe, although I don't recall seeing that in
22 the literature, although it may appear. I'm not

1 sure. We could easily do a PubMed search and see.

2 Q. Now, what is a PCR primer capture probe?

3 A. All right. So trying to be as concise as
4 possible in excerpting language from the claims,
5 in Claim Element 1.(c) it says "contacting said
6 second nucleic acid sample with a plurality of
7 capture probes, wherein said plurality of capture
8 probes hybridize to one or more polymorphisms,"
9 which are based on analysis.

10 Okay. So we have capture probes and they
11 hybridize.

12 So if we turn back to Column 31, Column 31
13 tells us that capture probes consist of many
14 different things, including capture probe sets
15 with -- typically the capture probe set comprises
16 a nucleic acid binding site.

17 So we can have sets of capture probes that
18 bind to DNA and can be used to target specific
19 polymorphisms. And that is precisely what the PCR
20 capture probes disclosed in Leary do. They bind
21 to the DNA in regions in which Leary identified
22 polymorphisms and allow Leary through the process

1 of PCR to capture those regions for subsequent
2 analysis.

3 Q. How is a PCR primer different from a PCR
4 primer capture probe?

5 MR. KRAUSE: Objection to form.

6 A. Again, if you survey the literature, the
7 literature is pretty broad. And there are lots of
8 different descriptions of variations on PCR.

9 So one variation is randomly primed PCR.
10 So one of the things that you could do in the
11 laboratory is take randomly generated
12 oligonucleotides. So you could make a 10-mer, a
13 20-mer -- and when we say "mer," we're referring
14 to the length of nucleotides, 10 mers, 20 mers.

15 When we synthesize them in each base,
16 allow instead of a fixed edition of specific
17 bases, any possible base. And one could throw
18 that into a PCR reaction.

19 And throwing them into a PCR reaction, one
20 would in principle -- and again, there are lots of
21 variations on how you run PCR. But in principle,
22 one would in a completely unbiased way amplify the

1 entirety of the genome. Right?

2 And again, "entirety" is sort of a
3 relative term, but a large fraction or a large
4 amount of the genome.

5 In the context of the '394 patent, '033
6 patent, the capture probes target specific
7 polymorphisms for subsequent stages of analysis.

8 So a randomly primed -- random primer
9 wouldn't meet the criteria of a PCR capture probe,
10 but those used by Leary to target specific
11 polymorphisms by binding to nucleic acids in that
12 polymorphism region meet the patent owner's
13 description of a capture probe and, therefore,
14 would be a PCR capture -- PCR primer capture --
15 PCR capture probes.

16 Q. So your contention is that "PCR primer
17 capture probe" excludes random primers?

18 A. We'd have to see how those random primers
19 are used. There may be an example in the
20 literature where one could characterize random
21 primers as PCR capture probes.

22 Again, I really perform my analysis in the

1 context of Leary. And the other references too,
2 we can talk about those. But Leary uses PCR as a
3 way of capturing polymorphic regions. So his PCR
4 primers are PCR capture probes.

5 I haven't done an exhaustive analysis of
6 the literature, but my understanding is to show
7 obviousness or anticipation all I have to show is
8 one instance where this occurs.

9 So I wouldn't want to limit my analysis in
10 that way. I would simply say in the context of
11 Leary, Leary's PCR primers targeting specific
12 polymorphisms could be characterized as PCR
13 capture probes and therefore meet the PCR
14 capture -- sorry -- the capture probe stipulation
15 of Claim 1.

16 Q. Is there any example of a PCR primer that
17 you can confidently say would not also be a PCR
18 primer capture probe?

19 MR. KRAUSE: Objection to form.

20 A. I'd have to see the PCR primers in the
21 context and how they're used. I'm not sure how
22 that's relevant.

1 I think what's relevant here is the fact
2 that Leary captures specific regions of the genome
3 using PCR. Therefore, based on the fact that
4 capture probes have to have nucleic acid binding
5 sites, they meet the definition of a capture
6 probe.

7 Q. Do you know if there's a difference
8 between a PCR primer and a PCR primer capture
9 probe?

10 MR. KRAUSE: Objection to form.

11 A. It would depend on how one uses it. I
12 could envision all sorts of variations on this
13 method that one could potentially use in a
14 laboratory setting.

15 All one has to do to show obviousness or
16 anticipation is show that there are limited number
17 of references in the literature which map to the
18 claim terms in the patent.

19 And I provide a very extensive analysis
20 claim by claim of Leary and how it maps to the
21 claimed invention in the '394 and then Forshew in
22 the '033 patents.

1 Q. You've given the example of random primers
2 as a situation where that might be a PCR primer
3 but not a PCR primer capture probe. Can you think
4 of any other examples?

5 A. So you asked me later could a PCR -- could
6 a random primer be a PCR capture probe. I would
7 say I wouldn't want to limit it. I would really
8 want to understand this in the context of how it's
9 being used.

10 Whether or not it could come up with some
11 hypothetical application where a PCR primer wasn't
12 a capture probe I'm not sure is relevant.

13 If you'd like, I could map out -- I could
14 sit here for a while and think about some
15 experiments and maybe map some out in which they
16 wouldn't be capture probes.

17 I gave you the example of random primers
18 to illustrate a situation in which they may not be
19 capture probes.

20 Again, what's relevant is in the context
21 of Leary. Leary uses DNA probes or probe sets
22 that have nucleic acid binding sites and target

1 polymorphisms and therefore meet what I understand
2 are the limitations of Claim 1.

3 Q. How would a person of ordinary skill in
4 the art know if they had a PCR primer capture
5 probe or just a PCR primer?

6 MR. KRAUSE: Objection to form.

7 A. So capture probes have been used in the
8 literature in many different ways. One would have
9 to interpret it in the context of what one was
10 reading or the experiments one were doing.

11 If we read the plain language of Claim 1,
12 we have a plurality of capture probes. So they
13 have to capture something -- wherein said
14 plurality of capture probes hybridize to one or
15 more polymorphisms which are based on criteria.

16 So they can't just capture anything. They
17 have to capture or hybridize to polymorphisms.

18 So the -- again, we can talk about all of
19 this in the abstract. In the context of the '394
20 patent, the capture probe is something very --
21 performs a very specific function. It captures
22 regions that are polymorphic that were identified

1 through other analyses like Leary's whole-genome
2 sequencing.

3 And the capture probe can be a probe or
4 probe set, and it has to have a nucleic acid
5 binding site.

6 So what does Leary do? Leary designs PCR
7 primers. They're oligonucleotides. They come in
8 pairs so they're a probe set. And they bind.

9 Where do they bind? They bind
10 specifically to the polymorphisms that Leary
11 analyzes.

12 So, you know, in the abstract I can dream
13 up all sorts of things. In the context of the
14 patent, Leary's PCR primers, whether they call
15 them primer capture probes or whatever we want to
16 call them, they meet the '394's definition of a
17 capture probe.

18 MR. WALTER: Okay. I think that was
19 nonresponsive.

20 MR. NAINI: Can we stop doing this every
21 time you don't like an answer, Derek?

22 MR. WALTER: No. When he's not

1 responsive, I need to note it for the record.

2 MR. NAINI: Okay. You note it for the
3 record; we'll note our disagreement.

4 Q. Let's go to Paragraph 66 of your '394
5 declaration.

6 A. All right.

7 Q. In Paragraph 66, you refer to
8 amplification and enrichment in the header above
9 it. Do you see that?

10 A. Yes, I do.

11 Q. Those are distinct concepts?

12 A. Depends on the application and the use of
13 the language. Enrichment can be amplification.
14 They can be used synonymously. They may not be
15 used synonymously. It's going to depend on the
16 context in which they appear.

17 Q. Can you give a general description about
18 amplification that is different from enrichment or
19 is that not possible because it only can be
20 analyzed in context?

21 MR. KRAUSE: Objection to form.

22 A. So I don't believe I rendered an opinion

1 in my report to try to distinguish between
2 amplification and enrichment.

3 Again, the use of terms is very
4 context-specific. And just like previously you
5 were asking me to come up with a hypothetical
6 example, I can come up with potential hypothetical
7 examples here, but I'm not sure how it's relevant.
8 And so I'm going to decline to do so.

9 The section you're referring to I actually
10 talk about or actually include both Mamanova and
11 Mertes, which we talked about earlier. I think
12 the Mamanova figure is a really nice figure
13 because Mamanova tries to look at different
14 technologies and show that they substantially
15 overlap.

16 So one could say, well, PCR is
17 amplification because it's polymerase chain
18 reaction and well known to amplify DNA. But it's
19 also enrichment and it's also a way of capturing
20 specific, in the case of the patents,
21 polymorphisms.

22 Q. Okay. You understand that you have to

1 answer my questions even though -- even if it
2 might encompass something that's not in your
3 report. Right?

4 A. I answered your question.

5 Q. Okay. Actually, you declined to do so.
6 You expressly declined to do so. That was what
7 you did in your last answer.

8 MR. KRAUSE: I believe the answer reflects
9 that he answered your question despite his
10 comment.

11 Q. Okay. I'll ask my question again. And I
12 understand you didn't render an opinion on this in
13 your report, but I'm asking you to do it now. And
14 if you are can't, just tell me you can't.

15 My question was, can you give a general
16 description about how amplification is different
17 from enrichment or is that not possible because it
18 can only be analyzed in context?

19 MR. KRAUSE: Objection to form, asked and
20 answered.

21 A. So I'd be hesitant to try to define the
22 limits of amplification and enrichment in the

1 current context of our discussion. There are
2 techniques where one can perform amplification and
3 also use enrichment.

4 If I sat and thought long enough, I could
5 think of enrichment-based technologies that may
6 not involve amplification.

7 So it will be hard for me to come up with
8 an abstract hypothetical that would provide a
9 clear answer to your question.

10 I'll refer you to the discussion in
11 Mamanova and Mertes and point out that PCR is
12 generally considered primarily an amplification
13 technique, but it's also considered an enrichment
14 technique.

15 And that if we look at hybridization with
16 capture probes, those are generally considered
17 enrichment techniques.

18 But all of them meet the definition
19 provided by the patent owners of capture probes,
20 which are probes or probe sets that hybridize to
21 DNA and, specifically in the context of Claim 1,
22 allow them to target polymorphisms that have been

1 identified in different analytical steps.

2 Q. I want to talk more about solution-based
3 hybrid capture, which you referred to in your last
4 answer.

5 Have you ever worked with hybridization
6 capture probes?

7 A. Yes, I have.

8 Q. And when did you first become familiar
9 with the concept?

10 A. I wouldn't want to give a year. I'd say
11 sometime in the mid 2000s. Well, I don't know
12 when the term first appears in the literature.

13 DNA is known to hybridize to its
14 complementary sequences and has been used to
15 capture through hybridization complementary DNA
16 sequences for a very long time.

17 So I don't know when the term first
18 appeared. I have been familiar with hybridization
19 since I started working in the biological sciences
20 in 1992 and probably before that.

21 Q. In Paragraph 76 to 78, you give an
22 overview of the hybrid capture probe technique.

1 Correct?

2 MR. KRAUSE: Objection to form.

3 A. So starting in Paragraph 76 and running
4 through Paragraph 78, so from page 36 to the top
5 of 39, I provide a high-level overview of
6 solution-based hybrid capture and provide one
7 example of hybrid capture.

8 Again, it's solution based, in which a
9 hybridization probe is allowed to bind to a
10 complementary nucleic acid target.

11 Q. Now, in Paragraph 77 you state, in the
12 third full sentence, "The catch is then pulled
13 down or fished out using beads to bind the biotin
14 that was incorporated into the baits." Do you see
15 that?

16 A. I see where it says that. Yes.

17 Q. Okay. When you're referring to "the
18 catch," what are you referring to?

19 A. So in some of the early literature
20 describing solution-based hybridization, the
21 hybridization probes were described as baits
22 because one is trying to fish out in those

1 applications complementary DNA sequences.

2 Those baits in some implementations had a
3 biotin tail attached to them. Biotin binds
4 almost -- it binds strongly but reversibly to
5 streptavidin.

6 And a common approach described in the
7 literature, and I believe there are commercial
8 products like Agilent SureSelect that were
9 available in the 2000s had oligonucleotides
10 conjugated to biotin where the oligonucleotides
11 could be added in solution. They would bind
12 targets. So the bait would capture or catch
13 nucleic acid fragments.

14 And then by binding them to beads,
15 magnetic beads, putting a magnet against the side
16 of the tube, washing the tube multiple times, and
17 then releasing the captured DNA or the catch, one
18 could use that as one of many alternative
19 enrichment strategies as a potential alternative
20 to PCR-based capture.

21 Q. Your paragraph goes on and refers to the
22 catch being, quote, pulled down. Do you see that?

1 A. Yes, I do.

2 Q. What do you mean by "pulled down"?

3 A. So in solution, the hybridized probes in
4 target DNA float around. By adding magnetic
5 beads, the magnetic beads are denser than water,
6 hence tend to sink.

7 What one does is typically put in the
8 magnetic beads and vibrate the DNA, create a
9 vortex, mix it around to allow the biotin to bind
10 to the streptavidin.

11 Those beads naturally settle to the bottom
12 of the tube. They're often referred to as
13 Eppendorf tubes. They settle to the bottom.

14 If I were to dump the tube over, they
15 would fall out. So the approach as commonly used
16 in the laboratory is to take that Eppendorf tube
17 and put it in a holder that has a strong magnet on
18 the side -- sometimes on the bottom but frequently
19 on the side.

20 That allows the magnetic beads to be
21 pulled to the side. Right? So often called a
22 pull-down assay. They're pulled to the side by

1 the magnetic field.

2 One can then dump out the solution. Those
3 DNA fragments that have not bound to the probes
4 and been captured on the beads are flushed out.
5 They're often washed. But it's pulled down
6 because they sink due to their density and they're
7 pulled further by the magnets that are used in the
8 assay.

9 Q. Now, you talked about how the capture
10 probes could sometimes be referred to as bait. Do
11 you recall that?

12 A. They're sometimes referred to as baits in
13 the literature, and I think they're referred to
14 here in Paragraph 77.

15 Q. Have you ever heard those probes or baits
16 referred to in the literature as "pull-down
17 probes"?

18 A. Possibly, yes.

19 Q. Why do you say "possibly, yes"?

20 A. It's not a term that immediately comes to
21 mind. But again, I'm sure it's referred to.
22 People use lots of terms in the biomedical

1 literature to refer to things. And I'm sure
2 somebody somewhere called them "pull-down probes."

3 Q. And why would someone refer to them as
4 "pull-down probes"?

5 MR. KRAUSE: Objection to form.

6 A. So I can't speculate in any particular
7 assay why one might refer to them as "pull-down
8 probes."

9 In the context of the example I provide
10 here at a high level, if they are probes in
11 solution and if they are biotinylated and if they
12 are caught in magnetic beads and they are pulled
13 down through the action of the magnetic field,
14 then one might in that instance refer to them as
15 "pull-down probes."

16 But in any particular reference, I
17 couldn't comment as to why someone might use that
18 term.

19 MR. WALTER: Do we need to go off the
20 record? I saw that a note was passed to the
21 videographer.

22 MR. NAINI: I just asked how much time we

1 have been on the record. I didn't want to
2 interrupt you.

3 MR. WALTER: Okay.

4 Q. Now, these baits or pull-down probes
5 you've been talking about, how long are those
6 typically in terms of the number of nucleotides?

7 MR. KRAUSE: Objection to form.

8 A. Sitting here today, I couldn't tell you
9 how long people make particular baits. It would
10 depend on the particular application. It would
11 depend on the laboratory conditions. It would
12 depend on a whole variety of factors.

13 I've probably seen situations where people
14 use combinations of biotinylated and other probes
15 that are ligated together. There are all sorts of
16 things people could do. I don't know how one
17 would determine the typical range. Sitting here
18 today, I couldn't tell you what that would be.

19 Q. You've been working with the -- you've
20 been familiar with pull-down probes since the
21 2000s. Right?

22 MR. KRAUSE: Objection to form.

1 A. I think I first saw them in the mid 2000s.
2 Yes. But I couldn't tell you accurately at which
3 date they first came to my attention.

4 Q. I'm not going to ever ask you for an exact
5 date.

6 But I guess my next question is, in the
7 roughly 15 to 20 years since you've been familiar
8 with them, what's the shortest probe length you've
9 seen in the literature that comes to mind?

10 A. Sitting here today, I couldn't tell you
11 honestly. It's not something I reviewed preparing
12 for today. It's not something I often think
13 about. It's one of those things that I would
14 think about in a particular context if I were
15 doing a very specific experiment.

16 Q. What's the shortest probe you've ever
17 designed?

18 MR. KRAUSE: Objection to form.

19 A. Honestly, I couldn't say. Again, it would
20 depend on the reaction conditions I was going to
21 try to use. I've designed probably tens of
22 thousands of PCR primers to use as capture probes.

1 There would be a range in sizes, again,
2 depending on reaction conditions. I couldn't tell
3 you what the shortest PCR primer would be.
4 Probably 15 or so bases, but I wouldn't stand
5 behind that. Typically a bit longer. It would
6 really depend on my application.

7 Q. Have you ever designed a PCR primer that
8 was only a single nucleotide long?

9 A. That wouldn't have much specificity, so
10 there wouldn't be really a point in doing that. I
11 also don't think the polymerase would bind to it
12 and extend, but I'm not sure.

13 Q. How about a solution-based hybridization
14 probe? Have you ever designed a solution-based
15 hybridization capture probe that was only a single
16 nucleotide long?

17 A. Again, it wouldn't have good specificity.
18 There wouldn't be a purpose in doing that, at
19 least not that I can think of.

20 Q. Okay. Now, with regard to the '394
21 patent, you don't identify any anticipatory
22 reference?

1 A. I don't believe I do. I believe the
2 argument I make is that Leary is rendered obvious
3 in the context of the claims of the '394.

4 And I believe that simply because in the
5 final stages -- if I recall the argument I laid
6 out, that Leary doesn't do sequencing of those
7 final products.

8 But as I present in my declaration, it
9 would have been obvious to one of ordinary skill
10 in the art that if one had DNA fragments and one
11 had sequenced them in Step 2, one could sequence
12 them in subsequent steps.

13 Q. You participated in the prior art search
14 for the '394 patent. Correct?

15 A. I believe I did. Yes.

16 Q. Okay. And you didn't find any reports of
17 anyone practicing the invention as claimed in the
18 claims of the '394 patent prior to the priority
19 date. Correct?

20 MR. KRAUSE: Objection to form.

21 A. So that's not true. I found -- and I list
22 these and laid out examples. So the first is

1 Leary, where Leary practices the claims of the
2 '394 patent from the perspective of a person of
3 ordinary skill in the art.

4 And Claim Number 2 or Ground Number 2, to
5 demonstrate the use of sequencing I included Ley.
6 And Ground 3, I combined Leary with Chan and Liao
7 in the context of what one of ordinary skill in
8 the art would do to demonstrate that these methods
9 were well known as of 2013.

10 Q. You didn't find any single literature
11 reference that disclosed all of the claim elements
12 of Claim 1 of the '394 patent as arranged in the
13 claim. Correct?

14 MR. KRAUSE: Objection to form.

15 A. Absolutely not. The clearest example is
16 Leary, which discloses each and every element when
17 viewed through the context of a person of ordinary
18 skill in the art.

19 In the context of my understanding of
20 anticipatory analyses, Leary does -- my opinion
21 was Leary doesn't fully anticipate it because
22 Leary doesn't perform sequencing on the final

1 products.

2 But again, it's obvious because one of
3 ordinary skill in the art as of 2013 would have
4 understood that sequencing could be used pretty
5 broadly.

6 So you know, I mentioned earlier I got the
7 first DNA sequencer, next-generation sequencer at
8 Dana-Farber. And as of 2013, we were moving
9 almost all of our assays to sequencing-based
10 assays.

11 So the use of sequencing was not something
12 that was -- if that's the only element missing
13 from Leary, turning a sequencer on that you can
14 buy from a commercial vendor doesn't seem to meet
15 the criteria of an invention.

16 Q. Okay. You don't find anybody out there in
17 the prior art prior to the priority date who
18 actually did all of the elements as arranged in
19 the claim reported in a single literature
20 reference. Right?

21 MR. KRAUSE: Objection to form.

22 A. So Leary fully renders all the claims

1 obvious. And I lay that out in my declaration.

2 Leary doesn't perform sequencing, so I
3 couldn't use it as an anticipatory reference.

4 But again, my understanding of obviousness
5 is that one should view this through the lens of a
6 person of ordinary skill in the art.

7 And if there's any deficiency in that
8 analysis, I also provide references to Leary in
9 combination with Ley or Leary in combination with
10 Chan and Liao to demonstrate that these claims are
11 obvious.

12 Q. You believe it would have been obvious and
13 natural to perform that third sequencing assay?

14 MR. KRAUSE: Objection to form.

15 A. A person of ordinary skill in the art as
16 of 2013 would have understood that one could
17 easily use sequencing. In the context -- so
18 Leary -- sorry.

19 The patent claims are sort of agnostic to
20 the particular application area. But one of the
21 most obvious is the use in cancer profiling.
22 That's what I'm very familiar with.

1 And by 2013, given where the cost of
2 sequencing had come, the use of a targeted panel
3 to monitor tumor development and progression,
4 again, would have been obvious. It was the sort
5 of thing that a lot of people were discussing
6 doing, had done. And the various references we
7 point to show that kind of analysis.

8 So turning a sequencer on is a pretty
9 obvious thing to do if you have a bunch of DNA.

10 Q. Okay. Would that have been obvious in
11 February of 2010 when Leary was published?

12 MR. KRAUSE: Objection to form.

13 A. If I looked at the Leary reference in
14 2010, I would have said Leary could easily have
15 sequenced the DNA in the third step. But also
16 looking at the analysis that Leary performed, I've
17 realized that Leary probably wouldn't have to do
18 that.

19 On the other hand, one of the things that
20 would have been obvious to someone in 2010, since
21 Leary used the size of the PCR products in
22 subsequent Steps 3 through 7 or 2 through 7

1 depending on how you count, because he looked at
2 seven different time points, it would have been
3 obvious to one of ordinary skill in the art that
4 if the size of one of those bands had changed,
5 that he would have sequenced those.

6 Because the first question you would ask
7 is if -- if I have an assay that tells me what's
8 there based on the PCR assay he had already
9 optimized, you don't need to sequence.

10 But if something changed in 2010, 2011,
11 somebody would have sequenced those to figure out
12 what was there.

13 Q. Do you have any explanation as to why
14 Leary didn't perform that third sequencing assay?

15 A. Because he probably didn't feel he needed
16 to at the time. He had already sequenced the
17 fragment. He knew what the sequence was. And if
18 the size of the fragments didn't change, then
19 determining their sequence -- he already knew the
20 sequence.

21 In designing these laboratory assays,
22 there are a lot of factors that go into it, go

1 into each one of them. And at that moment in time
2 for whatever reason he didn't -- he may have felt
3 he didn't need to.

4 But given the fact that Leary -- so Leary
5 was working with Victor Velachescu at Hopkins.
6 Right? They were sequencing all kinds of stuff.

7 It would have been obvious to Victor that
8 if he had any doubt about what appeared there, he
9 would have turned on the sequencer.

10 Q. Okay. Now, you stated that he had already
11 sequenced a fragment, so he didn't feel he needed
12 to.

13 Can you explain why the fact that he had
14 previously sequenced the fragment meant he didn't
15 need to do the third sequencing assay?

16 MR. KRAUSE: Objection to form.

17 A. So I can't speculate as to what drove the
18 decision. My best guess is that having sequenced
19 the DNA -- so remember, Leary is using PCR to
20 capture specific elements of the tumor DNA for
21 subsequent analysis.

22 Those PCR primers capture specific

1 regions. They're designed to capture them of a
2 specific size.

3 The size of those fragments was determined
4 in the second assay with the second nucleic acid
5 subset from the second nucleic acid sample.

6 The sequence of those was determined. So
7 if you think about this, we have a piece of this
8 genome where a polymorphism exists. In Leary,
9 they're translocations.

10 One primer binds on one side, one primer
11 binds on the other side, and there are
12 polymorphisms that exist that capture part of two
13 different chromosomes.

14 If Leary were to take those same PCR
15 capture primers and apply them to your DNA -- and
16 hopefully you don't have cancer or the specific
17 cancers he analyzed -- those PCR primers would
18 yield no product.

19 So if the patient were tumor free, there
20 would be no product. If the PCR amplified the
21 fragment and captured it, if that fragment size
22 did not change, then with a high degree of

1 confidence Leary would be able to say it's the
2 same translocation.

3 If the fragment size dramatically changed,
4 then I would assume that Leary would go back and
5 sequence it just to figure out what happened.

6 But in many of these clinical
7 applications, as we talked about earlier, the
8 exact break point can be much less informative
9 than the fact that we have a translocation.

10 And I'll point you again to the example of
11 multiple myeloma where one of the translocations
12 that's important to identify is at t(4;14), a
13 translocation between chromosomes 4 and 14.

14 And looking at those t(4;14)
15 translocations, if they appear, they appear. And
16 that's probably what Leary felt he needed to
17 know -- sorry, she; it's Rebecca -- what she felt
18 she needed to know.

19 So again, I can't speculate as to her full
20 reasoning, but I can provide an interpretation as
21 to why I think it's reasonable for her not to have
22 performed that sequencing step.

1 Q. Okay. Let's go to Figure 4 of Leary, in
2 particular 4A.

3 You understand that the gels in Figure 4A
4 are showing the PCR products from a chromosomal
5 rearrangement in each of two patients obtained by
6 doing PCR on cell-free DNA?

7 A. So Figure 4A actually shows what would
8 correspond to two different samples or two
9 different time points. In each, there is a
10 patient tumor sample, which is shown in the first
11 column. So there are two different patients,
12 HX402 and HX403. They are showing --

13 Q. Let me stop you right there.

14 So these were two patients, not two time
15 points. Right?

16 A. There are two things going on here. HX402
17 and HX403 are, I believe, two different patients.
18 So those are the patient identifiers.

19 There's also a tumor sample and a plasma
20 sample. And if you understand how scientific
21 papers are written, what one really wants to do is
22 demonstrate what you're measuring.

1 So if you remember, what Leary identifies
2 in her work is a translocation based on
3 whole-genome sequencing of the patient tumor.
4 That translocation, there were two. And one is a
5 chromosome 4, chromosome 8 rearrangement.

6 And what she identifies is a product of a
7 specific size. The second one -- and it could be
8 a concurrent plasma sample. I'm not sure. Again,
9 I'd have to read this in more detail.

10 But what she's showing is that it has the
11 same size. So again, based on what a person of
12 ordinary skill in the art would understand is that
13 those two captured fragments are the same.

14 And she sequences the captured fragment at
15 least at the first time point using Sanger
16 sequencing to determine the specific break point.

17 In patient 403, they don't have the
18 chromosome 8 rearrangement, but they appear to
19 have a chromosome 16 internal rearrangement, which
20 I'm assuming -- and again, I'd have to read this
21 in more detail, but I'm assuming is probably most
22 likely a deletion in chromosome 16, moving

1 fragments that should be -- moving pieces of the
2 chromosome that should be separated closer
3 together.

4 And again, what this is demonstrating in
5 the first column of HX403 is a first sample from
6 the patient that was subjected to the whole-genome
7 sequencing assay and then the second sample
8 showing this as the same size, reflecting that
9 chromosome 16 rearrangement.

10 So it's showing that what was found in
11 whole-genome sequencing can be replicated in the
12 second sample and that the product sizes are the
13 same. Given how PCR works, it indicates they are
14 going to have the same sequence.

15 Q. Now, for HX402, the chromosome 4 to 8
16 rearrangement was analyzed. Correct?

17 A. So they analyzed both, both the chromosome
18 4, 8 rearrangement and the chromosome -- I
19 believe -- again, I'd have to read this in
20 detail -- and the chromosome 16 rearrangement.

21 But it appears to me that since patient
22 402 didn't have the chromosome 16 internal

1 rearrangement, nothing appeared as if they were
2 normal for chromosome 16.

3 In the same way, patient 403 I believe was
4 tested for both rearrangements but only exhibited
5 in their tumor sample, their plasma sample, what
6 appeared in their primary tumor sample.

7 And again, if you look at Panel B, what
8 Leary clearly shows is that she repeated these
9 analyses at multiple time points.

10 And again, I sort of love this analysis
11 where -- this is a patient with colon cancer.
12 They had a colectomy, so the primary tumor was
13 removed. The amount of DNA in plasma drops. And
14 then the tumor starts to recur, probably distant
15 metastases. The patient receives chemotherapy,
16 and subsequently the level of tumor DNA drops.

17 Q. Now, in Leary you contend that the PCR
18 products from the plasma were subsequently
19 sequenced by Sanger sequencing. Correct?

20 A. I believe that's what Leary describes.
21 Yes.

22 Q. Now, Leary didn't use next-generation

1 sequencing for that sequencing of the PCR product
2 from the plasma sample. Right?

3 A. I don't believe Leary did. Again, I can
4 look through the methods, but I believe that Leary
5 used Sanger sequencing.

6 But I also don't recall any limitation
7 laid out in the claims of the '394 patent that
8 required next-generation sequencing, massively
9 parallel sequencing, or whole-genome sequencing
10 beyond the first -- the initial steps of the
11 analysis.

12 Q. Do you have any explanation for why Leary
13 didn't use any of the next-generation sequencing
14 platforms that were available, such as 454,
15 Illumina, or SOLiD?

16 MR. KRAUSE: Objection to form, calls for
17 speculation.

18 A. I can't speculate as to why she may have
19 made a particular choice. It could be that it was
20 simply the easiest thing to do.

21 It could be that, given the fact there
22 wasn't a huge number of PCR products that she

1 wanted to sequence that had been captured from the
2 tumor genome, that it might not have been
3 cost-effective for her. It may have been easier.
4 It may have been faster.

5 I'm not really sure. I don't know what
6 facilities they had available in their lab or at
7 the university at the time.

8 MR. WALTER: All right. Why don't we take
9 a break.

10 THE VIDEOGRAPHER: The time is 3:43.
11 We're off the record.

12 (Recess, 3:43 p.m. to 3:56 p.m.)

13 THE VIDEOGRAPHER: The time is 3:56.
14 We're back on the record.

15 BY MR. WALTER:

16 Q. Dr. Quackenbush, let's go back to the '394
17 institution decision.

18 A. I have it.

19 Q. Now, were you aware that at the end of
20 this institution decision there was a concurring
21 opinion?

22 A. I believe I saw that, but I don't recall

1 what it said.

2 Q. Okay. Let's take a look at that now. And
3 take a look at the last page on page 45.

4 The concurring opinion at the end states,
5 "Based on the disclosures in the '394 patent
6 specification noted above, I would have
7 preliminarily interpreted capture probe as
8 encompassing nucleic acid structures as small on
9 one nucleotide that may but are not required to
10 include linkers on labels." Do you see that?

11 A. I see where it says that. Yes.

12 Q. Okay. I think it was a typo. I think it
13 was meant to say "as small as one nucleotide."

14 Assuming that's the case, do you agree
15 this would be an appropriate construction for
16 "capture probe" in the context of the '394 and
17 '033 patents?

18 A. So the passage you read says that that
19 would have been the author of this concurring
20 opinion's preliminary interpretation.

21 And then in the previous paragraph, it
22 points out that yet the patent owner does not at

1 this stage grapple with such disclosures in its
2 patent, the idea that it could have included even
3 a single nucleotide, and instead appears to urge a
4 construction that is at once divorced from any
5 structural aspects of a capture probe as
6 defined -- described in the specification and is
7 instead forcing -- focused on importing a negative
8 functional feature that capture probes allegedly
9 exclude nucleic acid sequences if they are used or
10 intended to use as primers for PCR.

11 I see no adequate support at present to
12 justify the narrow interpretation advanced by the
13 patent owner.

14 So I think he or she is calling out the
15 fact that this is very broad, very vague, and
16 could potentially include a single nucleic acid.
17 Although, as she described previously in this
18 patent I talked about, doesn't talk at all about
19 the conditions under which any particular
20 limitation on the probes might or might not be
21 viable.

22 Q. You reviewed the specification of the

1 patents. Right?

2 A. Yes, I have.

3 Q. Having reviewed the specification and now
4 having taken a look at the concurrence, would you
5 construe "capture probe" to encompass
6 nucleotide -- nucleic acid structures that consist
7 of just a single nucleotide?

8 MR. KRAUSE: Objection to form.

9 A. Would you repeat the question, please?

10 Q. Having reviewed the specification and now
11 having taken a look at the concurrence, would you
12 construe "capture probe" to encompass a nucleic
13 acid structure that consists of just a single
14 nucleotide?

15 MR. KRAUSE: Same objections.

16 A. So I can understand how a reasonable
17 person would see the broad, vague description of
18 "capture probe" that's provided in the
19 specification of the '394 patent as not -- as
20 attempting to avoid any kind of limitation of what
21 a capture probe is.

22 There's no description at all about the

1 length or conditions under which these capture
2 probes would potentially operate.

3 Earlier you were asking me about length of
4 capture probes. And as I mentioned, the length of
5 any kind of effective DNA hybridization probe is
6 going to depend on a lot of factors.

7 I don't think I talked about all of them,
8 but temperature, salt concentration, a whole bunch
9 of different things.

10 And other than sort of a vague mention of
11 a capture probe, there's no real description of
12 what the limitations are.

13 So a reasonable person could read this and
14 see it as potentially encompassing even a single
15 nucleotide because, as we know, a single
16 nucleotide would hybridize to its complementary
17 sequence.

18 If I put on -- if I look at this through
19 the perspective of a person of ordinary skill in
20 the art, it would be hard for me to imagine a
21 single nucleotide.

22 But again, there's almost no guidance from

1 the definition of "capture probes" that tells me
2 anything. But obviously in reading this,
3 including elements like using probe sets, the fact
4 that the probe sets have to hybridize, and that
5 the capture probes can include things like bar
6 codes, it really sort of drives home the fact that
7 at the very least they would include PCR primers
8 as capture probes.

9 So, you know, I would agree with this
10 concurring opinion in that there's not really in
11 it an exclusion of PCR primers. But I don't
12 know -- it's hard for me to interpret what the
13 actual scope of what's claimed or what's described
14 here is.

15 Q. Do you understand with reasonable
16 certainty what "capture probe" means in the
17 context of the '394 and '033 patents?

18 MR. KRAUSE: Objection to form.

19 A. To the extent that Leary renders the '394
20 patent obvious, Leary's PCR primers are capture
21 probes that meet the definition laid out in
22 Column 31, in the top of Column 32, as to a

1 capture probe, consistent with the determination
2 at least laid out in this concurring opinion of
3 the meaning of "capture probe."

4 Q. And again, having reviewed the
5 specification and the concurrence, would you agree
6 that the definition adopted by the concurrence for
7 "capture probe" is appropriate in the context of
8 the '394 and '033 patents?

9 MR. KRAUSE: Objection to form.

10 A. So which definition in particular?

11 Q. Capture probe encompasses nucleic acid
12 structures as small as one nucleotide that may but
13 are not required to include linkers and labels?

14 A. So I don't believe that's actually the
15 definition adopted by the author of this
16 concurring opinion.

17 It says, "Based on the disclosures of the
18 '394 patent specification noted above, I would
19 have preliminarily interpreted capture probe as
20 encompassing nucleic acid structures as small as
21 one nucleotide that may but are not required to
22 include linkers and labels."

1 So you may read that differently than I
2 do. I don't read that as a defining definition of
3 a capture probe being a single nucleotide in
4 length.

5 Q. I didn't say it was. I said it was a
6 definition that allowed for it to encompass
7 structures that were only a single nucleotide and
8 nothing else.

9 Would you say that a capture probe within
10 the context of the '394 and '033 patents could be
11 a single nucleotide and nothing else?

12 MR. KRAUSE: Object to the form.

13 A. I don't believe that's what you asked me.

14 But if that's what you're asking now, I
15 would say that that interpretation as a person of
16 ordinary skill in the art does not make sense.

17 I will also say that the definition laid
18 out in Column 31 is vague enough that I don't know
19 what the boundaries are. But as I stated earlier,
20 if we read the definition laid out in Column 31,
21 it definitely encompasses Leary's PCR capture
22 probes that were designed after an analysis that

1 had followed his whole-genome sequencing.

2 Q. Is the preliminary interpretation offered
3 in the concurrence a valid interpretation of
4 "capture probe"?

5 MR. KRAUSE: Objection to form.

6 A. So the author of this concurring opinion
7 actually provides a great deal of detail. And I
8 have concentrated -- supporting his or her
9 conclusions.

10 And higher up on the same page, it
11 actually refers to Column 31. So I've spent a lot
12 of time talking about Column 31.

13 The author points to Column 41, lines 32
14 to 36, where it reads, "The capture probes,
15 primers, labels, and/or beads may comprise one or
16 more nucleotides."

17 So the capture probes may comprise one or
18 more nucleotides. The author of this concurring
19 opinion provides a great deal of analysis talking
20 about the failure to disclose any sorts of
21 conditions that might be used or that might be
22 envisioned as being used in these -- in the assays

1 that are claimed.

2 And again, it doesn't seem logical to me
3 that one would design a capture probe that was one
4 nucleotide in length. I can't understand how a
5 one-nucleotide capture probe would be specific to
6 any particular mutations or polymorphisms that one
7 would want to analyze.

8 But based on the way this written
9 description is presented, there are no limitations
10 laid out in Column 31.

11 And in Column 41, the patent owners
12 actually explicitly say that it could include one
13 nucleotide -- one or more nucleotides.

14 So I can understand how someone reading
15 this might have reached the preliminary
16 interpretation that a capture probe could
17 encompass one nucleotide.

18 Other than saying that he or she concurs,
19 I agree with the majority, and based on the
20 preliminary record that one reasonable
21 interpretation of "capture probe" encompasses, at
22 a minimum, PCR primer capture probes and

1 solution-based hybridization capture probes.

2 However, I find that the '394 patent's
3 disclosure is significantly broader than the
4 interpretation put forward by the majority.

5 I think the author of this is wrestling
6 with the same vagueness that appears in Column 31
7 and Column 41.

8 Q. Will you offer an opinion in this case
9 that you think a POSA would adopt the preliminary
10 interpretation offered in the concurrence?

11 MR. KRAUSE: Objection to form.

12 A. I don't see any reason why I would make an
13 argument about a preliminary interpretation.

14 My analysis is based on an obviousness
15 analysis derived from examining Leary and
16 comparing Leary to the claims of the '394 patent.

17 As this patent examiner points out, the
18 capture probes clearly include, at a minimum, PCR
19 primer capture probes and solution-based
20 hybridization probes.

21 I don't know what the limitations are as
22 to the construction of those probes because we

1 were not provided any guidance.

2 I will say that if the patent board asks
3 me to perform the analysis with a different
4 interpretation of "capture probes," I'd be happy
5 to do that.

6 Q. You're aware of the phenomenon of
7 circulating tumor DNA?

8 A. Yes, I am.

9 Q. Do you have an understanding of how big
10 those fragments of circulating tumor DNA are?

11 A. So circulating cell-free DNA independent
12 of source has a range of different sizes.

13 My understanding is that the average size
14 of circulating cell-free DNA is about 160
15 nucleotides. The reason for that is it really
16 comes from the structural elements of the genome
17 where DNA is wrapped around proteins called
18 histones and the average length or the average
19 circumference of a histone in DNA bases is about
20 160.

21 So the typical size -- and again, there's
22 distribution. But the typical size of circulating

1 cell-free DNA, tumor or otherwise, is about
2 160 bases.

3 Q. And are you familiar with the SOLiD
4 sequencing platform?

5 A. Yes. The SOLiD sequencer was developed by
6 Applied Biosystems. And it used -- rather than
7 sequencing by synthesis, it was technology based
8 on sequencing by ligation in which a series of
9 probes -- I think they were four bases in
10 length -- were hybridized to and ligated --
11 hybridized to DNA and ligated together to produce
12 a signal.

13 And this was done sequentially with
14 primers that differed in length to create
15 different offsets for the former hybridizations.

16 That's my best recollection of the
17 technology today. There could be details that
18 I've gotten wrong, since that technology has been
19 off the market for quite some time.

20 Q. And do you know what the read length is in
21 the SOLiD sequencing platform?

22 A. It changed over time. Sitting here today,

1 I couldn't tell you what the range was.

2 Q. Do you know what it was in 2010 when the
3 Leary paper was published?

4 A. Sitting here today, I couldn't tell you
5 how long that sequencing was -- how long that --
6 the sequencing reads were.

7 Q. Do you know what sequencing platform Leary
8 used for the sequencing that you contend is
9 whole-genome sequencing?

10 MR. KRAUSE: Objection to form.

11 A. So you'll recall that Leary used
12 whole-genome sequencing for their solid tumor
13 samples. These were the -- sorry. For the DNA
14 derived from their primary tumor samples.

15 These were 1.4 kilobase fragments. And as
16 described on page 5 of the Leary paper in the
17 right-hand column about two-thirds of the way
18 down, they talk about performing SOLiD library
19 preparation and sequencing. They provide some
20 details of the SOLiD sequencing platform.

21 One of the things I forgot is the
22 dye-based approach and their color-based way of

1 generating sequence.

2 It's described here in some detail in the
3 first paragraph of this subsection, and then says
4 for these 1.4 kilobase fragments that were
5 mate-paired and sequenced, all 25 base pair tags,
6 both individual tag and mate-paired tag analyses
7 were required to match the referenced genome
8 uniquely and without mismatches.

9 So I'm assuming that for their
10 whole-genome shotgun sequencing or whole-genome
11 sequencing, they used SOLiD and generated 25 base
12 pair fragments.

13 Q. 25 base pair reads?

14 A. 25 base pair reads. I'm sorry. From both
15 ends of the DNA.

16 MR. WALTER: Let's mark this as 2017.

17 (Exhibit 2017 marked for identification)

18 Q. I've handed you a document that's been
19 marked as Exhibit 2017. It's entitled
20 "Next-Generation Sequencing Technologies and
21 Applications for Human Genetic History and
22 Forensics."

1 Have you seen this one before?

2 A. I don't recall seeing it. I don't believe
3 I -- since it's got a new exhibit number, I don't
4 recall citing it in either of the two
5 declarations. I may have seen it in the past, but
6 it's not something I reviewed in preparation for
7 my testimony today.

8 Q. You don't recall having seen any portion
9 of this in the past?

10 MR. KRAUSE: Objection to the form.

11 A. Sitting here today, I don't recall.
12 Again, this is not a document I used in
13 preparation -- I reviewed in preparation for
14 coming here today. I may have seen it, I may not
15 have seen it. I simply don't recall.

16 Q. Are you familiar with the mate-pair
17 sequencing approach that was used in Leary?

18 A. Mate-pair sequencing involves sequencing
19 of both ends of a DNA fragment. That's why
20 they're referred to as mate pairs.

21 One of the things that's typically done is
22 those mate pairs are linked computationally.

1 Again, there are different implementations of it,
2 but they tend to be linked computationally.

3 And one of the reasons they're useful for
4 identifying translocation polymorphisms, as Leary
5 does, is that she's able to see that the two ends
6 of those fragments map to different regions of the
7 genome.

8 She would expect them to map to regions
9 that are about 1.4 kilobases apart. And
10 consequently, she would be able to detect
11 deletions or insertions in chromosomes if the
12 distance between them changed, or translocations
13 if the mate pairs map to different chromosomes.

14 Q. So that's one reason why a mate-pair
15 sequencing was used in the Leary reference.

16 Are there any other reasons why someone
17 would want to utilize a mate-pair sequencing
18 approach?

19 A. There are lots of potential reasons why
20 one might use mate-pair sequencing. I would
21 hesitate to list them because I would probably
22 miss a lot or forget a lot.

1 But mate pairs -- sequencing of paired
2 ends, it's often referred to as paired-end
3 sequencing. Sequencing of paired ends of DNA
4 fragments is an approach to generating sequence
5 data that has a long history.

6 One of the things -- I mean, it was used
7 in sequencing all different sorts of DNA fragments
8 in libraries in the context of sequencing the
9 human genome.

10 Q. All right. Let's take a look at Figure 2
11 of this figure. Excuse me. Of this paper of
12 Exhibit 2017. It's entitled "Principles for
13 Construction of Mate Pair Sequencing Libraries."

14 A. I'm sorry. Looking at Table 2?

15 Q. Figure 2.

16 A. Yes.

17 Q. And you see on the right-hand side in
18 Panel C there's a description of the procedure for
19 generating a mate-pair sequencing library for the
20 SOLiD platform? Do you see that?

21 A. Yeah. There's little cartoon schematic
22 showing the process.

1 Q. Are you familiar with that process?

2 A. In general terms, yes. I'd actually want
3 to probably review this if we were going to have a
4 detailed discussion. But in general, yes.

5 Q. Okay. So let's just walk through it. You
6 started out with double-stranded DNA molecules at
7 the top in Step 1.

8 A. So the figure legend tells me in her
9 analysis, in Berglund's analysis, that the SOLiD
10 process at least in the first few steps is the
11 same as the process for Roche 454 sequencing.

12 And Roche 454 sequencing starts with
13 original fragments which are shown up at the top
14 as essentially double-stranded fragments, although
15 Step 2 talks about end repair. So there could be
16 overhanging nucleotides on the ends of these
17 fragments.

18 Q. All right. In Step 2, you introduce an
19 adapter, one of which includes a biotin molecule.
20 Is that right?

21 MR. KRAUSE: Objection to form.

22 A. So original fragments, one, are end

1 repaired with unlabeled nucleotides, and biotin
2 labeled circularization adapters CA are ligated to
3 the fragment ends. So that's what Berglund is
4 telling us happens in Step 2.

5 Q. And for the SOLiD, those adapters that are
6 labeled as IA. Right?

7 MR. KRAUSE: Object to form.

8 A. So I believe they refer to them here as
9 internal adapters and consequently refer to them
10 as IA.

11 Q. And then in Step 3, the double-stranded
12 molecules with the adapters are circularized, and
13 there is a biotin molecule at the junction. Do
14 you see that?

15 MR. KRAUSE: Object to the form.

16 A. So in Step 3 after circularization 3, so
17 it's circularized. And in the circularization
18 process, the two what are referred to in SOLiD as
19 the internal adapters get ligated together. It
20 forms a circular double-stranded DNA fragment.

21 And at the conjunction of the two internal
22 adapters -- and earlier we talked about just

1 internal adapters being ligated on their other
2 elements of those adapters.

3 But in -- sorry. Anyway, where those two
4 internal adapters are ligated on, there is a
5 biotin molecule attached. Yes.

6 Q. And then the circularized molecules that
7 are prepared in Step 3, those are fragmented.
8 Correct?

9 MR. KRAUSE: Object to the form.

10 A. So my interpretation of what Berglund is
11 describing is based solely on what's presented in
12 the figure legend for Figure 2. And because this
13 is the third of three analyses that she's
14 describing, she simply says -- again, referring
15 back to the Roche 454 -- that after
16 circularization to fragmentation an affinity
17 purification occurs.

18 And so we're told the DNA is fragmented,
19 although there's no description in the figure
20 legend for how that fragmentation is carried out.

21 I'd be happy, if it becomes relevant for
22 the rest of our discussion, to try to understand

1 how that fragmentation has occurred, whether it's
2 through enzymatic action or physical shearing or
3 some other technique.

4 Sitting here today, I can't tell you. All
5 I can tell you is she describes this, the
6 transition from Step 3 to Step 4, as involving a
7 fragmentation.

8 Q. So you take the circularized DNA and you
9 fragment it. Correct?

10 A. That's what she's describing. Yes.

11 Q. And then you capture the fragments that
12 include the biotin molecule. Correct?

13 MR. KRAUSE: Object to the form.

14 A. So I believe the phrase she actually uses
15 is "affinity purification." So she's using the
16 affinity or she's describing the affinity between
17 biotin and streptavidin as being necessary for
18 purifying those fragmented elements.

19 Q. Actually, she uses "affinity capture."
20 Right?

21 A. Actually, it says right here "affinity
22 purification and library adapters."

1 Q. Okay. In the panel above where she's
2 referring us to -- she refers to "affinity
3 capture." Right?

4 MR. KRAUSE: Object to the form.

5 A. All right. So it says, "Preparation of
6 SOLiD mate-pair libraries Steps 1 through 4 are
7 analogous with preparation of Roche 454 paired in
8 libraries with a biotin labeled internal adapter
9 and two sequencing adapters, P1 and P2."

10 So if I look back at 454, it's Column B,
11 preparation of Roche 454 paired in libraries.
12 These are called paired end but are based on the
13 same principle as the mate-pair libraries and
14 other technologies.

15 Original fragments are won and repaired
16 with unlabeled nucleotides and biotinylated
17 circularization adapters.

18 So Roche refers to them as circularization
19 adapters -- SOLiD refers to them or ABI refers to
20 them as internal adapters -- are ligated to the
21 fragment ends, 2.

22 After circularization, 3, fragmentation

1 and affinity purification, library adapters are
2 ligated to the new fragment ends.

3 So I don't see the "affinity capture" in
4 the description of 454 or SOLiD.

5 Q. All right. That affinity capture, what
6 you understand that to be referring to is
7 capturing the fragments from the circularized DNA
8 that have the biotin using streptavidin. Correct?

9 MR. KRAUSE: Objection to the form.

10 A. So again, in the 454 description there's
11 no -- the SOLiD description refers me to 454. 454
12 says "affinity purification."

13 Q. What do you understand that to be
14 referring to?

15 A. Using streptavidin biotin to purify these
16 fragments from the reaction.

17 Q. The fragments you're talking about, the
18 fragments that result from fragmentation of the
19 circularized DNA. Correct?

20 MR. KRAUSE: Object to the form.

21 A. That seems to be the -- so it's
22 purification of these particular elements of the

1 sequencing library.

2 I think I understand what you're trying to
3 get to, that -- you keep referring to it as
4 "capture," although she refers to it as "affinity
5 purification."

6 And you're really driving home the point
7 that I made earlier, that if we call it
8 "capture" -- and I don't see her calling it
9 "capture," although you continue to do so.

10 If you can point me to where she calls
11 this in the 454 to SOLiD description "capture," I
12 don't know.

13 But in this context if you call that
14 "purification capture," that's different than the
15 capture that's referred to in the '394 patent.

16 And if we look at that --

17 Q. I don't --

18 A. No, no, no. Please.

19 If we look at that, there are examples of
20 capture probes being used in some of the other
21 references. And I'd have to go back and look at
22 them.

1 So if you make the argument that PCR-based
2 capture doesn't somehow meet the limitations of
3 capture probes and the institutional decision, at
4 least the concurring decision, the concurring
5 opinion says they clearly fall within the domain
6 of capture probes.

7 I provide other references that use
8 hybridization-based capture probes, and I believe
9 most of them use streptavidin and biotin.

10 So as Mamanova and Mertes point out, there
11 are lots of different strategies for capture. In
12 this context, we -- we could agree to call this
13 capture, although this is a different kind of
14 capture than the capture that's being carried out
15 in Claim 1 of the '394 patent.

16 MR. WALTER: Okay. That was nonresponsive
17 and unfortunately a waste of time.

18 MR. KRAUSE: We object to that
19 characterization. I know you disagree.

20 MR. WALTER: Okay.

21 A. Well, you keep on saying "capture probes."
22 And it doesn't say that. Or capture -- I don't

1 know -- it says "affinity purification." You keep
2 on changing the language and asking me about
3 things that aren't here. So I'm doing my very
4 best to interpret what you're asking.

5 Two or three times you've said something
6 about "capture," and it says "affinity
7 purification."

8 Q. The affinity purification that's being
9 referred to, that involves the binding of the
10 biotin to a streptavidin and then the collection
11 of the fragments of DNA that include the biotin
12 and have bound to the streptavidin. Correct?

13 MR. KRAUSE: Objection to the form.

14 Q. That's what you understand that to refer
15 to?

16 MR. KRAUSE: Same objection.

17 A. So you're asking me to sit here today and
18 to read a figure caption for a cartoon providing a
19 high-level overview of three different mate-pair
20 paired-end sequencing strategies that are laid out
21 in a reference I haven't reviewed.

22 If you'd like, I'm more than happy to take

1 the next hour and read this document end to end
2 and provide a detailed analysis and answer your
3 questions. It's not really fair to ask me to
4 provide detailed answers to a document that I
5 don't recall seeing -- and if I saw it, it was
6 some time ago -- and that I don't cite in any of
7 my declarations.

8 Q. Do you --

9 A. So you're asking me about in this cartoon
10 the binding of the biotin.

11 I can point you to my report where I talk
12 about hybridization-based enrichment strategies.
13 And one of those involved capture probes that have
14 biotin and streptavidin. We talked about them
15 earlier as pull-down assays. You asked a lot of
16 questions about pull-down assays.

17 This is something different. This is --
18 we're not -- there's no hybridization of a capture
19 probe. This is a ligation of an adapter to a DNA,
20 circularization, and then for your sake I'll call
21 it capture of that biotin and streptavidin.

22 You're asking about how it's removed from

1 solution. It's an affinity purification.
2 Typically the way that's done, although I haven't
3 read this reference in detail, but typically the
4 way it's done is by using magnetic beads which are
5 cultured with streptavidin.

6 Those magnetic beads are then pulled --
7 after fragmentation, they're pulled to the side of
8 the tube and used -- and the other DNA is eluted,
9 washed out. And then further laboratory steps are
10 carried out, which is what the rest of this
11 cartoon shows.

12 Okay? I'm giving you the best answer I
13 can based on reading a figure caption for a
14 cartoon figure and a document I haven't reviewed.

15 Q. Do you know how the mate-paired libraries
16 that were sequenced in the Leary reference on the
17 SOLiD platform were prepared?

18 MR. KRAUSE: Object to the form.

19 A. I don't believe Leary discloses these in
20 the short method section that appears in the
21 reference. There is an online method section
22 which I'm assuming provides more detail.

1 I'm assuming she used a pretty standard
2 protocol. As of 2010, I'm not sure exactly what
3 protocol Applied Biosystems provided with its kit,
4 so I don't know what kit she used. That's
5 probably in the online supplement.

6 I'm not sure. And I'm also -- I didn't
7 review that because I'm not sure how that's
8 germane to whether or not she performed
9 whole-genome sequencing, which she clearly did and
10 which is also -- her approach is also referred to
11 as whole-genome sequencing in other
12 contemporaneous references.

13 So, you know, you're asking me questions
14 about things that I didn't review, I don't have
15 the information to review, and documents I haven't
16 seen until 40 minutes ago.

17 Q. Do you know if the standard protocol for
18 preparing mate-paired libraries for the SOLiD
19 platform is consistent with what you see in
20 Figure 2C of Exhibit 2017, the Berglund reference?

21 MR. KRAUSE: Object to the form.

22 A. So in broad brushstrokes, yes. The

1 Berglund paper was published in 2011. I haven't
2 seen this paper until today. I don't know what
3 version or particular kits or particular assays
4 Berglund is referring to.

5 If we're referring back to the Leary
6 reference, this is a 2010 paper. I don't know if
7 the mate-pair library protocol was updated between
8 when she performed her assays in 2010 or 2009 and
9 when Berglund wrote her analysis in 2010.

10 So I can't answer that question because I
11 don't have the relevant information sitting in
12 front of me.

13 Q. And you didn't investigate how the
14 mate-paired libraries were prepared in the Leary
15 reference. Correct?

16 A. I don't know why I should have
17 investigated it. Leary tells us she did
18 whole-genome sequencing. And whether or not she
19 used an Applied Biosystems sequencer or a Roche
20 454 sequencer or Illumina sequencer seems to
21 matter less than the fact that she did
22 whole-genome sequencing using this mate-pair

1 library strategy or paired-end strategy.

2 Q. This mate-paired approach, you said you
3 understand it in broad brushes.

4 In Step 3, you understand that the
5 circularized DNA is fragmented and then the
6 fragments that have the biotin, they're collected
7 and extracted for subsequent sequencing. You
8 understand that. Right?

9 MR. KRAUSE: Object to the form.

10 A. So typically the DNA is circularized. The
11 fragments are -- the circular elements are
12 fragmented. Again, I'd have to read this to
13 understand what method for circularization was
14 used for fragmentation. I could imagine
15 sonication, and I can tell you potential
16 advantages and disadvantages of that.

17 There might be Type 2 or Type 3
18 restriction enzymes that are included in the
19 internal adapters that are used. I don't know,
20 sitting here today.

21 SOLiD is a technology that I think was
22 discontinued in -- I don't know. A number of

1 years ago. So it hasn't been on the market. So
2 it's not something that I'm as intimately familiar
3 with as I am with other technologies like Illumina
4 which are still on the market.

5 If you are ask me about details for 454,
6 my answer would be the same. It's so long ago, I
7 don't remember all the details. But somehow the
8 DNA is fragmented. The circular pieces are
9 fragmented.

10 A process they refer to as "affinity
11 purification" purifies those, so the biotin will
12 bind to streptavidin, use magnetic magnets to
13 attract them inside of the tube, wash everything
14 else away, and then perform the subsequent steps.

15 Q. So the sequencing -- let me ask a
16 different question.

17 The fragments from the circularized
18 molecules that don't include the biotin, those are
19 discarded. Correct?

20 MR. KRAUSE: Object to the form.

21 A. The fragments that don't include the
22 biotin are typically discarded. They're not

1 carried through the rest of the sequencing assay.

2 Q. The fragments that are carried through the
3 sequencing assay are the ones that have the
4 biotin. Correct?

5 A. No. The fragments that are carried
6 through the sequencing reactions are released from
7 the biotin.

8 Q. Okay. The fragments that are carried
9 through the sequencing assay previously had the
10 biotin before the sequencing. Correct?

11 MR. KRAUSE: Objection to form.

12 A. So the biotin is used in the affinity
13 purification process. And so those fragments that
14 are at the ends -- so those DNA elements that are
15 at the ends of the fragments are circularized and
16 linked to a biotin. The DNA is fragmented;
17 through what process, I cannot tell you, sitting
18 here today.

19 The biotin allows those fragments that
20 have the internal adapters on the ends -- because
21 remember, we had DNA with ends. It's now
22 circularized. The ends of those DNA are now

1 available.

2 So if you look at the cartoon, it's a
3 pretty good representation where we have -- I'll
4 call them the left fragment, which is depicted in
5 green, the internal adapters in kind of a yellow,
6 and the right fragment depicted in red.

7 And then additional sequencing adapters
8 are attached to those. And that's sort of what
9 happens in Step 4, if I'm reading this correctly.

10 Q. And so we're not told how big that
11 molecule is in Step 3. But a big chunk of that
12 black original DNA sequence is not going to be
13 sequenced because it's discarded after the
14 fragmentation process. Correct?

15 MR. KRAUSE: Object to the form.

16 A. Whether or not the middle part of that
17 particular molecule is sequenced in the
18 application for Leary doesn't really matter.

19 Leary never claimed to sequence the entire
20 fragments. Leary describes the use of mate-pair
21 sequencing. So Leary has pieces of DNA that are
22 1,000 -- approximately 1,400 bases apart.

1 She says 50 bases, so I'll take her at her
2 word, although I think she also describes later on
3 doing longer sequencing. Berglund talks about 50
4 to 75 base pair fragments.

5 I know that there were improvements in
6 sequencing technology probably while Leary was
7 generating her data. She sequences those. But
8 just because the center of that DNA molecule
9 wasn't sequenced doesn't mean the corresponding
10 sequence in the genome wasn't determined. Because
11 remember, we're sequencing ends of many fragments,
12 millions of fragments, not just those.

13 And remember that if one wanted to cover
14 that, the entirety of any of those fragments or as
15 near as one could get, all one would have to do is
16 sequence deeper, a technique that was well known
17 in the art.

18 So, you know, again, I'm really trying to
19 understand what the basis of the question is. For
20 a particular molecule, that piece -- the sequence
21 of that piece is not determined, but the
22 intervening sequence can very well be sampled and

1 very well be determined using the approach that
2 Leary lays out and using the SOLiD sequencing
3 approach.

4 The reason one does mate and pair
5 sequencing is one has additional structural
6 information about the genome based on the size of
7 the fragments that are sequenced. And that's what
8 Leary in a very clever way exploits to be able to
9 identify translocations.

10 Q. All right. Let's take a look at Leary,
11 and let's take a look at the description of the
12 approach on page 1. And it states, "The total
13 amount" --

14 A. Can you tell me where?

15 Q. The last sentence of the first full
16 paragraph on the right-hand column.

17 A. Okay.

18 Q. It states, "The total amount of genome
19 base pairs covered by the mate-paired analysis,
20 that is" --

21 A. I'm sorry. I lost it. So right-hand
22 column -- oh, I have the wrong paper. I'm

1 shifting between papers and I lost Leary.

2 Okay. I have it now. The right-hand
3 column. Okay. I found it. Sorry about that.

4 Q. "The total amount of genome base pairs
5 covered by the mate-pair analysis, that is
6 distance between mate-paired tags times number of
7 mate-paired tags was 53.6 gigabytes per sample."

8 A. Gigabases.

9 Q. Gigabases.

10 Do you see that?

11 A. Yes, I do.

12 Q. So for every mate-pair tag, you are
13 sequencing 50 base pairs. Correct? 25 times 2.
14 Right?

15 A. I believe that's correct. So Leary
16 sequences a large number of samples. I'd have to
17 look and see what particular sample this refers
18 to.

19 But yes, she generates 4.95 gigabyte --
20 gigabases -- now I'm doing it -- gigabases of
21 mappable reads per sample, so about 5 billion base
22 pairs of mappable sequence reads.

1 So she generates a lot more. 5 billion of
2 those bases are mappable. So her criteria, if I
3 remember, is that you can't have a mismatch with
4 the referenced genome.

5 So she's throwing out a lot of data to be
6 conservative. So she generates about 5 billion
7 bases of mappable reads. And that corresponds to
8 about 53.6 billion bases of physical DNA from the
9 chromosomes or about an eighteenfold physical
10 coverage of the genome.

11 Q. Okay. That eighteenfold physical coverage
12 of the genome, that's not stating that you
13 sequence the genome 18 times. Right?

14 MR. KRAUSE: Object to the form.

15 A. So she's not de novo sequencing the genome
16 to an average depth of coverage of 18. And for
17 her analysis, that wasn't what was required.

18 What she's looking for is translocations.
19 And so rather than sequencing the entire genome,
20 she's actually using something that's much more
21 informative for her particular application,
22 translocations. Because what she's looking for

1 are two pieces of DNA, each 25 bases in length,
2 that should be 1,400 bases apart. So you should
3 be able to map them back to the genome and see
4 they're 1,400 bases apart.

5 If there are wild differences in the
6 distance between them, if it's too small there's a
7 deletion; if it's too big there's an insertion.
8 If one maps to chromosome 8 and the other maps to
9 chromosome 4, there's a translocation.

10 So for her particular application that
11 eighteenfold coverage of physical distance is
12 what's important because that's what she wanted to
13 identify.

14 She actually claimed she sequenced an
15 average of 5 billion base pairs, so more than
16 onefold coverage of the genome. And anyone
17 skilled in the art would know that one could
18 simply sequence more to get deeper coverage and
19 asymptotically cover the entire genome.

20 Q. When she refers to "physical coverage,"
21 what is she referring to?

22 A. So the clones -- so if we were to think --

1 you know what, I'm not going to even draw a
2 picture because she has a beautiful diagram in
3 Figure 1.

4 So Figure 1 is really useful to understand
5 what she means. The DNA fragments -- and this
6 shows up in the left-hand column of Figure 1.

7 And what you can see is she has a variety
8 of different DNA fragments. For illustration
9 purposes, she's color-coded these with ends
10 either -- it looks like red or sort of blue, with
11 red or blue ends that represent sequences that
12 would map to one chromosome in blue or another
13 chromosome in red.

14 So the 25 base pair fragments are on
15 either end of a piece of physical DNA that's 1,400
16 bases long. She maps those back to the genome.

17 The sequence coverage is going to be if we
18 take 5 billion base pairs as her number, it's
19 going to be about 1.6-fold coverage based on
20 sequence. But the physical coverage, so the DNA
21 represented by those physical clones, is going to
22 be about eighteenfold.

1 And this is a very cost-effective strategy
2 of identifying translocations. Because rather
3 than having to sequence every base, she relies on
4 this additional information about the length of
5 the fragments.

6 Really smart because it lets you find
7 these things very, very efficiently. Because they
8 don't end at the same place, she can narrow down
9 where they are, which is what allows her to design
10 her PCR capture probes and perform her subsequent
11 analysis.

12 So she optimized for physical coverage
13 because she's looking for translocations. If she
14 wanted to optimize for other types of mutation or
15 polymorphism detection, she could have chosen a
16 different strategy.

17 And she, as a person skilled in the art,
18 would know that sequencing deeper would get her
19 greater sequence coverage if she had mate-pair
20 sequence in addition to greater physical coverage.

21 Q. All right. Let's go to Claim 1 of the
22 '394 patent. And there is a series of steps that

1 are --

2 A. Hold on. Sorry. I've got a lot of
3 documents. I've got it.

4 Q. There's a series of steps laid out in
5 Claim 1. And I want you to envision a situation
6 where someone of skill in the art knows the
7 individual steps but not the combination of steps.

8 Would a person of ordinary skill in the
9 art have a reasonable expectation of success of
10 being able to combine those steps into the ordered
11 method that's laid out in Claim 1?

12 MR. KRAUSE: Objection to form.

13 A. So I'm not sure if I understand your
14 question.

15 But Leary clearly did it, so there's
16 evidence that Leary was able to perform each and
17 every step in Claim 1.

18 Q. Not just each and everyone step
19 individually. But if someone knew the individual
20 steps on their own, would someone have a
21 reasonable expectation of being able to arrange
22 them into the ordered combination that appears in

1 the claim and perform the claim method?

2 MR. KRAUSE: Objection to form.

3 A. So I'm not sure what you're asking. If
4 someone already knew what was claimed --

5 Q. No, no. Not the claim. The individual
6 steps in the claim. Not the ordered combination
7 of steps as appears in the claim. Just the
8 individual steps.

9 MR. KRAUSE: Same objections.

10 A. Again, I'm not sure I understand your
11 question.

12 Leary performed each and every step of
13 Claim 1 and, to the best of my knowledge,
14 performed them in the order laid out in Claim 1.

15 There are lots of other references I can
16 point to that carried out the various individual
17 steps and that one skilled in the art -- the only
18 deficiency that I can find potentially in Leary is
19 that she didn't sequence the final products but
20 relied on her understanding of what was in those
21 products.

22 And I would guess she had no need to

1 sequence them. But given the fact she sequenced
2 them at Step 2, she could have easily sequenced
3 them at each subsequent time point.

4 So given the fact that we have concrete
5 evidence of someone performing each and every step
6 in order, including the final step of performing a
7 biomedical report, and at the very least, this is
8 a biomedical report because it reports on what she
9 found, it seems that she's carried out the entire
10 analysis.

11 Q. Let me try it a different way.

12 Assume that someone understood how to do
13 whole-genome sequencing, someone understood how to
14 identify mutations in whole-genome sequencing
15 data, someone understood how to use capture
16 probes, and someone understood how to sequence DNA
17 molecules that are identified that are captured
18 using capture probes.

19 If someone had all of those skills, would
20 someone be able to carry out the method of Claim 1
21 with a reasonable expectation of success?

22 MR. KRAUSE: Objection to form, incomplete

1 hypothetical.

2 A. So I don't know what the reasonable
3 expectation of success is. Between page 65 and 87
4 of my declaration in this IPR matter, I lay out
5 exactly what Leary did, map it exactly back to the
6 claims. So I would say at the very least, I don't
7 know about an expectation of success, but Leary
8 demonstrated success in carrying out these steps
9 in this order.

10 Q. Would a person of ordinary skill in the
11 art -- let me ask the question a different way.

12 Assume an individual understood
13 whole-genome sequencing, how to identify mutations
14 in whole-genome sequencing data, how to use
15 capture probes, and how to sequence DNA molecules
16 that are identified using capture probes.

17 Would that individual be able to then
18 carry out the method of Claim 1 of the '394 patent
19 without undue experimentation?

20 MR. KRAUSE: Same objections.

21 A. Again, I can't tell you how much
22 experimentation Leary did to arrive at what she

1 describes in her paper. I don't know how --
2 whether or not you would determine whether or not
3 there was undue experimentation, so I don't know
4 if she was able to do this overnight or if it took
5 her a couple months or longer. I mean, I don't
6 know.

7 What I can tell you is that in 2010, three
8 years before the patent was -- the preliminary
9 application or the patent was filed, Leary carried
10 out an analysis that can be mapped element by
11 element to Claim 1 and the other claims of the
12 '394 patent.

13 So I don't know how I'm supposed to
14 speculate about what someone would do in 2013 when
15 Leary already did it in 2010.

16 Q. Assume a person of ordinary skill in the
17 art understood whole-genome sequencing, how to
18 identify mutations in whole-genome sequencing
19 data, how to use capture probes, and how to
20 sequence DNA molecules that are identified using
21 capture probes.

22 Would that person of ordinary skill in the

1 art have been able to carry -- would that person
2 of ordinary skill in the art have had a reasonable
3 expectation of being able to successfully perform
4 the method of Claim 1 of the '394 patent in 2013?

5 MR. KRAUSE: Same objections.

6 A. In 2013?

7 Q. Yes.

8 A. Again, I'm completely dumbfounded by the
9 question because Leary did this in 2010.

10 So I also cite a number of other
11 references like Ley. I could more or less map Ley
12 to the claims of the patent. I could more or less
13 map Chan to the claims of the patent.

14 So the fact that Leary did this in 2010
15 means that she did it. So I don't know what her
16 expectations of success were. I know she was
17 successful.

18 You keep on asking the same question. I
19 don't know how to answer it other than Leary did
20 it three years before the patent was filed.

21 Q. You understand -- you've been an expert in
22 more than a dozen patent cases. Right?

1 A. That's probably true. Yes.

2 Q. And you're familiar with the concept of
3 the person of ordinary skill in the art?

4 A. Yes.

5 Q. And you've heard the concept of reasonable
6 expectation of success in the context of
7 obviousness and probably other IPR proceedings
8 you've done. Correct?

9 A. Yes.

10 Q. Okay. So let me ask my question again.
11 Given that you're familiar with this, I'll ask my
12 question again.

13 Assume a person of ordinary skill in the
14 art understood whole-genome sequencing, how to
15 identify mutations in whole-genome sequencing
16 data, how to use capture probes, and how to
17 sequence DNA molecules that are identified using
18 capture probes.

19 Would that person of ordinary skill in the
20 art have had a reasonable expectation of being
21 able to successfully perform the method of Claim 1
22 of the '394 patent in January of 2013? Can you

1 answer that in a straightforward way?

2 MR. KRAUSE: Object to the form.

3 A. Leary did in 2010. Okay? Leary performed
4 each and every element in the claimed invention
5 with the possible exception of sequencing the
6 final products.

7 I would say that, given the fact that
8 Leary sequenced the products in what we've been
9 referring to as Step 2, she would have had a
10 reasonable expectation of success, being able to
11 sequence them in subsequent steps.

12 Q. Who was Rebecca Leary?

13 A. She was the first author of the Leary
14 paper.

15 Q. Now, let me ask the same question as of
16 May 2012. Would a person of -- let me ask the
17 same question. I'll change the date.

18 Assume a person of ordinary skill in the
19 art understood whole-genome sequencing, how to
20 identify mutations in whole-genome sequencing
21 data, how to use capture probes, and how to
22 sequence DNA molecules that are identified using

1 capture probes.

2 Would that person of ordinary skill in the
3 art have had a reasonable expectation of being
4 able to successfully perform the methods of the
5 claims of the '394 patent in May of 2012?

6 MR. KRAUSE: Same objections.

7 A. So we've talked about Victor Velachescu.
8 He's a really good scientist. There are some
9 people whose work I read and you can't replicate
10 what they do. Victor, I can say I haven't
11 encountered a paper in which Victor has been a
12 senior author in which his work couldn't be
13 replicated.

14 So in 2010, in February of 2010, Rebecca
15 Leary and her colleagues at Johns Hopkins
16 published this analysis where they performed what
17 eventually turned into Claim 1 of the '394 patent
18 and that she demonstrated she could successfully
19 do all of this work.

20 Setting aside the '394 patent, I would
21 tell you that a person of ordinary skill in the
22 art could read Rebecca Leary's description with

1 the online method section and probably perform a
2 very similar analysis, right, could carry out each
3 and every step that Leary outlines, which I would
4 say that it would then demonstrate that a person
5 of ordinary skill in the art could carry out all
6 the steps that were claimed in the '394 patent.

7 I don't think I have Ley in front of me,
8 but I'd be happy to take a look at Ley.

9 I believe Ley does more or less the same
10 analysis, but Ley spends time looking at different
11 types of mutations and performs something which is
12 very similar.

13 And one could easily combine -- Ley could
14 have easily picked up Leary and added other types
15 of mutations and performed that analysis. And
16 that -- I forget the date -- let's see if I have
17 the date of the Ley paper. It's Exhibit 1012.

18 And Ley was published -- actually, Ley was
19 published in 2008. So Ley could have easily taken
20 what Leary did and applied what he had done four
21 years earlier and done the sequencing in
22 subsequent steps.

1 So really, I'm trying my best to answer
2 the question. Given that Leary had already done
3 it, I don't know -- I think anyone who read the
4 Leary paper, a person of ordinary skill in the art
5 would be able to practice what Leary described.

6 Q. How much experimentation would it have
7 taken for a person of ordinary skill in the art in
8 May of 2012 to practice all the steps in Claim 1
9 in view of the state of the prior art at that
10 time?

11 MR. KRAUSE: Object to the form.

12 A. I think Leary would have -- in 2012, Leary
13 would have been able to walk into a lab, take a
14 sample, and perform the analysis that she had done
15 in probably 2009, since the paper was published in
16 February of 2010.

17 Q. And would that have been true also for the
18 '033 patent?

19 MR. KRAUSE: Object to the form.

20 A. So we haven't discussed the '033 patent in
21 great detail today. But in the declaration that I
22 provided in this IPR matter for the '033 patent, I

1 present a very clear argument that Forshew
2 anticipates Claim 1 of the '033 patent.

3 So the analysis is fairly lengthy, and I'm
4 not going to step through the entire analysis. I
5 don't have Forshew in front of me, so I can't tell
6 you the exact date since you're talking about
7 2012. I don't know the exact date in which
8 Forshew was published. I will tell you that
9 Forshew was published in 2012.

10 While I can't tell you how much work it
11 would take Leary to replicate what was in Forshew,
12 I can tell you that Jim Forshew as of 2012
13 demonstrated that he could carry out all of the
14 steps of the '033 patent because the work in his
15 manuscript fully anticipates Claim 1 of the '033
16 patent.

17 Q. Okay. Let's start with the '033 patent.

18 How much experimentation would it have
19 taken for a person of ordinary skill in the art in
20 May of 2012 to practice all the steps of the
21 claims of the '033 patent in view of the state of
22 the prior art at that time? And I'm not asking

1 about what Leary could do and if Leary could
2 replicate Leary or Forshew could replicate
3 Forshew. I'm asking about the claims of the '033
4 patent.

5 How much experimentation would it have
6 taken for a person of ordinary skill in the art in
7 May of 2012 to practice all the steps of the
8 claims in view of the state of the prior art at
9 that time?

10 MR. KRAUSE: Objection to form.

11 A. So I don't have the Forshew publication.
12 I don't know what date it was published.

13 Q. I'm not asking about Forshew.

14 A. I don't have the Forshew publication. I
15 don't know what date the Forshew paper was
16 published. I'm assuming since you're asking about
17 May 2012 that Forshew was published in 2012. I
18 could be wrong.

19 Forshew in 2012 -- I don't know the date,
20 but prior to the publication of his paper clearly
21 carried out an analysis that encompasses all the
22 steps of the '033 patent. I can't tell you how

1 much experimentation he had to do, but he did.

2 So I would tell you that him having
3 completed that, that a person of ordinary skill in
4 the art could pick up his paper and read it and
5 replicate his analysis and apply it to other
6 samples.

7 Q. Putting aside the Forshew publication.

8 If a person didn't have the Forshew
9 publication, if a person of ordinary skill in the
10 art didn't have the Forshew publication, how much
11 experimentation would it take that person to
12 practice the claims of the '033 patent in May
13 of 2012?

14 MR. KRAUSE: Objection to form.

15 A. So I don't know when Wagle and Chan were
16 published. You're asking me sort of speed,
17 rapid-fire questions about dates. I think I have
18 Chan, and Chan was published in 2013. I don't
19 know when Wagle was published.

20 In Ground 3 of my declaration for the '033
21 patent, what I lay out are analyses that Claims 1
22 through 9 and 11 through 23 would have been

1 obvious over Wagle in view of Chan.

2 I don't have Wagle here right now. I'm
3 happy to read through my report to refresh my
4 memory of what's in Wagle or I'd be happy to read
5 Wagle and offer an opinion.

6 But as of -- let's see. Do we have Wagle?
7 So Wagle was published in 2012. I don't know if
8 it was May, before or after May. I'm assuming
9 Wagle did his work prior to May of 2012.

10 And if we lived in a universe that
11 Forshew -- in which Forshew was never born and
12 never published his paper, in that hypothetical
13 universe I'm sure that if we read Wagle we'll see
14 Wagle and the work provided -- the work described
15 in Wagle as -- especially in view of Chan, as
16 demonstrating that one -- that a person of skill
17 in the art could perform an analysis similar to
18 Forshew's.

19 It doesn't make sense to talk about
20 performing the steps of a patent that had not yet
21 been filed since they wouldn't have been trying to
22 perform those steps.

1 But Forshew clearly did. If we imagine
2 Forshew wasn't born -- why we would do that, I
3 have no idea. But if we did, my guess -- and
4 again, I'm more than willing to spend time and do
5 a deep analysis and deep dive.

6 Sitting here right now, I can't tell you
7 of any particular elements of the '033 patent that
8 weren't originally described by Wagle, but I would
9 bet Wagle could do it.

10 MR. WALTER: All right. I don't have any
11 further questions.

12 MR. KRAUSE: All right. Let's take a
13 quick break.

14 THE VIDEOGRAPHER: The time is 5:19.
15 We're off the record.

16 (Recess, 5:20 p.m. to 5:25 p.m.)

17 THE VIDEOGRAPHER: The time is 5:24.
18 We're back on the record.

19 MR. KRAUSE: And, Dr. Quackenbush, we
20 don't have any questions for you. Thank you for
21 your time.

22 THE WITNESS: Thank you.

1 THE VIDEOGRAPHER: The time is 5:24.

2 We're off the record.

3 (Off the record at 5:25 p.m.)

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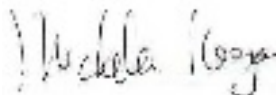
1 COMMONWEALTH OF MASSACHUSETTS

2 SUFFOLK, SS.

3
4 I, Michelle Keegan, Registered Merit Reporter
5 and Notary Public in and for the Commonwealth of
6 Massachusetts, do hereby certify that JOHN
7 QUACKENBUSH, PH.D., the witness whose deposition
8 is hereinbefore set forth, was duly sworn by me
9 and that such deposition is a true record, to the
10 best of my ability, of the testimony given by the
11 witness.

12 I further certify that I am neither related to
13 or employed by any of the parties in or counsel to
14 this action, nor am I financially interested in
15 the outcome of this action.

16 In witness whereof, I have hereunto set my hand
17 and seal this 25th day of September, 2023.

18
19 

20 Notary Public

21 My commission expires:

22 May 15, 2026

E R R A T A S H E E T

I, JOHN QUACKENBUSH, PH.D., do hereby certify that I have read the foregoing transcript of my testimony, and further certify that said transcript is a true and accurate record of my testimony (with the exception of the following corrections listed below):

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Signed under the pains and penalties of perjury
this day of , 2023.

JOHN QUACKENBUSH, PH.D.

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