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

ILLUMINA INC. : CASE NO. IPR2024-01419
Petitioner :
VS. : PATENT NO. 11,840,730
MOLECULAR LOOP BIOSCIENCES, :
INC. :
Patent Owner :

ORAL DEPOSITION OF JOSEPH D. PUGLISI, PH.D.
PALO ALTO, CALIFORNIA
WEDNESDAY, SEPTEMBER 17, 2025

REPORTED BY:
DEBBIE LEONARD, CSR, RDR, CRR
CSR NO. 14350
PAGES 1 to 147

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ILLUMINA INC.	:	CASE NO. IPR2024-01419
Petitioner	:	
	:	PATENT NO. 11,840,730
VS.	:	
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MOLECULAR LOOP BIOSCIENCES,	:	
INC.	:	
Patent Owner	:	

ORAL DEPOSITION OF JOSEPH D. PUGLISI, PH.D., at
Palo Alto, California, beginning at 9:14 a.m. and ending
at 2:37 p.m., on Wednesday, September 17, 2025, before
Debbie Leonard, CSR, RDR, CRR, Certified Shorthand
Reporter No. 14350.

A P P E A R A N C E S

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EXHIBIT	DESCRIPTION	PAGE MARKED
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REPORTER'S NOTE: All quotations from exhibits are reflected in the manner in which they were read into the record and do not necessarily denote an exact quote from the document.

1 THE REPORTER: My name is Debbie Leonard,
2 California CSR #14350. And with that, I will swear in
3 the witness.

4 JOSEPH D. PUGLISI, PH.D.,
5 having been first duly sworn, testified as follows:

6 EXAMINATION

7 BY MR. BROUGHAN:

8 Q Good morning. Would you please state your name
9 for the record.

10 A Yeah. Joseph Daniel, or Jody, Puglisi.

11 Q And have you been deposed before?

12 A Yes, I have.

13 Q Approximately how many times?

14 A Probably six times.

15 Q You may be generally familiar with deposition
16 procedure, but I'll just go over a few basics.

17 If I ask a question and you don't hear me or
18 understand what I said, please ask me, and I'll be happy
19 to repeat it or rephrase.

20 If you answer, I'm going to assume that you
21 understood my question, that you heard it and understood
22 it.

23 Our court reporter is going to be typing down
24 everything we say today, so we need to be careful that we
25 don't speak over each other.

1 Similarly, when I ask you a question, the record
2 won't pick up nods or gestures, so please answer
3 verbally.

4 A Yes.

5 Q If you need to take a break for any reason, just
6 let me know, and we can. You know, if there's a question
7 pending, I'll ask you to answer the question first. And,
8 you know, maybe there's a line of questioning that we can
9 talk about, but otherwise, happy to take a break if you
10 need it.

11 Is there any reason you cannot give full and
12 complete answers today?

13 A No, there is not.

14 Q Are you familiar with the '730 patent?

15 A Yes, I am.

16 Q And if I call it the '730 patent or the Porreca
17 patent, you would understand what I'm referring to?

18 A Yes, I will.

19 Q When were you retained in this matter?

20 A Probably in the late spring of 2025, if I
21 remember correctly.

22 Q Approximately how much time have you spent on
23 this matter?

24 A Total or for preparation of the deposition?

25 Q Total.

1 A Total? Oh, I don't know. Maybe 24 hours, let's
2 say. Something like that.

3 Q Prior to this case, did you know Greg Porreca?

4 A I did not. I have never met him.

5 Q Had you heard of Greg Porreca prior to this
6 case?

7 A Probably. I've read his papers. But it's not a
8 name that resonates with me.

9 Q Had you heard of Illumina before this case?

10 A Obviously, yes.

11 Q When did you first hear of Illumina?

12 A Before -- when they were a bead company -- a
13 bead array company. So in the early 2000s.

14 Q Have you used their sequencers?

15 A Yes, I have.

16 Q Do you regularly use Illumina's sequencers?

17 A Yes, when I do sequencing.

18 Q How often do you do sequencing?

19 A Not -- maybe once a month probably.

20 Q That's more than me. Let me switch here a
21 little bit.

22 Do you know what an oligonucleotide is?

23 A Yes, I do.

24 Q What is it?

25 A It's a stretch of individual nucleotide elements

1 that are stitched together by phosphate bonds. And
2 "oligo" just means relatively short, probably anywhere
3 from two to, let's say, 30 nucleotides in length. So
4 it's a polymer.

5 Q Are oligos naturally occurring?

6 A Oligonucleotides can be naturally occurring,
7 often made as degradation products or some kind of
8 abortive process in the synthesis that happens in the
9 cell. But usually it's used in terms of making synthetic
10 DNA or RNA.

11 Q The term "oligo" usually refers to synthetic DNA
12 or RNA?

13 A Usually. That's the common usage of it.

14 Q What is PCR?

15 A Polymerase chain reaction.

16 Q What does it do?

17 A Polymerase chain reaction was invented by Kary
18 Mullis famously in the 1980s. I think I was a graduate
19 student at the time. And it's a method of amplification
20 of a DNA sequence.

21 So if you have a small number of copies of a
22 given DNA sequence, you use primers and a DNA polymerase.
23 You use the DNA polymerase to copy the target strand
24 using the primers as a way to start the process of
25 polymerization.

1 That makes additional copies, which then those
2 primers can bind to and then amplify the original
3 sequence exponentially. And you go through cycles of
4 amplification, sometimes using temperature and then in
5 later versions, you know, not using temperature but other
6 methods to get the amplification.

7 So it's a very common technique in molecular
8 biology.

9 Q Using PCR, you start with a sample of -- strike
10 that.

11 Okay. Using PCR, you start with a sample of
12 nucleic acids, and you then amplify by making copies of
13 each nucleic acid in the sample?

14 A No. So the copying is often targeted to a given
15 region, and so you're not amplifying -- you can, but
16 you're not amplifying all of the sample. You're often
17 designing primers that go after a certain region of
18 sample that you're interested in.

19 If you're interested in a disease or some kind
20 of genetic trait, you would focus on that region, and the
21 primers would be designed to bind to that region to
22 amplify.

23 So I think that answers what you're asking.

24 Q The amplification process takes portions of the
25 nucleic acids in the original sample and makes copies of

1 those --

2 A Yeah, makes copies of them so you have more
3 abundant nucleic acid for subsequent analysis.

4 Q Does PCR make the same number of copies of each
5 target molecule?

6 A You know, it depends. There's lots of artifacts
7 that occur in polymerase chain reaction. The number of
8 copies you would make --

9 Let's say we have a Target 1, all right, and
10 then there's a Target 2, which is a different sequence.
11 You would design different primers for those different
12 targets.

13 And, you know, due to the idiosyncratic nature
14 of DNA polymerases, et cetera, you know, one might not be
15 copied as well as the other, and so you may not get the
16 same number of copies of Target 1 versus Target 2 even
17 though you did the same number of cycles of polymerase
18 chain reaction.

19 Q So using PCR, you may have some molecules that
20 are over-represented in the final amplified sample and
21 some that are under-represented in the final amplified
22 sample?

23 A If you were amplifying two separate regions,
24 yes, that could occur. And that's a common source of
25 error in polymerase chain reaction.

1 Q If you're amplifying the same region, can you
2 still end up with more copies of certain versions of that
3 region than others from the original sample?

4 A I'm trying to understand "same region." I mean,
5 the same region if we're talking -- are we talking about
6 a diploid organism, where there might be two different
7 sequences of that same region, or --

8 Q Yes.

9 A -- are we talking about one individual molecule?

10 Q The first one, diploid organism.

11 A The first one? Yeah. Then, yes, absolutely,
12 you could get different representations of the different
13 sequences, subsequences, that are in that sample.

14 Q That was a known problem in 2009; is that
15 correct?

16 A In 2009, yes. Polymerase chain reaction had
17 been around for two decades, roughly.

18 Q Sorry. Let me re-ask that question because I
19 made a mistake in what I said. So let me just do it
20 again.

21 A Okay.

22 Q The problem that PCR will amplify some molecules
23 more than others from the starting sample was a known
24 problem in 2009, correct?

25 MR. WUESTE: I object to form.

1 THE WITNESS: The -- what was known in 2009 was
2 that you could get amplification biases from individual
3 samples.

4 BY MR. BROUGHAN:

5 Q What is amplification bias?

6 A It's that you would get -- a given sequence may
7 be over-amplified versus another sequence, and so the end
8 populations of molecules that were amplified and the
9 proportions of the individual sequences does not
10 represent properly the initial proportions of those
11 sequences in the sample, if that clarifies.

12 Q What is a genotype?

13 A A genotype is the sequence -- so a gene is a
14 region of the genome that often encodes for a protein,
15 usually encodes for a protein, and genotype would be the
16 sequence of that gene on a copy of the chromosome.

17 So for diploid organisms, you know, genotypes
18 involve two sequences, you know, on the two copies of the
19 chromosome.

20 Q For a particular gene, how many genotypes can
21 there be?

22 A There can be lots of genotypes, right, because
23 there can be lots of polymorphisms, or changes, to the
24 sequence that happened, right? That's why you're
25 different than me, thankfully for you.

1 Q What is a polymorphism?

2 A Polymorphism is just a change of DNA sequence,
3 DNA length. So polymorphisms can be a change of the
4 actual sequence.

5 So you have the four-letter genetic code, and so
6 one of those letters could be changed. Okay? That's
7 called a single nucleotide polymorphism.

8 You can have deletions of nucleotides. You can
9 have insertions of nucleotides.

10 And you can have larger-scale changes, which are
11 usually really bad, which are called structural variants,
12 where, you know, pieces of DNA rearrange with respect to
13 one another. Large chunks can be deleted or added. That
14 often happens in cancers, for example.

15 Q Are polymorphisms naturally occurring?

16 A Yes, they are.

17 Q What is a genotype call?

18 A Now we're getting in -- a genotype call, when
19 you say the word "call," we're getting into DNA
20 sequencing methodologies.

21 But a call from -- historically in genetic
22 analysis would be, you would make a sequence, okay, of
23 your DNA region. And, you know, you're trying to say, is
24 that an A, T, C, or G at that sequence? And originally,
25 this would have been done using gel electrophoresis back

1 in the day.

2 When you have a, quote, polymorphism -- let's
3 just talk about a simple polymorphism -- like a
4 nucleotide change, right, you're trying to say, is there
5 an A at that position or a T at that position? Right?

6 So that's a -- that's a polymorphism call, all
7 right, that you're trying to identify precisely what
8 nucleotide is at that position or if there's a mixture of
9 nucleotides.

10 Q What's a polymorphism call?

11 A A polymorphism call would be identifying that in
12 the sample, there are changes to the DNA, all right, or
13 diversity to the DNA, that maybe one strand has a T and
14 one strand has an A, for example.

15 Q Is a polymorphism call the same thing as a
16 genotype call?

17 A It can be. It can be, yes.

18 Q Are there differences?

19 A Well, again -- I would probably say it's the
20 same thing, yeah, yeah.

21 Q You mentioned the word "call," and I believe you
22 said that that indicated we were talking about DNA
23 sequencing. Is that accurate?

24 A Yes.

25 Q So you understand the word "call" to refer to

1 something in DNA sequencing?

2 A Well, to make a call, right, you have to look at
3 what the string of letters in your genotype is, which is
4 a collection of DNA nucleotides, right. So in order to
5 make a call, you have to read the letters, and so that
6 requires DNA sequencing technology.

7 Q There are multiple types of calls in DNA
8 sequencing, correct?

9 A Yes, there are.

10 Q You could have a base call, correct?

11 A Yes.

12 Q That -- you could also have a sequence call?

13 A Sequence call? I mean, you have a sequence
14 readout. Usually "call" is on a nucleotide -- my
15 understanding of it, right, I think a POSA's
16 understanding of it would have been on a nucleotide by
17 nucleotide basis.

18 Q A moment ago, you mentioned a genotype call or a
19 polymorphism call. Is that a call on a single
20 nucleotide?

21 A I mean, a genotype call would be -- I would go
22 through letter by letter in my nucleotide -- of my
23 nucleotide sequence. I would be making base calls, okay.
24 We're using "call" in multiple senses here, all right.
25 So that's -- I'm reading the sentences, okay, and then

1 subsequently, with subsequent analysis, I can make a call
2 about the genotype. There's a mutation here. There's a
3 rearrangement here.

4 So the analysis is happening in multiple steps.
5 One is reading out the DNA sequence, and the second is
6 you're then analyzing the DNA sequence to make a global
7 call about what exactly was -- the sequence of letters,
8 what did that mean in terms of genotype.

9 Q The gen- --

10 A If that clarifies things.

11 Q A genotype call involves going nucleotide by
12 nucleotide and making a base call for each one and then
13 making an overall call on what the genotype is. Is that
14 fair?

15 MR. WUESTE: Object to form.

16 THE WITNESS: I mean, the way DNA sequence
17 analysis occurs is first you have to read out the
18 sequence, right. And so there are -- you know, every
19 sequencing technology has a different way of doing this,
20 of saying, okay, what is the sequence of the DNA I'm
21 analyzing, okay. So that's base calling. That is
22 nucleotide calls, okay.

23 And then you stitch those letters together.
24 Just like in my text that I wrote here, I wrote a series
25 of letters, all right, that I can make a typo, okay, but

1 then afterwards, I read the whole thing to get the sense
2 of what I -- what I read.

3 So that's what I'm trying to clarify.

4 BY MR. BROUGHAN:

5 Q When determining what a sequence is, first you
6 will make base calls nucleotide by nucleotide to
7 determine the sequence. Is that accurate?

8 MR. WUESTE: Object to form.

9 THE WITNESS: In a DNA sequencing approach,
10 okay, regardless of, you know, which technology you use,
11 you are usually reading out the sequence nucleotide by
12 nucleotide. Lots of different ways to do that. But --
13 and so yes, you're making base calls at individual
14 nucleotide positions during the process of reading the
15 sequence.

16 BY MR. BROUGHAN:

17 Q After reading the sequence, you can then make a
18 genotype call on the -- using the whole sequence?

19 A Well, depends on the quality of the sequence
20 reads, you know, what the analysis tells you. So
21 sometimes you can; sometimes you can't. I think it
22 requires the details.

23 Q What is an allele -- allele?

24 A Allele. An allele is the sequence of DNA in a
25 given gene, all right, and it can have, you know, two

1 copies of that allele in a genome. Plants have multiple
2 copies because they have higher ploidy.

3 Q I've read that word more than I've said it, as
4 you can probably --

5 A You're not missing much. Don't get me to
6 pronounce legal terms. I will also mess up.

7 Q For a given gene, there can be multiple alleles
8 that appear in the population?

9 A Sure. Certainly. Yeah, that's a reason for
10 population diversity.

11 Q To use an example, the color of people's eyes
12 are often determined by which alleles for eye color they
13 have?

14 A Absolutely. Classic genetics.

15 MR. BROUGHAN: Would you mark this as 1042,
16 please.

17 (Exhibit 1042 marked for identification.)

18 BY MR. BROUGHAN:

19 Q Take a moment -- the court reporter has handed
20 you what's been marked as Exhibit 1042.

21 A Yeah.

22 Q You can take a moment to page through it, but
23 it's really just the first two pages that have content on
24 it.

25 A Okay. Let me just take a look at this.

1 [Reviewing.]

2 I'm just trying to understand what is -- these
3 are slides of some sort?

4 Q Sorry. This is a -- Exhibit 1042 is a printout
5 of the definition of the word "allele" taken from
6 www.genome.gov.

7 A Genome.gov, so we should trust it. Okay.

8 [Reviewing.]

9 Uh-huh. There's pictures.

10 Q Just printed out from the web page.

11 A Yeah.

12 Q There are other things you can click on but --

13 A Just making sure the DNA is right-handed.
14 People screw that up a lot.

15 Cool. All right. Yes, I reviewed it.

16 Q Individuals can inherit two alleles, one from
17 each parent, at any given genomic location; is that
18 correct?

19 A Yes. Mendelian genetics. If we're talking
20 about humans.

21 Q And on the second page, there's a figure at the
22 top.

23 Do you see that?

24 A Yes.

25 Q And it provides some examples where this looks

1 like it is hereditary passing down of genes --

2 A Yeah.

3 Q -- is that correct?

4 A Yes.

5 Q And in this example on page 2, it shows that
6 individual can receive two of the same allele from the
7 parents --

8 A Yes.

9 Q -- or one of each allele from the parents.

10 Do you see that?

11 A Yes, I do.

12 Q If a person receives two copies of the same
13 allele, the person is homozygous at that genetic
14 location?

15 A Yes, correct.

16 Q And if a person receives two different alleles,
17 a different one from each parent, the person is
18 heterozygous at that genetic location?

19 A Yes, correct.

20 Q The terms "heterozygous" and "homozygous" in the
21 context of this DNA analysis is referring to the concept
22 in the image that we're looking at in Exhibit 1042?

23 MR. WUESTE: Object to the form.

24 THE WITNESS: I don't understand the question.

25 Can you repeat it?

1 MR. BROUGHAN: Yeah, not the best question. Let
2 me do it this way. This has been previously marked as
3 Exhibit 1001.

4 (Previously marked Exhibit 1001 referenced.)

5 THE WITNESS: Okay.

6 BY MR. BROUGHAN:

7 Q And you recognize Exhibit 1001 as the Porreca
8 patent?

9 A Yes, I do.

10 Q If we turn to column 32, starting -- I'll let
11 you get there.

12 A 32. Right here, yes.

13 Q If you look at column 32 starting at line 26,
14 the Porreca patent references -- or states that, "It is
15 possible that a locus that is heterozygous is called
16 homozygous," and then it goes on.

17 Do you see that?

18 A Yes.

19 Q When the '730 patent refers to homozygous and
20 heterozygous, it's referring to the concept that was
21 shown in the figure in Exhibit 1042 we were just looking
22 at?

23 A Just give me a second. Let me just read this
24 paragraph.

25 [Reviewing.]

1 So yes, because it says -- since there are two
2 alleles at every locus, the diagram that you presented to
3 me in Exhibit -- I'm sorry -- 1042 on the second page is
4 indeed an example of what is being discussed in the
5 '730 patent, yes.

6 Q Could we look at Figure 5 of the '730 Porreca
7 patent.

8 A Figure 5.

9 Q Uh-huh.

10 A The figures are at the beginning; is that
11 correct?

12 Q The beginning.

13 A Yeah. One of my least favorite things about
14 patents is the way figures are incorporated into them.

15 Q Yes.

16 A They should be throughout the text.

17 Okay. Yes.

18 Q You've seen Figure 5 before?

19 A Yes, I have.

20 Q In the middle of the figure, there's an example
21 that I believe shows biased amplification, but it has --
22 I believe it's seven T's and eight A's.

23 Do you see that?

24 A Yes, I do.

25 MR. WUESTE: Object to form.

1 BY MR. BROUGHAN:

2 Q If an individual is either homozygous or
3 heterozygous, wouldn't the presence of any A's at all
4 indicate that the individual being tested is
5 heterozygous?

6 A When you say "the presence of any A's at all,"
7 at what step are we identifying the presence --

8 Q The --

9 A -- in Figure 5?

10 Q The middle step.

11 A The middle step.

12 No. I mean, you could imagine that A's -- the
13 DNA polymerase, when it was doing the amplification step,
14 made a mistake and put A -- in the early steps of the
15 application swapped a T for an A, and then that mistaken
16 copy gets amplified.

17 So the presence of any A's there, you know, on
18 first glance does not say that you're heterozygous
19 because there are other -- there could be other possible
20 origins for an A being in that middle column there, if
21 that -- if that's clear.

22 Q If you look at -- we're going to go away from
23 that figure.

24 A Okay.

25 Q Column 1.

1 A Column 1 of the patent?

2 Q Yes. Column 1, line -- it's under Summary of
3 the Invention. It's, like, 57 to 61 or so.

4 A Okay. Give me a second here. 57 to 61,
5 column 1. Okay. "Aspects of the invention"?

6 Q Yes.

7 A Okay. Do you want me to read that paragraph?

8 Q Yes. And I want to ask you about the term
9 "allelic identity." But read it and let me know when
10 you're finished.

11 A [Reviewing.]

12 Okay. I've read it over.

13 Q What is an allelic identity -- well, how would
14 you pronounce it? "Allelic"? "Allelic"?

15 A "Allelic." Allelic identity.

16 Q What is an allelic identity?

17 A If we go back to, you know, your figure here, it
18 would be is it a big B or a little b, or big B and little
19 b, right, is what he's saying there, okay, for
20 determining -- or identities in the diploid organism.

21 Identities would be little b and big B in
22 your -- in your .gov figure, whatever that is, page 2.

23 Q Determining the allelic identity is determining
24 which alleles are present in the organism?

25 A According to this paragraph, yes.

1 Q What are allelic variations?

2 A Well, allelic variations would be -- the
3 example, if we go back to your figure from the slide
4 deck, it would be changes in the sequence, in this case,
5 little b versus big B. That's one example of allelic
6 variation. And those can occur, of course, you know, at
7 different places in the gene, in the allele.

8 Q Allelic variation is variations within one
9 allele itself? Is that --

10 A Allelic variation is variation amongst a
11 population of a given allele sequence, of a given gene
12 sequence.

13 Q Allelic variation would be variations amongst,
14 for example, the big B allele?

15 A No, big B and little b are alleles of a given
16 gene. Okay? And so, you know, you're looking at
17 variation in that gene.

18 So you have that little stretch there of dark
19 blue, and you're looking at variations in that gene,
20 which could lead to different proteins being produced
21 with different sequences, right, or different expression
22 levels of the messenger RNA. That happens in you versus
23 me versus him versus her.

24 Q If the universe of alleles was big B, little b,
25 and, let's say, G, would allelic variation be that

1 there's three different alleles, or does it have to do
2 with, like, the combination of all the alleles?

3 A Well, if you add another sequence, right, B, b,
4 and G, right, those are three different alleles. Those
5 are three different DNA sequences that encode for,
6 perhaps, different messenger RNAs or different proteins
7 down the line.

8 Q If you look at that figure at the top of
9 Exhibit 1042 --

10 A Yeah.

11 Q I think it's on the back of that page.

12 A This figure here?

13 Q Yes.

14 A Okay.

15 Q At the top of the figure, it shows "Allele 1"
16 and "Allele 2."

17 A Yeah.

18 Q Do you see that?

19 A Yeah.

20 Q And then at the bottom of the figure, it shows
21 the different combinations of Allele 1 and Allele 2.

22 A Yeah.

23 Q Is allelic variation the top of figure -- the
24 figure at 1042, or is it the bottom of that figure?

25 MR. WUESTE: Object to form.

1 THE WITNESS: I mean, to me -- okay. All right.
2 I'm going to say I'm not a geneticist. All right? But
3 to me, allelic variation is changes in DNA sequence in a
4 genetic locus or a gene, all right, that encodes for a
5 protein or messenger RNA. Okay?

6 And you get different combinations of alleles,
7 right, when you have a diploid organism. Obviously,
8 then, if there's a G here -- big B, little b, and a G,
9 the number of combinations become much more complex.
10 Right? That's just the nature of diploid organisms.

11 BY MR. BROUGHAN:

12 Q Does allelic variation refer to the
13 combination -- all the possible combinations of alleles
14 at a given gene?

15 A Well, an allelic variation, okay, is -- let's --
16 again, let's talk about simple, you know, autosomal-
17 dominant type of -- or autosomal-recessive types of
18 diseases, right, not something more complicated. Right?

19 You have a sequence at, you know, locus B, okay,
20 and that sequence can vary. All right. And you can have
21 different copies within an individual. Okay? So that's
22 identifying the allele, whether it's homozygous or
23 heterozygous. And then throughout a population, you can
24 have different sequences there. All right?

25 So there's allelic variation across a

1 population, right, and there's, of course, sequence
2 variation that occurs within an individual. All right?
3 And so, you know, it depends on the experiment that
4 you're doing, if you're analyzing a population or if
5 you're analyzing an individual.

6 Q Allelic variation refers to the different
7 combinations of alleles that can occur in a population?

8 A Yes. Yes, I agree with that statement.

9 Q Okay. Could we look back at the '730 patent,
10 please.

11 A Yes.

12 Q Column 3.

13 A Column 3.

14 Q Okay. Lines 5 to 9 says, "In some embodiments,
15 the genetic loci possesses one or more polymorphisms
16 (e.g., one or more polymorphisms from Table 2), the
17 genotypes of which correspond to disease-causing
18 alleles."

19 What is the genotype of a polymorphism?

20 A So "In some embodiments, the genetic loci
21 possess one or more polymorphisms, the genotypes of which
22 correspond to" -- I'm just reading the statement.

23 "In some embodiments, the genetic loci possess
24 one or more polymorphisms, the genotypes of which
25 correspond to disease-causing alleles."

1 Okay. So what he's saying there is, you have a
2 locus, okay, and some person has cancer, some disease,
3 some genetically -- a disease of genetic origin.

4 And there could be a sequence change there.
5 There can be a deletion, an insertion of a nucleotide,
6 you know, all the different polymorphisms that we talked
7 about before that's occurring at that locus, which then
8 causes something faulty in the biology of the cell.
9 Right? So that's a disease-causing allele. All right.

10 So the final sequence, the genotype of -- or
11 sequences -- of that polymorphism are leading to a
12 messenger RNA and then a protein that is somehow
13 defective in biology, leading to a disease. That's the
14 way I read that statement.

15 Q If you go back to column 2 of the '730 patent,
16 around line 52.

17 A 52.

18 Q I guess the sentence starts at 49 and goes to --

19 A Okay. "In some embodiments, the use of" --

20 Q Yes.

21 A Okay. Let me just read that.

22 [Reviewing.]

23 Okay.

24 Q Actually, if you could just read down to
25 line 60.

1 A Read down? Okay.

2 Q To line 60, yeah.

3 A All right. "In some embodiments" --

4 Q Oh, no. I'm sorry. Before answering the
5 question, just read down to line 60.

6 A I did read down to line -- I thought you wanted
7 me to read out --

8 Q Oh, no, no, no. Sorry. I told you line --
9 okay, you're good. Sorry.

10 A Yeah, yeah.

11 Q I'll ask the question now. What is a genetic
12 lesion?

13 A Again, in the use in this paragraph, they give
14 the examples. It's the type of polymorphisms that we
15 said.

16 A point mutation is a change of a single
17 nucleotide in the sequence. An insertion and a deletion
18 is, you add an extra nucleotide in -- that can change the
19 sense of the gene -- or you delete a nucleotide. That
20 happens during DNA replication or error correction. And
21 then length polymorphisms is bigger changes in the length
22 of a gene.

23 So that's what the genetic lesion is in the
24 sense here, all right, that would lead to some kind of
25 change in phenotype, or behavior, of the cells or the

1 organism.

2 Q What's a phenotype?

3 A Phenotype is just an observable behavior of an
4 organism.

5 Q What is the clinical setting? Sorry. What is a
6 clinical setting?

7 A "Is advantageous in the clinical setting."

8 It's just that many diseases are caused,
9 obviously, by changes in our DNA sequences. That's what
10 underlies the disease. And they're saying that it would
11 be useful to identify those mutations to make clinical
12 decisions, you know, care about cancer, et cetera.

13 I would assume that's what's meant by "in the
14 clinical setting."

15 Q Does "clinical" refer to patient care?

16 A I mean, "clinical" involves human patients and
17 diseases. Whether it leads to improved patient care,
18 obviously, that's the goal.

19 I think in 2009, the idea here was doing DNA
20 analysis in more detail on patient samples would lead to
21 improved interventions around a variety of diseases. And
22 that's turned out to be correct.

23 Q You mentioned earlier a length variation -- a
24 length polymorphism.

25 A Yeah.

1 Q What is -- what does that mean?

2 A Sometimes, you know, when DNA molecules are
3 being replicated, they undergo rearrangements that can
4 occur. There's something called recombination. There
5 are other things that the DNA polymerase can do to make
6 mistakes. There's damage that happens to our chromosomes
7 that then get repaired.

8 In the process of all of those steps, sometimes
9 you get larger changes in DNA, where all of a sudden, now
10 a gene is twice as long or it's duplicated or it's lost a
11 large chunk. So it's a larger loss of real estate in
12 terms of nucleotides than just a single nucleotide
13 change.

14 Q Okay. If you go to column 3 on the next page,
15 lines -- I'm looking at lines 1 through 5.

16 A "It should be appreciated"?

17 Q Yes.

18 A [Reviewing.]

19 Okay. I've read that paragraph.

20 Q What is a diagnostic method?

21 A A diagnostic method would be some method that's
22 used on a patient to allow a medical practitioner to make
23 a decision about what disease may be occurring, what
24 infection a patient may have, in order to make an
25 actionable determination of the clinical state of a

1 patient.

2 Q What is a multiplex -- sorry. Let me try that
3 again.

4 What are multiplex diagnostic methods?

5 A Multiplex just refers to the idea of making
6 multiple measurements on distinct samples combined to
7 make it much more efficient.

8 And so I think what is meant in this paragraph
9 is, I can analyze multiple possible disease-causing genes
10 or multiple, let's say, viruses or multiple bacteria in
11 parallel, in one experiment, I think is what is meant by
12 "multiplex" -- let's see exactly what it says here --
13 "multiplex diagnostic methods," yeah.

14 Q Do you understand "diagnosis" to refer to
15 something that's used on a human patient?

16 A Again, I would imagine -- I mean, obviously,
17 diagnosis can occur on plants if you're in agriculture,
18 in veterinary settings if you're a veterinarian, but I
19 think the meaning here is targeted towards human
20 patients, yes. But it has a broader sense than that.

21 Q The broader sense of "diagnosis" would refer to
22 something that's used on a living organism?

23 A Yeah, on a living organism to make some kind of
24 actionable response to a disease. My tomatoes are
25 getting some kind of blight, or I have cancer, or my dog

1 is sick. All right? Those all could involve diagnoses.

2 Q Do you grow tomatoes?

3 A I do, and they don't turn out well.

4 Q I had the same issue for many years, and I gave
5 up. To spend, you know, \$200 to get --

6 A Three tomatoes. Better to go to the store.

7 Q Okay. You have your declaration, I think.

8 A I do, in front of me, yes.

9 Q Let me find my copy.

10 THE REPORTER: Did you want to mark that?

11 BY MR. BROUGHAN:

12 Q Your declaration was previously marked as
13 Exhibit 2023, correct? At the bottom.

14 A Yeah, Exhibit 2023.

15 (Previously marked Exhibit 2023 referenced.)

16 BY MR. BROUGHAN:

17 Q And if you would turn to paragraph 44, which is
18 on page 28, please.

19 A Okay. Yeah.

20 Q You state that, "At the time of the invention,
21 next-generation sequencing technologies were becoming
22 increasingly utilized in diagnostic applications."

23 Do you see that?

24 A Yes.

25 Q What do you mean by "diagnostic applications" in

1 paragraph 44?

2 A Exactly the same sense that was used in the
3 discussion previously. It's using sequencing as a way to
4 identify, are there changes in DNA and also changes in,
5 you know, RNA levels, for example, that are linked to
6 disease so that you can make some kind of actionable
7 clinical decision about next steps in the therapy,
8 et cetera.

9 Q Turn to paragraph 50. In paragraph 50 you state
10 that, "The '730 patent also recognized that the accuracy
11 of next-generation sequencers in 2009 was 'relatively
12 low,' and that therefore oversampling the genomic loci of
13 interest was crucial," and then you have some quotes.

14 Do you see that?

15 A Yes.

16 Q What do you mean by "the accuracy of
17 next-generation sequencers was relatively low"?

18 A So let's go back in time to that period. It was
19 really the first wave of next-gen sequencing technology
20 was coming out. Illumina bought Solexa and was coming
21 out with their genome analyzer, I think it was called at
22 that time, and it was 454.

23 And, you know, what both of those technologies
24 did -- and they were revolutionary technologies, let's be
25 clear -- was take what was very low throughput, painful

1 sequencing process that had been sped up during the human
2 genome project, which is called Sanger sequencing, which
3 originally involved electrophoretic separation of
4 individual DNA chains and then was sped up by using
5 capillaries, et cetera.

6 Took that and performed sequencing analysis in
7 parallel, mainly using fluorescence imaging as ways to
8 sequence millions of molecules simultaneously in
9 parallel, and really was a game-changing set of
10 technologies.

11 The problem was the gain that was obtained at
12 that time period, the gain that was obtained in terms of
13 numbers of molecules you could sequence, came at a cost,
14 and it came at a cost of what's called accuracy.

15 Accuracy is the ability to get the correct
16 sequence of a given DNA molecule or collection of
17 molecules using that sequencing technology. It just --
18 and we can talk more extensively about the sequencing
19 technology.

20 But essentially, the technology was making more
21 mistakes in terms of reading the sequence than the prior
22 Sanger sequencing methods were obtaining.

23 So you got more data, but the data had higher
24 error rates, and so you needed to compensate for that.
25 That's what I'm trying to say in this paragraph.

1 Q How does oversampling the genetic loci of
2 interest compensate for the low accuracy rates in
3 next-gen sequencers?

4 A Well, if I have a locus, and I sample it once,
5 and in that, quote, read I got a mistake at a given
6 position, statistically, if I sample that locus again and
7 again and again and if the error rate is 1 in a hundred,
8 right, and I -- actually, at that time, it was probably
9 even worse than that. It was probably a couple percent.
10 You know, you do it a hundred times, 98 times you're
11 going to get the right answer; two times you'll get the
12 wrong answer. So statistically, the errors will wash
13 themselves out if they're not some kind of systematic
14 error.

15 So that's what the oversampling method is, and
16 it's still used today to oversample, although the
17 technologies have gotten far superior in the last two
18 decades.

19 Q How is it that the mistakes get washed out?

20 A Again, assuming that it's not some kind of
21 systematic problem and it was just -- I mean, the way --
22 if we want to get into the details, you know, sometimes a
23 wrong nucleotide was added to the DNA and that -- the
24 software says, "I think there's a T there," when there's
25 an A. Sometimes some of the chemistry fails in the

1 sequencing.

2 All of these can lead to errors, but they're
3 stochastic. They're random errors. They're not
4 systematic errors.

5 And when something is random, then by doing
6 multiple samples, you can wash out that random error
7 because it shouldn't happen again and again and again.
8 If something is a systematic error, of course, that will
9 happen over and over again.

10 If there's some sequence context, et cetera,
11 that the sequencing technology just doesn't work on,
12 well, even though you keep doing it again and again,
13 you're not -- you're still going to get errors, but most
14 of the errors -- many of the errors were random errors.

15 Q When you say that "the accuracy of next-gen
16 sequencers was relatively low," you're referring to the
17 fact that they sometimes make sequencing errors when
18 reading the DNA?

19 A Yeah --

20 MR. WUESTE: Object to form.

21 THE WITNESS: The -- the errors that I'm talking
22 about are the sequencing technology and subsequent
23 analysis of those signals that come out of the sequencing
24 technology led to higher mistakes being made versus a
25 ground truth sequence.

1 And then when I say "relatively low," I'm
2 comparing that to the -- let's say the gold standard at
3 that time, which was Sanger sequencing, which had higher
4 accuracy but was more expensive and slower, et cetera.

5 BY MR. BROUGHAN:

6 Q Next-gen sequencers had more sequencing errors
7 than Sanger sequencing; is that correct?

8 A Again, more -- we have to -- I just want to be
9 precise here. "More" is a higher rate per nucleotide
10 read sequencing errors. It's a frequency of errors that
11 is the right term than "more."

12 Q So next-gen sequencers had a higher rate of
13 sequencing errors than Sanger sequencing, correct?

14 A That is a correct statement.

15 Q And earlier we mentioned -- sorry. Strike that.
16 Earlier we discussed amplification bias.

17 Do you recall that?

18 A Yes. Yes, I do.

19 Q Is amplification bias different than sequencing
20 errors?

21 A They're caused by different phenomena.
22 Amplification bias is occurring during the sample
23 preparation steps before you sequence, leading to changes
24 in sequence. And then the sequencing errors are
25 occurring during the process actually of sequencing.

1 And, you know, that comes from the chemistry of
2 the different sequencing technologies, and they're all
3 very different. Illumina uses different technology than
4 454, et cetera.

5 So yeah, the end result is you get the wrong
6 sequence out, okay, but the origin of the mistakes are
7 coming at different steps in the process, if that
8 clarifies my answer a little bit.

9 Q If you oversample a particular genomic loci, how
10 does that help reduce sequencing errors?

11 A Okay. I'll -- maybe I wasn't clear in my
12 answer. Okay. Let's take a given sequence of DNA, okay,
13 that we -- that has a -- that has a ground truth
14 sequence, a correct sequence that was in the original
15 sample.

16 Let's ignore amplification bias. Say we amplify
17 it. There was no -- there's no mistakes in the
18 amplification. Okay.

19 Now I want to read out the sequence of that DNA,
20 and I put it on to a next-generation sequencer. We won't
21 go through the details of, you know, how those sequencers
22 work, but multiple copies of that same DNA are spread out
23 onto a -- let's say a microscope slide, called flow cell.

24 Now I'm going to read out the sequence of this.
25 And the way these sequences work is by colors, you know.

1 Each nucleotide has a different color, a different color
2 combination.

3 And I focus on one of those molecules, and I'm
4 reading the sequence of it. Okay? And just the
5 chemistry makes a mistake. All right? And so I get a
6 sequence out that is not the right sequence on that
7 molecule, but now I'm going to oversample.

8 I'm going to go to other places on the
9 microscope slide and read the same sequence out using the
10 same chemistry, and because it was just a random failure
11 of chemistries at that position, there's no reason to
12 believe I'm going to get the same failure at the same
13 position in the other molecules.

14 So the other molecules, I get it right. And
15 then statistically, because my errors are, let's say, 1
16 in a hundred or 1 in 50, okay, if I look at enough
17 molecules, most of them are going to get the right
18 answer, right?

19 So that's what the oversampling phenomenon, how
20 that works when you have stochastic, which means random,
21 error. Hopefully that clarifies.

22 Q Oversampling a particular genotype loci can help
23 reduce sequencing errors because during the final phase
24 you have some error correction process that compares the
25 different readouts.

1 Is that fair?

2 MR. WUESTE: Object to form.

3 THE WITNESS: In error correction process, I
4 mean, you have multiple reads being made, and then there
5 will be an analysis statistically of all of those reads,
6 and, you know, depending on the sequencer, depending on
7 the analysis pipeline, different companies and different
8 PIs handle their sequence data in different ways.

9 You would take that collection of statistical
10 data, okay. Let's say I made a hundred reads, 98 of them
11 had one sequence and two had another. And then there
12 would be some kind of analysis to say, hey, do you know
13 what, those two that I saw, those are sequencing errors,
14 because I know what the accuracy of my chemistries are,
15 and that's consistent with that. All right?

16 And so that's the kind of analysis that would be
17 done to correct for those, quote, sequencing errors that
18 are happening, you know, that are random and due to
19 chemistries.

20 BY MR. BROUGHAN:

21 Q Would you call the analysis of those multiple
22 reads of the segments an error correction analysis, or
23 would you call it something else?

24 A I mean, it's not just error correction, right?
25 You're trying to look at -- you're looking at sequence,

1 and you're trying to -- that's a signal. Okay? Sequence
2 is a signal. It's a collection of signals. All right?

3 And there are different steps of analysis, but
4 the first step is, what does the signal mean and what
5 mistakes or errors might be in that signal? What's
6 caused by chemistry problems? What are technical issues?
7 You know, what are limitations of my technology?

8 All that goes into kind of a first wave of
9 analysis of information, raw information that's coming
10 off of a sequencer. All right?

11 So some errors are being corrected at that
12 stage, all right, because those are errors of the
13 technology, the signals that are being detected,
14 et cetera.

15 Then there's a subsequent analysis, right, which
16 takes those raw signals, whatever they may be, flashes of
17 light of different colors, et cetera, and turns that into
18 a sequence, and then that is subsequently analyzed.

19 So errors are being corrected throughout the
20 flow of any next-gen sequencing technology. It doesn't
21 happen all at once, if that's -- if that's more
22 clarifying.

23 Q Let me ask a couple of different questions here.
24 If you flip back to the Porreca patent.

25 A '730?

1 Q Yes. '730 patent. Column 55.

2 A The table or --

3 Q I'm sorry. The text below it.

4 A "Nucleonic Acid Target Length Evaluation"?

5 Q Yes. The question really is, there's a
6 reference to Fragile X syndrome.

7 Do you see that?

8 A Yes.

9 Q What is Fragile X syndrome?

10 A Fragile X syndrome is, I think, the leading
11 cause of mental retardation, and it's a change in the
12 length of the FMR1 gene, if I remember correctly, that is
13 caused by -- there is a -- there are repeats of -- I
14 forget what it is -- CGG or CCG. I'm forgetting what it
15 is.

16 The gene has a collection of these repeats
17 that's naturally there, and then when you get the
18 disease -- as the DNA is being replicated, sometimes you
19 make mistakes in those repeats, and the polymerase gets
20 confused, and it adds in more of these repeats.

21 And so you get a mutation, which is called a
22 repeat expansion. So those -- that three-letter word of
23 CGG goes from being there -- I don't know -- ten times to
24 being there a hundred times or a thousand times.

25 So the length of the gene is changing, and that

1 leads to -- I guess the X chromosome can break. That's
2 why it's called Fragile X. But that leads to a
3 problem -- the cognitive problems of people.

4 So there's been a lot of interest, obviously, in
5 this, and a lot of other diseases are caused by these
6 so-called repeat expansions.

7 So those would be -- those would be length
8 polymorphisms in a gene, related to what we discussed
9 earlier. Obviously, a lot of interest in this.

10 Q The Porreca patent's techniques can be used to
11 detect issues with Fragile X syndrome? Or sorry. Strike
12 that.

13 The Porreca patent is disclosing that its
14 techniques can be used to detect Fragile X syndrome,
15 correct?

16 MR. WUESTE: Object to form.

17 THE WITNESS: I think what -- I think what is
18 proposed here -- and I believe they show data to support
19 this -- is that using their methods, they could
20 distinguish a normal patient from Fragile X because there
21 would be -- I don't know -- 20 repeats -- I'm forgetting
22 the length number here -- versus someone who's on the
23 verge of getting the disease.

24 These repeat expansion diseases are a continuum,
25 and the more repeats you have, the longer your gene

1 becomes, usually the more severe the disease is. That's
2 why some of these neurological diseases come in different
3 flavors.

4 And so what I think he's proposing is that you
5 could measure those different length distributions using
6 his tagging technology.

7 BY MR. BROUGHAN:

8 Q Sorry. Different -- different topic.

9 A Yes, sure.

10 Q You understand that the board issued an
11 institution decision in this case?

12 A Could you explain that to me?

13 Q Let me -- yeah.

14 A Yeah, sorry.

15 Q You know this is an IPR?

16 A This is like -- this is like allele.

17 Q Yeah, yeah, yeah, exactly.

18 You know this is an IPR?

19 A Yes, I do.

20 Q And in an IPR, a board of the Patent and
21 Trademark Office --

22 A Yeah.

23 Q -- is considering the IPR.

24 A Sure, yes.

25 Q Are you aware that the PTO board has issued a

1 decision starting this proceeding?

2 A Yes, I am.

3 Q And have you read that decision?

4 A Probably, but it wouldn't -- it wouldn't hurt me
5 to read it again.

6 Q I can just point you to paragraph 3 of your
7 declaration.

8 A Okay. Paragraph 3, yes. Yeah. The board's --
9 yeah, yeah, I see it there, yeah.

10 Q So you considered the board's institution
11 decision in forming your opinions?

12 A Yes.

13 Q Do you know what a claim construction is?

14 A Yes, I do.

15 Q Are you aware that the board construed several
16 claim terms?

17 A Yes, I am.

18 Q Did you apply the board's claim constructions in
19 your analysis?

20 A I believe I did, yes.

21 MR. BROUGHAN: We've been going for
22 approximately an hour. Why don't we --

23 THE WITNESS: Okay.

24 MR. BROUGHAN: -- take a -- take a break.

25 THE WITNESS: Stretch break? Great.

1 (Recess taken from 10:22 a.m. to 10:38 a.m.)

2 BY MR. BROUGHAN:

3 Q I'm going to hand you a couple exhibits. We're
4 handing you what's been previously marked as
5 Exhibit 2006.

6 And what's been previously marked as
7 Exhibit 2007.

8 And what's been previously marked Exhibit 2008.
9 (Previously marked Exhibit 2006, Exhibit 2007,
10 and Exhibit 2008 referenced.)

11 BY MR. BROUGHAN:

12 Q Have you seen these documents before?

13 A Yes.

14 Q Start with Exhibit 2006.

15 A Yes.

16 Q Let's start at the first paragraph, "Field of
17 Invention." There's a reference to "downstream
18 quantitative applications."

19 Do you see that?

20 A Yes.

21 Q And then under the "Background of Invention,"
22 somewhere in the middle, there's a reference to
23 "quantitative measurements."

24 Do you see that?

25 A Let's see here.

1 "In order to make quantitative measurements,"
2 yeah.

3 Q Then there's one more reference here. In the
4 paragraph that starts, "A common problem to overcome" --

5 A Uh-huh.

6 Q -- second sentence, there's a reference to
7 "downstream quantification techniques."

8 Do you see that?

9 A Yeah.

10 Q Okay. What is a downstream quantitative
11 application or technique?

12 A So, again, at the time of this invention, people
13 wanted to count nucleic acids. They wanted to be able to
14 understand the frequency of a mutation in a given gene,
15 if it's at the DNA level, and they also wanted to look at
16 expressions of levels of messenger RNAs, which are made
17 from genes.

18 This was a large area of research, all right,
19 which is, under some condition of the cell, is there
20 different levels of messenger RNAs from different genes
21 being expressed, and could that explain biology writ
22 large?

23 All right. So in order to do that, you need to
24 have a quantitative method that somehow could measure
25 relative or absolute amounts of nucleic acids and their

1 given sequences.

2 And so those are the quantitative measurements,
3 and I think they say, "including genotype calling and
4 gene expression profiling." That's the latter thing
5 around messenger RNAs that I just mentioned.

6 So these are counting -- I want to be able to
7 know how many of a given type of nucleic acid I have.
8 All right? I think that is what is meant by
9 "quantitative measurements."

10 Q Quantitative analysis is determining the
11 absolute or relative amounts of DNA in a sample?

12 A Of DNA --

13 MR. WUESTE: Object to form.

14 THE WITNESS: So, again, it would be measuring
15 the amount of an allele, okay -- what's the frequency of
16 an allele -- or it could be the measurement of different
17 messenger RNA levels that has been messenger RNAs turned
18 into a complementary, or cDNA, in order to get the
19 amounts of those different messenger RNAs that all have
20 different sequences. All right?

21 So those are the quantitative applications that
22 are being discussed here.

23 BY MR. BROUGHAN:

24 Q You view "quantitative" as referring to counting
25 the amount of DNA?

1 A Well, counting a given DNA sequence. So it
2 involves a sequence and a count.

3 Q Is that a standard use of the term
4 "quantitative"?

5 A "Quantitative" just means, you know, making a
6 measurement of some sort and, you know, making sure that
7 it's rigorous.

8 "Qualitative" would be, oh, there's a little bit
9 more of this sequence than another, and "quantitative"
10 would be, there is 37 percent more of this sequence
11 versus another. Right? So putting numbers as
12 adjectives.

13 Q Genotype calling is an example of a
14 quantitative, as opposed to a qualitative, measurement?

15 A Yes.

16 Q Under the "Background of Invention," in the
17 first paragraph, the last sentence -- and, really, I'm
18 looking at the last clause. It says, "these methods
19 utilize the counts of sequencing reads of a given genomic
20 locus as a proxy for the representation of that sequence
21 in the original sample of nucleic acids."

22 Do you see that?

23 A Yes, I do.

24 Q Why is the -- why are the counts being used as a
25 proxy?

1 A Because they are a readout that's happening
2 after multiple steps, right? And so you have in some
3 sample Nucleic Acid 1, 2, and 3, and they're at some
4 ratio or some -- three copies of one, two copies of B,
5 and one copy of C. All right?

6 And then what you're hoping is, through the
7 process, at the end, all right, you're going to get
8 sequences out, all right, that hopefully represent the
9 sequences and the relative ratios in the original sample.
10 All right?

11 So that's why it's a proxy. You're not --
12 you're not reading the original copies of those DNA in
13 the original sample. You are reading samples that have
14 been prepared in a certain way.

15 Q Through the quantitative analysis, you're trying
16 to determine the relative abundance of each of those
17 molecules in the original sample; is that --

18 A That is correct. That's what that sentence is
19 saying.

20 Q Is -- oh, sorry. Strike that.

21 I guess on page 3 -- okay. I think -- I think
22 it's the same thing.

23 The first full paragraph, "The number of reads
24 of a given sequence is typically taken" --

25 A Yeah.

1 Q That's the same thing we were just talking
2 about, right?

3 A Let me -- let me just read it, just to make
4 sure. I don't want to --

5 [Reviewing.]

6 It's -- I mean, the first part is what we
7 discussed before, and then there's some discussion about
8 ways to fix this problem or ensure better quantitation.

9 Q If you could turn to page 5.

10 Sorry. I put these quotes here, and then it's
11 hard to find them in the document when I want to ask you
12 about them. Give me a second.

13 A Sure.

14 Q In that first paragraph, the second full
15 sentence starts with the word "However."

16 A The first paragraph --

17 Q That spills over --

18 A That partial paragraph --

19 Q Yes.

20 A -- yeah. "However, if we also"?

21 Q Yes.

22 A [Reviewing.]

23 Q You appear to still be reading.

24 A Yes, I read it. Sorry.

25 Q All right.

1 A Sorry.

2 Q No, that's all right.

3 In that paragraph, it states, "the sequences
4 with the over-represented barcode all originated from the
5 same single molecule."

6 Do you see that?

7 A Yeah.

8 Q What is the significance of being able to
9 determine that sequences with an over-represented barcode
10 originated from the same molecule?

11 A Again, here, the goal, as outlined in this
12 disclosure, is to get what was in the original sample
13 quantitatively in terms of different DNA sequences. All
14 right?

15 So by tracing your sequence information back to
16 an original single molecule, all right, then you can
17 start to do those counting exercises because biases would
18 be represented in the final sequencing reads by the -- by
19 the different barcodes.

20 So, again, the goal here is the same as we
21 discussed earlier. It's trying to get a clear view
22 quantitatively of what were the sequences and what were
23 their quantitation in the original sample.

24 Q If there are sequences that all have the same
25 barcode, you could treat them as one instance of that

1 molecule in the original sample?

2 MR. WUESTE: Object to form.

3 THE WITNESS: I mean, it depends on how you
4 design the barcodes, et cetera, and depends on how you're
5 doing the analysis. But the idea is the barcode should
6 be identifying unique individual molecules in the
7 original sample.

8 BY MR. BROUGHAN:

9 Q If you observe multiple copies of the same
10 barcode, does that mean that you have redundant sequences
11 of the original molecule?

12 A It could mean that. It could mean that.

13 Q What else could it mean?

14 A You could have done a poor job of designing your
15 barcodes so that there isn't enough diversity so that
16 individual barcodes are attached to individual molecules.
17 That's one.

18 You know, there could be, you know, errors that
19 occur, you know, when you're doing the sample
20 preparation.

21 So yeah, there are ways that that could fall
22 apart. But the goal is what you just outlined, to have
23 one barcode per individual molecule in the starting
24 sample.

25 Q In your declaration, paragraph 76, I believe.

1 A 76. Yes.

2 Q Sorry.

3 A Claim 3?

4 Q Yes. Well, keep that open. But just for your
5 reference, I also handed you -- I'm going to ask you
6 about 76 in a second, but I also handed you Exhibits 2007
7 and 2008.

8 A These two figures?

9 Q Yes.

10 A Okay.

11 Q And you understand that Exhibit 2007 and 2008
12 are figures that accompanied Exhibit 2006, which is the
13 document we were looking at a moment ago?

14 A Yes.

15 Q Okay. In paragraph 76 of your declaration, near
16 the end, you state, "The figures accompanying the
17 March 6th application show how differentiator tags can be
18 used to detect and correct for amplification and
19 sequencing errors."

20 Do you see that?

21 A Yes, I do.

22 Q Where does the March 6th application and figures
23 disclose correcting for sequencing errors?

24 A I think if you look -- I think it's -- what is
25 it? Exhibit 2008. If you look -- I mean, there's

1 correction for amplification errors, obviously. That's
2 what's going on here.

3 You know, a sequencing error would be reflected
4 in some kind of skewed population after you do the
5 collapsing of the barcodes. Okay?

6 So a sequencing error would be reflected in --
7 in this case, there was no sequencing error, okay,
8 because you have the right representation of the original
9 population, whereas a sequencing error would be something
10 skewed with relation to the barcodes in the actual
11 sequencing.

12 And so they would be reflected in an incorrect
13 population after the collapsing of the barcodes.

14 Q The figure in Exhibit 2008 does not show
15 correcting a sequencing error, correct?

16 A It does not show an explicit sequencing error in
17 the actual reads.

18 Q It does not show an implicit sequencing error
19 either, correct?

20 A It does not show an implicit -- it shows -- it
21 does not show a sequencing error.

22 Q In Exhibit 2007, does that depict an
23 amplification or a sequencing error?

24 A Figure -- Exhibit 2007 is just talking about the
25 preparation of the -- of the barcode samples. So it

1 doesn't involve any kind of amplification or subsequent
2 sequencing, so it doesn't discuss sequencing.

3 Q You're familiar with a reference called
4 McCloskey?

5 A Yes.

6 Q And just so we're all on the same page, let me
7 hand that to you.

8 Here I'm handing you what's been previously
9 marked as Exhibit 1012.

10 A Thank you.

11 (Previously marked Exhibit 1012 referenced.)

12 BY MR. BROUGHAN:

13 Q Do you recognize Exhibit 1012 as the McCloskey
14 reference?

15 A Yes.

16 Q And you considered this in forming your
17 opinions?

18 A Yes, I did.

19 Q McCloskey discloses the use of barcodes,
20 correct?

21 A It's one of the -- one of the aspects of
22 McCloskey, yes.

23 Q Each barcode has several components, correct?

24 A Can you point me exactly to where they're
25 talking about that?

1 Q Uh-huh.

2 A Don't want to give an incorrect answer.

3 Q Where is it? If you look in -- if you look in
4 paragraph 17 of McCloskey.

5 A One second. "A first aspect of the invention"?

6 Q Yes. And about midway through it says, "wherein
7 the bar-coded oligonucleotide comprises a first sequence
8 complementary to the target nucleic acid molecule, a
9 second sequence providing a random barcode, and a third
10 sequence that is not complementary to any sequence in the
11 sample."

12 Do you see that?

13 A Yes, I do.

14 Q So the random barcode can include a first,
15 second, and third sequence, correct?

16 A Correct. In McCloskey.

17 Q Yes.

18 A Yes.

19 Q And if you turn to paragraph 27.

20 A "In some embodiments, the bar-coded" --

21 Q Yes.

22 A Yes.

23 Q -- "oligonucleotide further comprise a fourth
24 sequence."

25 Do you see that?

1 A Yes.

2 Q The fourth sequence can be a batch-stamp.

3 Do you see that?

4 A Yes.

5 Q And the fourth sequence can also be a sample
6 identifier, correct?

7 A Yes.

8 Q If you look at paragraph 21. With respect to
9 the second sequence of the barcode that is described as a
10 random barcode that can uniquely identify a target
11 nucleic acid in the treatment.

12 Do you see that?

13 A Yes.

14 Q McCloskey's barcodes can have a unique barcode
15 that's unique to a molecule in a sample as part of it,
16 correct?

17 A Again, depends on the design of that barcode and
18 how many different sequences are being analyzed versus
19 how many randomized positions you have. But the goal is
20 what you just stated.

21 Q McCloskey's barcode also includes a component
22 that is a sample identifier to identify what sample the
23 molecule came from?

24 A Yes, I think --

25 MR. WUESTE: Object to form.

1 THE WITNESS: There is a fixed sequence, okay,
2 that is what he calls the batch-stamp, right, which could
3 be used to identify a sample coming from me versus a
4 sample coming from you. I think that's the idea of the
5 batch-stamp. But that's not a randomized sequence.

6 BY MR. BROUGHAN:

7 Q What do you mean, "that's not a randomized
8 sequence"?

9 A A randomized sequence is one that when we
10 synthesized it, the four different nucleotides were added
11 at equal probability at each position. So you get lots
12 of different random sequences out.

13 Whereas a batch-stamp is a particular sequence
14 that is designed into the DNA which will vary for
15 different batches, but for that batch, it will be a fixed
16 sequence.

17 So the way they're made is different.

18 Q McCloskey discloses that its barcodes can be
19 used to identify -- to uniquely identify individual
20 samples; is that correct?

21 A Can you just show me where he says that
22 precisely?

23 Q I believe it's generally described in
24 paragraph 27.

25 A Let's just make sure --

1 [Reviewing.]

2 So he says a batch-stamp -- the batch-stamp,
3 which is that fixed DNA sequence that he puts in, "may
4 identify a sample, a patient, or an analysis date." Yes.

5 Q You agree that barcodes -- sorry. Strike that.

6 You agree that McCloskey's barcodes may be used
7 to uniquely identify individual samples?

8 MR. WUESTE: Object to form.

9 THE WITNESS: The batch-stamp, as defined here
10 in paragraph 27, is to provide an identifier for a
11 sample, whether it's from a patient -- so the idea would
12 be, I would have a different batch-stamp than you versus
13 him versus my fine lawyer here.

14 So if that answers your question, yes.

15 I think you have to be careful with "uniquely."
16 "Uniquely" requires you know what the population is
17 you're trying to look at, how many samples you're trying
18 to look at.

19 BY MR. BROUGHAN:

20 Q Would it be fair to say that McCloskey discloses
21 barcodes that may be used to uniquely identify individual
22 samples?

23 MR. WUESTE: Object to form. Asked and
24 answered.

25 THE WITNESS: He has -- he has a batch-stamp.

1 It's not the barcode. The barcode is something else.

2 BY MR. BROUGHAN:

3 Q Is it incorrect to say that McCloskey's barcodes
4 may be used to uniquely identify individual samples?

5 A Okay. So now I'm confused. When you say
6 "individual samples," is that all samples coming from me,
7 or is that all samples of a given DNA sequence region
8 coming from me?

9 Q I'll see if I can help you with that.

10 A Yeah, sorry. I'm just -- I'm unclear.

11 Q Would it be incorrect to say that McCloskey's
12 barcodes may be used to uniquely identify individual
13 samples, for example, patients?

14 A So at this time, and the methods of McCloskey
15 were directed towards, you know, Sanger sequencing, which
16 we discussed earlier is kind of slow and expensive, there
17 was a desire to combine samples and have, like,
18 identifiers coming from different samples.

19 So that's what his batch-stamp is, is a sequence
20 code that says, "Oh, that comes from the Jody Puglisi
21 sample," or "That comes from the Wueste sample."

22 So, you know, that's what the goal is of his
23 batch-stamp, which is make it easier to deconvolute a
24 mixture of samples to make it maybe a little bit more
25 cost effective.

1 Q The batch-stamp is part of the barcode, correct?

2 A No. The barcode -- the barcode is the
3 randomized sequence -- if we look at the -- maybe we're
4 just getting into semantics. Where is it? Yeah,
5 Figure 1.

6 In Figure 1, the barcode is the NNNNN. Okay?
7 That's the barcode, and that's what's being randomized
8 when that oligonucleotide is being -- is being
9 synthesized. That's being randomized.

10 There are other stretches -- I don't know if we
11 want to call it 2 or 5. I'd have to look at the figure
12 legend. Or 4. There are other stretches that have a
13 fixed sequence, and that's the batch-stamp.

14 So I just want to be clear. The barcoding here
15 is the randomized nucleotide in the McCloskey definition.

16 Q McCloskey's barcode uniquely identifies target
17 nucleic acid molecules in a sample, correct?

18 MR. WUESTE: Object to form.

19 THE WITNESS: The McCloskey technology, as
20 outlined here, has a barcode which is hopefully allowing
21 you to identify a sequence that you targeted this to, and
22 it has a batch-stamp to allow you to distinguish Sample 1
23 from Sample 2, Patient 1 from Patient 2.

24 Those are the two aspects of the McCloskey
25 technology.

1 BY MR. BROUGHAN:

2 Q The barcode and the batch-stamp are different,
3 in your opinion?

4 A In my opinion, they are different.

5 Q If you look at paragraph 53 of McCloskey.

6 A Am I looking at the right thing here? Yes, I
7 am. 53.

8 Q It's on page 6. I'm going to ask you about the
9 word "redundant." If you want to take a moment to just
10 look at paragraph -- or read through paragraph 53.

11 A It's the "132 sequences"?

12 Q Yes.

13 A [Reviewing.]

14 Okay.

15 Q What does McCloskey mean by "redundant
16 sequences"?

17 A And so McCloskey did 132 sequences by Sanger
18 sequencing, 22 sequences with a barcode that was
19 identified to a sequence already obtained, okay, meaning
20 he had the same barcode sequence, all right, so meaning
21 that those originated from the same original molecule.

22 And then the other 110 sequences had distinct
23 barcodes that were long enough -- five nucleotides
24 long -- to say that they had a separate origin, all
25 right, from a different DNA. But these were all from the

1 same sample because all the sequences had the same
2 batch-stamp sequence.

3 That's what this paragraph is saying.

4 Q The "redundant sequences" mean that there's
5 multiple copies of the same molecule from the starting
6 sample?

7 A That when they -- when they amplified this
8 sample, however they did the sample prep -- it's not --
9 I'd have to read the details in more -- in greater
10 detail -- but yes, that they were getting -- because the
11 same barcode was represented, that's an
12 over-representation of how much that sequence was in the
13 original sample.

14 Q McCloskey discards the redundant sequences?

15 MR. WUESTE: Object to form.

16 THE WITNESS: He doesn't say that. There's no
17 discarding here. It's just stating numbers.

18 BY MR. BROUGHAN:

19 Q McCloskey's analysis focused on the 110
20 sequences with distinct barcodes, as opposed to the
21 entire population with the redundant ones?

22 MR. WUESTE: Object to form.

23 THE WITNESS: There's -- there's no description
24 of what he does afterwards. We're making assumptions.

25 BY MR. BROUGHAN:

1 Q Would you assume that he focused his analysis --
2 or that she focused her analysis on the 110 distinct
3 sequences?

4 MR. WUESTE: Object to form. Calls for
5 speculation.

6 THE WITNESS: Yeah, I can't say what she would
7 do subsequently. This was testing a technology.

8 BY MR. BROUGHAN:

9 Q Okay. She says that -- where is it --
10 "indicating that those sequences originated from separate
11 cells, or separate genomic target molecules."

12 What does this -- do you know what she means by
13 "separate cells"? Or how do you interpret "separate
14 cells" there?

15 A Again, I'd have to look exactly at what she was
16 doing. Obviously, she was isolating DNA from -- this is
17 not -- at this time period, there was not single cell
18 analysis, so she was collecting DNA from a tissue sample,
19 I imagine.

20 It's from a given -- one given sample because
21 the batch-stamp is correct, but there can be genomic
22 heterogeneity, especially for these repeat expansion
23 diseases. There could be cell to cell variability from
24 the sample. Again, I'd have to look at exactly what the
25 sample was.

1 In that -- in the original sample, a barcode was
2 put onto a DNA from that locus from Cell 1, which was
3 different, and then there was a DNA that was attached to
4 DNA that originated from Cell 2.

5 But, again, I'd have to read exactly how she did
6 the sample prep and what was the starting material.

7 Q She also says, "The ability to distinguish
8 redundant from valid data is an immensely powerful tool."

9 Do you see that?

10 A Yes.

11 Q Do you agree with it?

12 A Yes.

13 Q Go to paragraph 93, please.

14 A Yes.

15 Q I think I have questions about multiple parts of
16 the paragraph, so if you want to take a moment to read
17 through it, please.

18 A [Reviewing.]

19 Okay.

20 Q What is PCR redundancy?

21 A PCR redundancy is that you get multiple copies
22 of a given sequence, again this over-representation in
23 the final population due to skewed amplification from
24 PCR, what we talked about earlier.

25 Q Near the end of the paragraph, the second-to-

1 last sentence, I think, says -- she says, "Each genomic
2 fragment is marked prior to amplification, allowing us to
3 identify contaminant and redundant sequences and to
4 quantify accurately the proportion of cells carrying a
5 particular sequence variant by counting only distinctly
6 tagged sequences."

7 Do you see that?

8 A Yes, I do.

9 Q What do you understand "quantify accurately the
10 proportion of cells carrying a particular sequence
11 variant" to refer to?

12 A Yeah, so reading this paragraph, what she's
13 talking about is the challenges of, you know, what we
14 discussed earlier, which, of course, is the biases that
15 occur through PCR amplification, and then the second
16 piece, which is also a major challenge at this time
17 period, which is having a limited amount of starting
18 material.

19 And so, obviously, you have to do amplification
20 to get more DNA to perform, in this case, the Sanger
21 sequencing method.

22 And so she's talking about a particular
23 application here, which is bisulfate methylation analysis
24 and -- bisulfite -- excuse me -- methylation analysis.

25 And this is a tricky business because what you

1 do in bisulfite methylation analysis is, you react --
2 what you're trying to look at is methylation of
3 cytosines, which is a post-replicative DNA modification
4 that's involved in epigenetics and controlling gene
5 expression.

6 What you're doing there is, you're taking your
7 sample of DNA, and then you're reacting with a chemical,
8 bisulfite, that reacts in a certain way when there's a
9 methyl group there or not. All right?

10 And when the methyl group isn't there, what
11 happens is the cytosines get converted -- sorry. When
12 the methyl group is there, the cytosine gets converted to
13 a thiamine, if I remember correctly.

14 And so you read out the methylation state by the
15 reaction that occurs in the presence or absence of a
16 methyl group with this bisulfite.

17 So it was a tricky business at this time to get
18 good sequencing data out, and she's proposing a nice
19 solution, you know, that -- people knew about this
20 problem, and they knew about -- that you needed to have
21 barcoding in order to get around biases, and she's saying
22 that with her, you know, barcode method, she'll be able
23 to identify, you know, the presence or absence of these
24 modifications in a DNA sample.

25 And so yes, I agree with the statement that

1 she's making. It needs to be considered in the context
2 of what she was trying -- the problem she was trying to
3 solve here.

4 Q If you go to paragraph 106.

5 A 106.

6 Q Yes.

7 A Yes.

8 Q I'll give you a moment to look through that.

9 A Yeah.

10 [Reviewing.]

11 Got it.

12 Q A little over -- approximately halfway down,
13 there's a sentence that says -- starts by "Bar-coding
14 allows for quantification of the relative abundance of
15 genomic methylation patterns or polymorphic sequences by
16 correcting for skewing that can arise from PCR
17 amplification or the cloning of products."

18 Do you see that?

19 A Yes.

20 Q You would agree, then, that the barcoding allows
21 for quantification of the relative abundance of the
22 polymorphic sequences by correcting for skewing?

23 MR. WUESTE: Object to form.

24 THE WITNESS: What the authors here are saying
25 is -- they demonstrate, I think, in the example that

1 they're able to get appropriate methylation patterns
2 using their method and use that to correct for skewing.

3 They're making a conjecture that this approach
4 could also be used for all the polymorphic changes that
5 we talked about earlier in our discussions, the single
6 nucleotide changes, the deletions and insertions, et
7 cetera.

8 But that's just conjecture. I don't think --
9 believe they demonstrate that here.

10 BY MR. BROUGHAN:

11 Q You don't dispute that the sentence states that
12 "Barcoding allows for quantification of the relative
13 abundance of polymorphic sequences by correcting for
14 skewing"?

15 A I do not disagree with what is written on the
16 page, of course.

17 Q In McCloskey's design, each target nucleic acid
18 in the original sample has a unique barcode, correct?

19 A Again, we're going back to the discussion we had
20 earlier. It depends on the number of Ns that he puts
21 into his -- what is usually a hairpin type of adapter
22 molecule.

23 So if he's done the design correctly and the
24 synthesis of the barcodes has been performed correctly
25 circa 2009, he should be able to do an experiment where

1 individual molecules would have -- each have an
2 individual barcode.

3 But I don't know if he's demonstrated that.
4 It's just hard to do at that time period with Sanger
5 sequencing.

6 Q If, during the amplification process, three
7 copies of a molecule in the starting sample were made, in
8 the final output, you would find three copies of that
9 molecule. So you'd see the barcode three times, and
10 you'd see the target three times?

11 A Okay. So I'm just trying to understand your
12 example. In the original sample, I have three copies of
13 the same molecule; is that correct?

14 Q One copy of the molecule.

15 A You have one copy of the molecule.

16 Q You make three copies of it.

17 A Oh, sorry. And then in the amplification step,
18 we amplify it. And the -- that one molecule may have a
19 barcode, may not? Is that what you're saying?

20 Or just let's say it has a sequence. Okay? We
21 amplify that. Let's assume the amplification did not
22 introduce any errors, so the three copies are identical
23 to the original copy.

24 And then what are we doing?

25 Q If you have three copies that are identical to

1 the original copy --

2 A Yeah.

3 Q -- you will see the barcode three times?

4 A So we have a barcode?

5 Q Yes.

6 A Okay. In the original? Okay.

7 Q And you'll see the target three times?

8 A So I have one molecule. It has a barcode. I
9 amplify it. I get three molecules, no errors made, same
10 barcode.

11 Q Correct.

12 A Okay. And then I go, and I sequence that. Is
13 that what you're saying?

14 Q Yes.

15 A All right. I'll get barcode plus sequence.

16 Q Yes.

17 A Yes.

18 Q So if you were trying to determine the number of
19 copies of a molecule that are in the original sample, you
20 can do that in McCloskey by looking at the tag alone,
21 correct?

22 MR. WUESTE: Object to form.

23 THE WITNESS: If I want to determine the number
24 of copies in the original sample, first of all, I need to
25 get enough data on the tags using Sanger sequencing in

1 order to make that numerical call. Okay? So it requires
2 a lot of experimentation to get the appropriate number of
3 tags.

4 But the purpose of McCloskey is to correct for
5 skewing errors that occur during PCR and using that tag.

6 BY MR. BROUGHAN:

7 Q McCloskey can correct for the skewing errors
8 using the tag, correct?

9 MR. WUESTE: Object to form.

10 THE WITNESS: McCloskey is attempting to correct
11 for skewing errors as demonstrated in the bisulfite
12 sequencing application that occurs when you have limited
13 sample, and then PCR is needed to do the amplification.

14 BY MR. BROUGHAN:

15 Q McCloskey also discloses correcting for skewing
16 when dealing with polymorphisms, correct?

17 A There is the statement about polymorphisms.

18 MR. BROUGHAN: Can you mark this as 1043.

19 (Exhibit 1043 marked for identification.)

20 BY MR. BROUGHAN:

21 Q Okay. The court reporter has handed you what's
22 been marked as Exhibit 1043.

23 A Yes.

24 Q This is a slightly modified version of Figure 5
25 of Porreca.

1 A Uh-huh.

2 Q And at the top, there's a figure that is titled,
3 "Tag: Target."

4 Do you see that?

5 A Yes.

6 Q In the bottom, there's a figure titled, "Tag."
7 Yes?

8 A Yes.

9 Q Okay. Let's start with the one on the bottom.

10 A Okay.

11 Q So in the boxes are the tags. 1000 -- or 1011,
12 that is the tag in the red box.

13 Do you see that?

14 A Yes.

15 Q 0010 is the tag in the blue box.

16 Do you see that?

17 A Yes.

18 Q We have 0001 in the yellow box.

19 A Yeah.

20 Q And 1111 in the purple box.

21 A Yes.

22 Q Okay. You can collapse on the tag alone because
23 the tags are all unique, correct?

24 MR. WUESTE: Object to form.

25 THE WITNESS: I mean, that's what this -- that's

1 what this version of the figure is showing, is
2 collapsing -- is using the tags to identify individual
3 reads.

4 BY MR. BROUGHAN:

5 Q You can also use the combination of a tag and a
6 target to collapse, correct?

7 A That's what's being done on the top part.

8 Q In McCloskey, where the tag is uniquely
9 associated with the target, there's no difference between
10 collapsing on both the tag and the target together or the
11 tag alone, correct?

12 MR. WUESTE: Object to form.

13 THE WITNESS: No, I disagree with that.

14 BY MR. BROUGHAN:

15 Q Why is that?

16 A Because the tag alone is not the sequence. The
17 tag could also have -- there could be polymorphisms or
18 other errors that are introduced along the way that you
19 do want to have both the sequencing read, the region, and
20 the tag as well.

21 So, you know, I don't think that's what
22 McCloskey is able to do. I don't think he shows any kind
23 of sequence calling in his -- in his application.

24 Q If there's a polymorphism -- sorry.

25 If there's an error introduced along the way,

1 wouldn't that result in counting duplicates of the
2 molecule because you're counting not only the original
3 but also the one with the error?

4 A Well, it depends where the error is being
5 introduced. Is it being introduced during amplification?
6 Which, of course, we've talked about skewing errors due
7 to preferential amplification which, of course, is
8 happening because the 01 -- 010 is being over-represented
9 in the population that then gets sequenced.

10 But errors can happen in terms of sequence
11 during the amplification, and they can occur, as we
12 mentioned before, in the actual sequencing technology,
13 and both -- both would change the output.

14 You can also get errors in the tags, of course,
15 right? Tags are not -- when the tags are amplified,
16 there could be errors introduced into them as well.

17 Q If the goal is to reduce skewing, there is no
18 difference if you collapse tags alone or tags plus target
19 in McCloskey's system?

20 MR. WUESTE: Object to form. Asked and
21 answered.

22 THE WITNESS: Again, the idea of correcting for
23 skewing in terms of the population that you're
24 sequencing, okay, was known in the art. I mean, that's
25 the reason -- one of the reasons people introduced

1 barcodes back in the day, long before even McCloskey's
2 patent.

3 How that use of the barcode is used for
4 subsequent sequence analysis, that is what differs
5 between what is patented in the '730 patent and what
6 McCloskey is talking about.

7 So I think it's important to talk -- to
8 distinguish effects of skewing and what that does to the
9 sample population and how subsequent sequence information
10 is being used to correct for that skewing, if that
11 clarifies things a little bit.

12 BY MR. BROUGHAN:

13 Q It does not.

14 What is the subsequent analysis in the '730
15 patent that you think makes it different?

16 A What is the subsequent analysis? That seems
17 like a broad question.

18 Q I believe you stated how the use of the -- how
19 the barcode is used for subsequent sequence analysis,
20 that's what differs between what is patented in the '730
21 and what McCloskey is talking about.

22 So, okay, I'm sorry. Let me ask -- actually ask
23 you a question that's correct here.

24 A Okay.

25 Q What subsequent analysis is in the '730 patent

1 that makes it different than McCloskey?

2 A So --

3 MR. WUESTE: Object to form.

4 THE WITNESS: Again, both -- first of all, the
5 patents are different time frames. All right? McCloskey
6 is talking about Sanger sequencing. Okay? The '730
7 patent is a little bit more broad in what it's talking
8 about in terms of sequencing technologies, including
9 next-gen sequencing.

10 But, you know, what -- what is happening in the
11 '730 patent is a two-step process, right, in that you are
12 sequencing the sample, okay, and that includes sequencing
13 the barcode and the -- let's say the sequence of the gene
14 that you're interested in that was barcoded. Okay?

15 You're getting reads out, you know, for that.
16 Okay? And then what you're doing is taking both the gene
17 of interest region and the barcode and you're collapsing
18 ones that are the same. All right?

19 And so that could include, you know -- that
20 includes the heterozygosity, if it's occurring,
21 nucleotide changes, to give you the final proper
22 population that involves both the barcode and the
23 sequence of interest. It's not just the barcodes alone
24 that are, quote, being collapsed. And it's not a
25 consensus call, which is the standard in the field, where

1 you're just going, I see more T's than A's, so that's a
2 T.

3 And so that's the differentiating approach of
4 the '730 patent versus what McCloskey has laid out in his
5 earlier patent, if that's useful.

6 BY MR. BROUGHAN:

7 Q You have the '730 patent in that pile somewhere?

8 A Somewhere, yes. Here.

9 Q If you look at claim 1, which is on the last
10 page.

11 A Yes.

12 Q Around line 47 it says, "correcting for error or
13 bias introduced during said workflow by collapsing target
14 differentiator tag combinations observed more than once
15 into a single count."

16 A Yes.

17 Q Do you see that?

18 A Yes, I do.

19 Q Where does that collapsing limitation require
20 you to determine heterozygosity or homozygosity?

21 MR. WUESTE: Object to form.

22 THE WITNESS: You're doing that determination
23 after the fact. Right? You're collapsing the combined
24 target tag sequences, right, and then afterwards you're
25 making a call about homozygous or heterozygous.

1 BY MR. BROUGHAN:

2 Q Claim 1 does not require making a genotype call,
3 correct?

4 A There's nothing about calling in claim 1.
5 Claim 1 goes up until the upper right-hand of your
6 figure, before there's correct call.

7 Q What is different between McCloskey and claim 1
8 of the '730 patent? What is the subsequent analysis step
9 that's different there?

10 A Again, I'm not clear what it is -- that sounds
11 like a very broad question. I think you want it to be a
12 more specific question. Could you reframe that?

13 Q Is there subsequent analysis required by claim 1
14 of the '730 patent that makes it different than
15 McCloskey?

16 A Is there subsequent analysis? Again, claim 1
17 has no subsequent analysis. It just does correcting of
18 error bias by collapsing, right, and making a list.
19 Okay?

20 What happens after that is in other claims or is
21 not part of claim 1. Okay?

22 Could you point to me where you want me to
23 comment about McCloskey's -- you know, where McCloskey
24 claims something similar? Maybe the claims of McCloskey?
25 I'm not sure what you want me to opine on.

1 Q Not McCloskey's claims.

2 McCloskey has the ability to identify redundant
3 sequences, correct?

4 MR. WUESTE: Object to form.

5 THE WITNESS: I mean, one of the goals of
6 McCloskey is use the barcode to get around PCR biases. I
7 mean, I think that's the -- and also provide the batch-
8 stamps for different samples.

9 BY MR. BROUGHAN:

10 Q McCloskey can correct for bias by collapsing on
11 the barcodes, correct?

12 MR. WUESTE: Object to form.

13 THE WITNESS: I don't believe McCloskey says at
14 all the word "collapsing on barcodes." Right? He's
15 trying to get around amplification bias to get a better
16 view of what was authentically in the original sample.

17 BY MR. BROUGHAN:

18 Q McCloskey corrects for amplification bias by
19 using the barcodes to ignore redundant sequences,
20 correct?

21 MR. WUESTE: Object to form.

22 THE WITNESS: I would like to see where in the
23 claims -- I'm trying to remember where he talks about
24 correcting for redundant sequences. I mean, we talked
25 about an example. I agreed with it there. I mean, it's

1 clearly written.

2 It's almost implicit in what they're -- they're
3 implicitly -- you're implicitly saying they're correcting
4 for redundant sequences, but this is really about using
5 the barcodes and batch-stamps and preparing the samples
6 in given ways.

7 BY MR. BROUGHAN:

8 Q McCloskey discloses -- well, sorry. Strike
9 that.

10 What McCloskey discloses is different than what
11 McCloskey claims, correct?

12 A McCloskey has examples that are disclosed,
13 right, and makes statements about those examples that
14 could extend into, you know, identifying polymorphisms in
15 single molecules. Okay?

16 But, really, what McCloskey is disclosing is
17 that his method can account for amplification biases.

18 He does not propose a method whereby the
19 barcodes are being used for some kind of subsequent
20 analysis.

21 Q McCloskey's barcodes are used to correct for
22 amplification bias?

23 MR. WUESTE: Object to form.

24 THE WITNESS: That is in the -- that is stated
25 as one of the applications in the specification, but it

1 is not what is claimed. Okay?

2 BY MR. BROUGHAN:

3 Q By "not what is claimed," you're saying, not
4 what is claimed in McCloskey?

5 A In McCloskey's claims, yes. In any DNA
6 sequencing application, the devil is in the details of
7 how you're using that information to then, you know -- if
8 you want to use it for subsequent analyses.

9 So he's definitely barcoding. There's no
10 question about it. He's using the barcodes as a way to
11 address samples and combine them. He's using barcode --
12 claims to use barcodes as a way to correct for
13 amplification bias. That, there's no doubt about.

14 Q Are your views about what McCloskey teaches
15 someone in the art limited by what McCloskey claims?

16 A No. I read McCloskey, and I read the examples
17 that he presents, and I read it also in light of what
18 technologies were being applied at the time. I mean, he
19 was limited in 2007, beforehand, to Sanger sequencing.

20 Q Do the '730 claims require next-gen sequencing?

21 A No, I don't believe they do, no.

22 MR. BROUGHAN: I don't know how long we've been
23 going. I have some more questions about different
24 references. Keep going?

25 MR. WUESTE: If you're switching off McCloskey,

1 I didn't want to interrupt you, but for the record, it
2 was a Megan McCloskey. So just want to properly
3 attribute that it should be "her" and "she."

4 MR. BROUGHAN: Yes, yes, "she." "She," yes,
5 yes. I tried to use "she" that time.

6 THE WITNESS: You did. Better than I was.

7 BY MR. BROUGHAN:

8 Q I'm handing you what's been marked as
9 Exhibit 1017.

10 (Previously marked Exhibit 1017 referenced.)

11 BY MR. BROUGHAN:

12 Q This is an article by David Bentley.

13 A Uh-huh.

14 Q Have you seen this article before?

15 A Yeah, I believe I did.

16 Q Do you know David Bentley?

17 A I do not.

18 Q If you turn to page 548, on the right-hand side,
19 there's a heading that says, "Cost, Throughput, Accuracy
20 and Completeness."

21 A Yes.

22 Q Do you agree that with sequencing technology,
23 you have to balance the cost, throughput, accuracy, and
24 completeness when designing your solution?

25 A Yes, I would agree with that.

1 Q You can be more accurate, but it might cost
2 more?

3 A Could cost more. Completeness is a different
4 statement. It's, if you're trying to do a whole genome,
5 how much are you covering that genome? But yes, these
6 are always the concerns around sequencing technology.

7 Q If accuracy is important, it may be worth it to
8 increase the cost; is that fair?

9 A There's a cost-benefit, yes, to each of these
10 parameters. And depending on your application, you might
11 choose to prefer one of the parameters over another.

12 Q On the next page, 549, near the bottom, there's
13 a heading that says "Accuracy."

14 A Uh-huh, yes.

15 Q And there's a reference to something called -- I
16 think it's Phred.

17 A Phred score.

18 Q Yeah. What's a Phred score?

19 A It's a statistical measure of just how good a
20 read -- what's the probability of an error in a read, I
21 guess is the right way to say it.

22 Q And then there's a sentence that kind of spans
23 the two columns, and there's a -- it says "estimate" --
24 "estimate" -- or "estimate of the probability of error
25 for each base-call in a raw read."

1 A Yes.

2 Q What's a raw read?

3 A Again, this is -- this is talking about Sanger
4 sequencing. And so, you know, in Sanger sequencing, a
5 raw read would have been one lane in a capillary gel,
6 okay, where a DNA copy is being made of the target
7 sequence that you're trying to sequence.

8 That copy has chain -- what are called chain
9 terminators that the DNA polymerase can't fully extend.
10 And those terminators have different fluorescent dyes on
11 them, and so you can read off the sequence of that length
12 of DNA.

13 As the DNA passes down a capillary, there's a
14 laser -- in the versions of 2006, a laser that's shining
15 a light on those dyes. And as the DNA passes through,
16 you go, "Oh, that's a C, the next one is a G," et cetera,
17 from the colors.

18 So what the Phred score is using is that read,
19 which is really just fluorescent intensities as a
20 function of length of the DNA and turning that into a
21 sequence. Right?

22 And so that's the raw read, would be -- the raw
23 read would be those signals that are going to be turned
24 into base calls.

25 Q Further down in that paragraph, Bentley says,

1 "For example, multiple reads from the same sample can be
2 aligned and used to derive a consensus base-call at each
3 position."

4 A Yes.

5 Q Do you see that?

6 A Yes.

7 Q What do you understand Bentley to mean by
8 "consensus base-call"?

9 A So what's going on here is, I took my Sanger
10 sequencer, and it happened 50 times to sequence the same
11 sample. All right? So I get 50 raw sequence reads that
12 my algorithm is saying is a given sequence, all right,
13 and then I'm aligning those. And just based
14 statistically on who the winner is at each position, you
15 make a consensus base-call.

16 So if in those 50 reads there was 49 times a G
17 and 1 time an A, the consensus call would be a G, okay,
18 et cetera, et cetera. So that's what's being discussed
19 there.

20 And the paragraph continues that all of these
21 parameters are dependent on how good the sequencing
22 technology is. The quality, the errors in each
23 individual read tell you how many sequences you really
24 need to be able to analyze in order to make a consensus
25 call.

1 Q Is Bentley's use of the term "consensus base-
2 call" consistent with how that term was used in the art
3 at the time?

4 A Yes, I would say that it is, yes.

5 Q Go to the next page.

6 A Yeah.

7 Q There's, like, a figure at the top.

8 A Yeah. 5.

9 Q Is it Figure 5? Figure 2.

10 A "Viewing sequence alignments," yeah.

11 Q Yes. That's Figure 2, yes?

12 A Yes.

13 Q Okay. All right. Figure 2 of Bentley, this is
14 showing how you could use multiple sequence reads to come
15 up with a consensus base-call, correct?

16 A That is correct.

17 Q And there's a small vertical column on one base,
18 and that's similar to what you were saying a moment
19 ago --

20 A Yeah.

21 Q -- where you take which one appears more and
22 pick that as the winner?

23 A Yes.

24 MR. BROUGHAN: I'm about to switch topics.
25 Maybe take a break now?

1 MR. WUESTE: Happy to do that.

2 Dr. Puglisi, if --

3 Yeah, depending on how long the next topic might
4 be.

5 MR. BROUGHAN: The next one is a long one. I
6 mean, it makes sense to take a break now.

7 MR. WUESTE: Okay.

8 MR. BROUGHAN: I'm saying it as an option, but
9 really, it's, like, we should take a break now.

10 THE WITNESS: Sounds good.

11 (Recess taken from 11:54 a.m. to 12:41 p.m.)

12 BY MR. BROUGHAN:

13 Q Could you open your declaration, please --

14 A Yes.

15 Q -- to paragraph 134.

16 In the middle of the paragraph, you reference
17 something call "10x average coverage."

18 A Yes.

19 Q What is that?

20 A It's just the number of times you read that
21 sequence over and over again. So that would be ten
22 times, tenfold.

23 Q Is 10X coverage standard for next-gen sequencing
24 systems?

25 A It really depends on the application. Again, it

1 goes back to the discussion we had earlier. The number
2 of times you read a sequence corrects for random errors.

3 And it depends on what the final application is
4 and what you're -- you know, what are you trying to
5 identify; you know, what is the statistical rigor you
6 need to do whatever subsequent analysis it is. 10X is,
7 you know, relatively common.

8 Q 10X would mean that each portion of the genome
9 that you care about is read at least ten times?

10 A Yes.

11 Q Some portions might be read more?

12 A It could be, yeah, just depending on what the
13 sample distribution is.

14 Q If you go to paragraph 136 --

15 A Yes.

16 Q -- in the third line, looks like you're equating
17 skewing errors to quantitative errors.

18 Do you see that?

19 A Yes.

20 Q Are all skewing errors quantitative errors?

21 A I mean, a skewing error would lead to a
22 quantitative error because you're changing the
23 distribution, but that -- not every quantitative error is
24 a skewing error, I guess would be the right way to state
25 that.

1 Q I see.

2 And you also state that collapsing in the '730
3 patent corrects for skewing errors and that's different
4 than correcting for sequence errors; is that fair?

5 A Well, let's see. Where do I say that exactly?
6 I just want to make sure.

7 Q Read the first sentence, please.

8 A [Reviewing.]

9 Yes, correct. Sorry. I just needed to read the
10 full sentence.

11 Q Do you have the '730 patent?

12 A Yes.

13 Q Let's go to claim 1 again. It will be the last
14 page.

15 Do you know what a preamble is?

16 A Yes.

17 Q So the preamble says, "A method for correcting
18 errors or bias."

19 Do you see that?

20 A Yes.

21 Q And then the last element similarly says
22 "correcting for error or bias."

23 A Yes.

24 Q What type of error is covered by the claim?

25 A Well, I think the claim is not specific about

1 the type of error. It's just -- it's general about any
2 error that's occurring during the workflow, and the
3 workflow goes all the way up through sequencing. So I
4 don't think it's --

5 Q Does the claim cover correcting for a sequencing
6 error?

7 A It's an error. It's saying that it's covering
8 errors.

9 Q Is an error -- is bias different than error?

10 A Is bias different than error? I mean, again, if
11 what we're talking about -- let's define bias. If bias
12 is that we have a population of original molecules, those
13 are processed in a certain way to lead to another
14 population of molecules where the original population is
15 not represented properly, right, that's an example of
16 bias.

17 There can be other forms of bias that would be
18 more systematic errors. At this time, you know,
19 sequencing technologies had biases that read -- certain
20 sequence contexts were read more accurately than others.
21 That's an example of a systematic bias.

22 But I think in the way that you're using it,
23 bias is that population bias that we talked about in our
24 earlier discussions.

25 Q In the context of claim 1 of the '730 patent, is

1 there a difference between bias and error?

2 A Well, they say error or bias, so --

3 Q How is error different than bias in the context
4 of claim 1?

5 A An error could be an error that happens in your
6 sample workup. Okay? It could be that, you know,
7 whatever nucleic acid polymerase or, you know, other
8 manipulation enzymes that you use to prepare the sample
9 led to incorrect nucleotides or changes in the sequence
10 happening during that process.

11 That would be an error that was introduced in
12 the process, whereas bias is, you're not changing the
13 sequence, you're changing the relative populations of the
14 sequences.

15 So they are different things, but I think what
16 the claim is stating is they are different than one
17 another.

18 Q In the context of claim 1, could error mean
19 sequencing error?

20 A Again, I think it says -- it says error in a
21 nucleic acid workflow, analysis workflow, so sequencing
22 would be part of that analysis workflow.

23 Q Is there a definition for the word "collapsing"
24 as used in the claims?

25 A Is there a definition?

1 Q What definition did you apply of the word
2 "collapsing" in your analysis?

3 A Yeah, I used the definition -- kind of the
4 common definition of, as applied to a number of sequence
5 reads and turning them into a single read if they were
6 identical to one another, I guess, would be the way I
7 would call collapsing, but there wasn't a specific
8 technical definition that was used.

9 Q Is the word "collapse" or "collapsing" commonly
10 used in the field?

11 A I mean, collapsing various sorts of information,
12 yeah, that's a relatively common term in the field.

13 Q If you go to paragraph 150 of your declaration.

14 A Yes. "Instead"?

15 Q Yes.

16 A [Reviewing.]

17 Yes.

18 Q You start the paragraph by saying, in the
19 collapsing step -- sorry -- by saying, "The collapsing
20 step is a specific process performed prior to any
21 subsequent analysis."

22 Do you see that part?

23 A Yes.

24 Q If analysis of the sequence reads occurs before
25 collapsing, does that mean that you can never collapse?

1 A Again, collapsing here is, I'm making individual
2 reads. All right. I have analysis software that is
3 taking whatever raw signals from the sequencing
4 information and turning that into a sequence for that
5 read.

6 I collect those reads, and then I collapse after
7 the fact. All right? So that is the key aspect of this.
8 Because if I just do a consensus call -- and I think we
9 referred to Bentley, there was a nice figure in Bentley
10 about consensus calling -- there, they're not collapsing.
11 They're just taking essentially an average of all the
12 reads and what the sequence was at those -- at those
13 different positions and making a call based on whether
14 it's statistically greater than the average or not. So,
15 you know, it's a very different -- different procedure.

16 So hopefully that distinguishes the two
17 processes.

18 Q Does collapsing need to occur before there is
19 any analysis of a sequence read?

20 MR. WUESTE: Object to form.

21 THE WITNESS: Well, again, any analysis of a
22 sequence read, I mean, you have to -- before you
23 collapse, you need to read the sequence read, right, and
24 determine the sequence read.

25 So that analysis is happening before collapsing,

1 but that's part and parcel of any kind of sequencing
2 technology.

3 BY MR. BROUGHAN:

4 Q You state, "The collapsing step is a specific
5 process performed prior to any subsequent analysis."

6 A Yes. Again, analysis here, let's -- let me be
7 specific. Analysis is taking the sequence information
8 that has come off of a sequencer for a collection of
9 reads, which, of course, that information has been
10 analyzed. It's been analyzed by the -- by whatever
11 software was used to make the sequencing calls.

12 I get a list of sequences from those reads. I
13 collapse, and then any kind of subsequent bioinformatic
14 computational analysis that I'm doing is happening
15 subsequently, if that clarifies what I'm saying in the
16 report.

17 Q At the end of the paragraph, 150, you state,
18 "Thus, collapsing is not simply obtaining a single
19 consensus base-call for all reads with the same unique
20 tag and using that for subsequent analyses, because doing
21 so would not eliminate amplification bias."

22 Do you see that?

23 A Yes.

24 Q Does the claim require eliminating amplification
25 bias?

1 A It's -- the claim is correcting for errors or
2 bias. Okay? Again, it's a little bit broad in terms of
3 whether those are amplification biases or not. So the
4 claim definitely comprises amplification bias because
5 it's a broad claim.

6 Q Claim 1 also recites correcting errors, correct?

7 A Yes.

8 Q Claim 1 could encompass correcting sequencing
9 errors, correct?

10 MR. WUESTE: Object to form. Asked and
11 answered.

12 THE WITNESS: Again, sequencing errors -- it's a
13 little tricky, okay, because a sequencing error that
14 happens in a read, okay, most likely would be
15 statistical.

16 There are sequencing errors that can occur
17 during the sequencing process, because certainly in,
18 like, this generation of Illumina technology, there are
19 amplification steps that are happening during sequencing.
20 It's part of the sequencing process, and that could lead
21 to errors that could be corrected by this technology.

22 Again, I think it's important to be specific
23 about what kind of sequencing errors could be corrected
24 and what couldn't be corrected.

25 BY MR. BROUGHAN:

1 Q What kind of sequencing errors could be
2 corrected?

3 A Of the genre I just talked about. Anything that
4 leads to changing the sequence when you're then reading
5 it out, that's a sequencing error because it's happening
6 during the sequencing workflow that's on the instrument.
7 I would call that a sequencing error.

8 Q Why is it that collapsing is not simply
9 obtaining a single consensus base-call for all reads with
10 the same unique tag and using that for subsequent
11 analysis?

12 A Because you're trying to get -- you're trying to
13 get calls that include both the region of interest and
14 the -- and the -- and the coding tag so you can make the
15 correct genotyping call or quantification that you want
16 to do subsequently.

17 Q Genotyping is not required by claim 1, is it?

18 A Any kind of quantitative analysis. So you're
19 correcting for errors or bias so that the subsequent
20 quantitative analysis gives you the right original
21 population of molecules of correct sequence.

22 Q In your view, claim 1 then is limited to
23 correcting for errors or bias that impact the
24 quantitative analysis?

25 A It's just -- errors or bias, period. But by

1 definition, errors or bias will affect subsequent
2 analyses because you're using the wrong data to perform
3 subsequent analysis.

4 So errors are biased that happen during the
5 nucleic acid workflow, which is what claim 1 is all
6 about, okay, would then funnel in and would propagate --
7 in the proper statistical sense, would propagate into
8 subsequent analyses and make those analyses probably
9 flawed.

10 Q In paragraph 150, the last sentence, you say
11 that, "Collapsing is not simply obtaining a single
12 consensus base-call for all reads with the same unique
13 tag and using that for subsequent analyses, because doing
14 so would not eliminate amplification bias."

15 What relevance does it have that it would not
16 eliminate amplification bias if claim 1 is not limited to
17 that?

18 MR. WUESTE: Object to form. Asked and
19 answered.

20 THE WITNESS: Again, as I mentioned before, it's
21 a bias, right, and if that bias is amplification bias and
22 I want to then perform any kind of analysis of the data
23 I'm obtaining, the bias that was obtained during the
24 sample preparation period, i.e., amplification bias is
25 one example, would then propagate into subsequent

1 analyses.

2 So I do want to get rid of amplification bias
3 because it's an example of a bias that is introduced
4 during a nucleic acid workflow.

5 BY MR. BROUGHAN:

6 Q You could satisfy the correcting step of claim 1
7 without correcting for amplification bias, correct?

8 MR. WUESTE: Object to form.

9 THE WITNESS: I'm sorry. Just repeat the
10 question. Sorry. I just spaced out for a second.

11 BY MR. BROUGHAN:

12 Q That's all right.

13 The correcting step of claim 1 could be
14 satisfied without correcting for amplification bias,
15 correct?

16 MR. WUESTE: Same objection.

17 THE WITNESS: Again, the method is broad. It's
18 trying to correct for errors or -- or bias that are not
19 just amplification biases, and we talked about other
20 examples of those. So it includes amplification bias,
21 but it includes other sample preparation biases that
22 occur due to problems with ligation, problem with DNA
23 polymerase, et cetera, et cetera.

24 BY MR. BROUGHAN:

25 Q The correcting step could be satisfied by

1 correcting a sequencing error without eliminating any
2 bias, correct?

3 MR. WUESTE: Object to form.

4 THE WITNESS: The claim is satisfied for
5 correcting any error that occurs during a nucleic acid
6 workflow that involves obviously the subsequent steps
7 from the preamble.

8 BY MR. BROUGHAN:

9 Q Then why, in paragraph 150, did you say that
10 "collapsing is not simply obtaining a single consensus
11 base-call for all reads with the same tag" --

12 MR. WUESTE: Object to form --

13 BY MR. BROUGHAN:

14 Q -- "because doing so would not eliminate
15 amplification bias"?

16 MR. WUESTE: Sorry about that.

17 Object to form. Asked and answered multiple
18 times.

19 THE WITNESS: Yeah, again, I think I walked you
20 through the various steps here of how that is
21 distinguishing different error types by looking at the
22 tag and the coding sequence from the beginning of the
23 process through the process of sequencing that sample
24 with whatever sequencing technology that you're using and
25 then getting reads off of that and then performing the

1 collapsing step afterwards. Okay? And I think the
2 claims are very clear about what those steps are.

3 The biases or errors that are being collected --
4 corrected are manifold, and they include amplification
5 biases as we discussed earlier.

6 BY MR. BROUGHAN:

7 Q Claim 1 could be satisfied without correcting
8 any amplification bias at all, correct?

9 MR. WUESTE: Object to form. Asked and
10 answered.

11 THE WITNESS: Claim 1 is satisfied to correct
12 errors or bias, whatever they may be, I would say is the
13 correct answer to that question.

14 BY MR. BROUGHAN:

15 Q I'm handing you what was previously marked as
16 Exhibit 1010.

17 A 1010.

18 (Previously marked Exhibit 1010 referenced.)

19 THE WITNESS: This is the Chee patent.

20 BY MR. BROUGHAN:

21 Q Yes. You've seen 1010, the Chee patent before?

22 A Yes.

23 Q We'll get to Chee in one second. Could we get
24 back to paragraph 150, which I think is still open.

25 A Back to 150?

1 Q The last sentence.

2 A Yeah.

3 Q If we were to cross out everything starting from
4 the word "because" -- it says, "because doing so would
5 not eliminate amplification bias." And if instead the
6 statement read, thus collapsing is not simply obtaining a
7 single consensus base-call for all reads with the same
8 unique tag and using that for subsequent analyses, would
9 you still agree with that?

10 MR. WUESTE: Object to form.

11 THE WITNESS: Again, I can't rewrite what I
12 wrote without rereading my entire application, so I just
13 don't feel comfortable answering that question. I'd have
14 to rewrite my report.

15 BY MR. BROUGHAN:

16 Q Sitting here today, you cannot say that the
17 statement "Thus, collapsing is not simply obtaining a
18 single consensus base-call for all reads with the same
19 unique tag and using that for subsequent analyses" is
20 correct?

21 MR. WUESTE: Object to form.

22 THE WITNESS: I mean, that statement is correct
23 because I wrote it.

24 BY MR. BROUGHAN:

25 Q Even without the "because doing so would not

1 eliminate amplification bias"?

2 A Again, a modifying phrase is exactly that. It's
3 modifying what I'm saying in the prior clause. So you
4 are changing the sense of what it is I'm writing by
5 deleting selectively parts of my -- of my report. So,
6 again, not super comfortable with that.

7 Q Chee. If you go to column 14, lines 46 to 50, I
8 think. Yes, 46 to 50.

9 A [Reviewing.]

10 Q How do you understand Chee to create the
11 consensus sequence derived from multiple clonal copies of
12 a construct?

13 A This is -- this is part of the specification of
14 Chee, and -- just talking about sequencing errors, and I
15 think we discussed this -- this before, is -- you know,
16 sequencing platforms all have different errors rates.
17 They have different intrinsic biases, and they have their
18 intrinsic accuracies.

19 And what Chee is saying -- and this was known in
20 the art, in the field -- is you could correct for those
21 errors or identify those errors by sticking in a unique
22 identifier, could be a barcode of some sort, so that if
23 you get multiple reads of the same molecule with the
24 unique identifier, that would point back to the original
25 sequence of it and account for the errors.

1 Chee, if we're talking about -- if you want me
2 to talk about how does the patent of Chee reflect this
3 statement, which is just --

4 Q Yes.

5 A -- a statement of what was known in the art, you
6 know, Chee's business -- and this is -- this is a
7 fascinating patent. Chee was really occupied with DNA
8 synthesis at the time, and in particular applications to
9 synthetic biology. And I enjoyed reading this patent
10 because it brought me back to the good ol' days.

11 So what Chee was trying to do is, to do
12 synthetic biology, you need to synthesize genes. You
13 need to synthesize them de novo or synthesize, as was
14 done in the mid-2000s, an entire genome. That's millions
15 of bases at a minimum, base pairs at a minimum.

16 So how do you assemble big pieces of DNA and how
17 do you get big pieces of DNA? Well, at the time, the way
18 you got big pieces of DNA was making them chemically.
19 And chemical synthesis of DNA has been around for, let's
20 see, 2009, probably 30 years, late '70s, Marv Caruthers.

21 And what Chee was saying was, look, I have to
22 make these long pieces of DNA. There's errors when I
23 make DNA in the laboratory chemically. One mistake,
24 99.9 percent coupling efficiencies, .1 percent, probably
25 good, probably in 2009, not quite that.

1 I'm going to get errors in making my DNA, and I
2 want some way to say -- because I'm going to take that
3 DNA that I made and I'm going to put it into an organism
4 or put it into a gene, I don't want to have mistakes
5 built into my gene. I want some way to identify that I
6 made the right piece of DNA.

7 And he very cleverly applied -- I mean, Chee is
8 the master of beads. He's Mr. Bead, I call him. He
9 applies this really clever approach of put a sequence tag
10 on -- you know, use solid supports in various ways, but
11 put a sequence tag, a barcode, on to a region that has
12 been synthesized, which he calls a region of interest.
13 And then using that can say, ah, that DNA, which is maybe
14 on that bead, that's the right DNA, this is the wrong
15 DNA, and then use that to then purify or enrich in the
16 DNA.

17 So very necessary technology at the time, still
18 necessary technology, to ensure that you're getting the
19 right DNA fragments.

20 So that's the application of Chee, why Chee is
21 so concerned about -- what's a sequencing error, he's
22 less concerned about that. He's more concerned about
23 what is a synthesis of DNA error and how can I -- how can
24 I get around that. That's the way I read Chee.

25 And, again, really prolific inventor who's done

1 lots of interesting things.

2 Q Chee states that, "A variation in the sequence
3 of a single copy of a construct is most likely to be a
4 synthesis or sequencing error if it differs from a
5 consensus sequence derived from multiple clonal copies of
6 the construct, which are identified as identical by
7 descent via the shared unique identifier."

8 Do you see that?

9 A That's in his -- that's in that -- that kind of
10 general description. And yes, of course, you know,
11 there's two reasons I could see an error in my DNA; I
12 made a mistake making it or I made a mistake reading it
13 out. Right? So yes, that is correct.

14 The emphasis here, though, is on the making
15 part, right, and that's really what the focus of this is.
16 So yes, that paragraph points to sequencing errors,
17 which, of course, he was concerned about because his
18 readout of, did I make a mistake when I made DNA is going
19 to be sequencing. Well, you can't correct a mistake with
20 a mistake. You can, but it's -- that's not really the
21 right approach to take.

22 So, again, I read Chee as being concerned that,
23 uh-oh, I'm going to try to identify an error in a DNA
24 that I want to put into some organism to do synthetic
25 biology, but instead, the method I'm using to identify

1 it's right or wrong also has errors involved in it.
2 Different ones, but errors nonetheless.

3 And so, I mean, that's, again, the way I read
4 him, you know, knowing the field at the time and where it
5 was pointing.

6 Q To derive the consensus sequence, Chee first
7 looks at the sequencing reads and identifies all the ones
8 that have the same unique identifier, correct?

9 A Again, point to me where he's getting the
10 sequencing read. Are we talking about claims? I just
11 want to see exactly --

12 Q 14, 46 to 50.

13 A Back to 14.

14 Q To derive the consensus sequence, Chee first
15 looks at the sequencing reads and identifies all the ones
16 that have the same identifier, correct?

17 MR. WUESTE: Object to form.

18 THE WITNESS: I mean, that is what he is saying,
19 again, in this paragraph about issues around accuracy.
20 So to say this is what Chee's invention is, you know,
21 he's really just talking about how to use a barcode and
22 multiple reads to identify errors, which, again, other
23 people knew about.

24 It's the application of this to synthetic DNAs,
25 et cetera, that is, you know, what is at stake here in

1 Chee. But I'm not arguing with what is written between
2 46 to 50.

3 BY MR. BROUGHAN:

4 Q I just want to understand how the process
5 works --

6 A Yeah.

7 Q -- not where the DNA came from to begin with.

8 To identify the consensus sequence, Chee is
9 first going to find all the sequencing reads with the
10 same unique identifier, right?

11 A Chee is using the unique identifier to then, you
12 know, classify different reads.

13 Q After kind of grouping the ones from the same
14 identifier, Chee will use those to identify a consensus
15 sequence by looking at each of them and finding for each
16 base call which one occurred, for example, most
17 frequently?

18 MR. WUESTE: Object to form.

19 THE WITNESS: I have to go look exactly how Chee
20 is proposing to do data analysis. So if you could point
21 to me exactly how Chee is using both the ROI, which is
22 what he defines it as, and the unique identifier, because
23 he uses them in different ways throughout the patent.
24 He's using them as ways to purify. He's using them as
25 ways to enrich. He's using them as ways to get sequence

1 information.

2 BY MR. BROUGHAN:

3 Q In column 14, line -- at line 48, Chee uses the
4 phrase "consensus sequence derived from multiple clonal
5 copies of the construct." How would you understand
6 creating a consensus sequence derived from multiple
7 clonal copies of the construct?

8 A At each position throughout the sequence, he's
9 doing what Bentley did. That's the way I read it.

10 Q The results of Chee determining this consensus
11 sequence is that Chee takes multiple copies with the same
12 unique identifier and creates one sequence that's
13 associated with all those copies?

14 MR. WUESTE: Object to form.

15 THE WITNESS: I'm sorry. Just repeat that. I
16 just want to make sure I got all the steps.

17 BY MR. BROUGHAN:

18 Q Yes. The result of Chee determining a consensus
19 sequence for a particular unique identifier is that Chee
20 has taken multiple copies with that same unique
21 identifier and synthesized it down to one sequence?

22 MR. WUESTE: Object to form.

23 THE WITNESS: I mean, as written in this
24 paragraph, he's getting a consensus sequence of both the
25 unique identifier and the region of interest, and he's

1 trying to get multiple reads to do standard consensus
2 sequencing.

3 BY MR. BROUGHAN:

4 Q So if you --

5 A And bin things by molecular identifier, meaning
6 they came from an original molecule, okay, that he wants
7 to identify and say, oh, that piece of DNA, that looks
8 like the right sequence because the consensus sequence
9 that comes out, according to unique molecular identifier
10 number 00110, okay, that would be this bead over here,
11 okay, that set of DNAs, that has the right original
12 sequence. That's the one I want to use to build my gene.
13 That's what Chee is doing.

14 Q You have Bentley over there still?

15 A I do.

16 Q Could you grab it, please.

17 A Sure. Somewhere is our good friend Bentley.

18 Q Page 550, Figure 2.

19 A Yeah. Okay. This one? Yeah.

20 Q Yes.

21 A Yeah.

22 Q Figure 2 in Bentley is showing a process of
23 generating a consensus sequence?

24 A Yeah.

25 Q In Bentley -- sorry. Strike that.

1 When Bentley creates a consensus sequence, he
2 synthesizes multiple reads --

3 Do you see read 1, 2, 3?

4 A Yeah.

5 Q -- down into one consensus read, correct?

6 MR. WUESTE: Object to form.

7 THE WITNESS: Again, what a consensus read is, I
8 go letter by letter or position by position. I look at
9 all the reads at that position. And then based
10 statistically on whether I see more of one nucleotide or
11 another, I make a call, a 1 out of 4 call. I'm going to
12 put a T, A, G, or C at that position based on looking
13 down the column. And I go letter by letter. So I think
14 that -- I think we're saying the same thing.

15 BY MR. BROUGHAN:

16 Q Although Chee stops numbering them, there's 11
17 reads above the consensus. You can count if you'd like.

18 A Although Chee stops --

19 Q He stops at read 3.

20 A Oh, Bentley stops --

21 Q I'm sorry. Thank you.

22 A Yes.

23 Q In Figure 2 of Bentley, there's 11 reads --

24 A Yes.

25 Q -- above the consensus.

1 A I trust you.

2 Q Bentley collapses those 11 reads down into a
3 single consensus sequence, correct?

4 MR. WUESTE: Object to form.

5 THE WITNESS: He's not -- you can -- you can use
6 the word "collapsing." It's not the way it's used in the
7 '730 patent. But he is statistically making a call at
8 each position. Okay? You can go to one column to the
9 left of where he's boxed things, and everything is a C
10 there. So that's easy. Consensus call C.

11 And then you go to this position here, and the
12 sequencing had a little bit of a problem. Sometimes it's
13 a C, sometimes a G. But more often than not, it's a G.

14 So the algorithm isn't collapsing anything.
15 It's making a consensus call. On average, my reads say
16 that that's a G there. So statistically, I'm going to
17 say that's a G, and the reason we saw C's is that's an
18 error of some sort or that's some sort of variation. And
19 then I go over, and the next line is a T, et cetera,
20 et cetera.

21 So, you know, again, that's the way these
22 algorithms worked at the time.

23 BY MR. BROUGHAN:

24 Q Why isn't what's shown in Figure 2 of Bentley
25 collapsing?

1 A Because I'm not merging -- I'm not merging all
2 of the reads into one. Okay? In collapsing, what I'm
3 doing is I'm taking a sequence that is, you know, a
4 collection of barcodes and sorting my reads.

5 So, for example, you know, if this was done
6 using the '730 patent, let's say the C and G's are
7 actually different sequences, so I have a heterozygous
8 sequence from my original sample. The C's would have a
9 barcode 1, and the G's would have a barcode 2, and I
10 would have binned them. Okay?

11 That's different than what's being done here
12 where everything is being collapsed down into one
13 nucleotide. Okay? That's -- it's a different approach
14 than what's being done with consensus base-calling.

15 Q So any time there's a sequencing error, the '730
16 patent is going to separately bin those?

17 MR. WUESTE: Object to form.

18 THE WITNESS: I mean, again, it depends on what
19 the read is. Okay? But if the read has a sequencing
20 error, right, that will be a specific sequence that will
21 be, you know, associated with a barcode. That's assuming
22 the sequencing error is not in the barcode, which, of
23 course, it also can be. So yeah, that would be an entry
24 in our little table.

25 BY MR. BROUGHAN:

1 Q Why isn't -- sorry. Strike that.

2 You said Bentley is not merging 11 reads into
3 one. But when I look at Figure 2, I see him merging 11
4 reads into a consensus sequence. Why is my understanding
5 incorrect?

6 A I think you are correct to say merging -- I
7 mean, this is all semantics. Okay? I am taking 11
8 independent measurements of a sequence, okay, and I'm
9 asking, using a statistical model, what is the best
10 representation -- on a nucleotide per nucleotide basis,
11 what is the best information of those 11 independent
12 measurements. All right?

13 So because we're not good at looking at 11
14 things, we're good at looking at one, right, that's what
15 the consensus sequence is. So yes, the data is being
16 merged, okay. I'm taking 11 independent measurements,
17 just like if I made 11 independent measurements of, you
18 know, the length of this glass, right, you wouldn't be
19 interested in those 11. You'd want to know what the mean
20 is or the average, right?

21 That's statistically what this is doing. So I
22 agree with you. 11 measurements are being converted into
23 a single one, all right, but it's using that kind of
24 logic that I just outlined.

25 Q How is Bentley's merging of 11 reads into one

1 different than collapsing into a single count?

2 A I think I already answered that. I gave the
3 example about the C's and G's. So yeah, already covered
4 that.

5 Q Okay. So Chee notes that there can be problems
6 with skewing.

7 Does that sound familiar to you?

8 A Let's go back to Chee, somewhere.

9 Q Let's look at column 9, line 18.

10 A "In addition, the unique"?

11 Q Do you see -- it's the paragraph that goes 12 to
12 21.

13 A Okay.

14 Q Paragraph starts, "The ability to" --

15 A Okay.

16 [Reviewing.]

17 Yes, I read it.

18 Q So Chee says that the unique identifiers can
19 allow for the identification of technical bias such as a
20 skewed proportion of a specific construct in the sample,
21 correct?

22 MR. WUESTE: Object to form.

23 THE WITNESS: Correct, I agree with what you
24 read.

25 BY MR. BROUGHAN:

1 Q Chee recognizes that skewing during
2 amplification can be a problem?

3 A Yes. We've already discussed that this was a
4 well-known problem in the field. So Chee was definitely
5 aware of this issue.

6 Q And in column 5, lines 9 to 14 -- I'll let you
7 get there.

8 A [Reviewing.]

9 Q Chee, again, is recognizing that there can be
10 problems arising from amplification bias when -- sorry.
11 Strike that.

12 Chee -- in column -- in column 5, lines 9
13 through 14, Chee again recognizes that there can be
14 problems caused by amplification bias, correct?

15 A In 9 through 14?

16 Q Yes.

17 A [Reviewing.]

18 Yes. Yeah, absolutely. As we mentioned, he was
19 well aware of this problem.

20 Q And Chee says that "potential bias in
21 quantitative analysis."

22 Do you see that?

23 A Yes.

24 Q Quantitative analysis refers to determining the
25 absolute to relative amount of things?

1 A Yes, we discussed that earlier, yes.

2 Q And if you go to column 23 of Chee, line 50
3 says, "Improved Quantification of ROIs."

4 Do you see that?

5 A Yes.

6 Q Starting at line 59, Chee points out that "Thus,
7 if a nucleic acid is either over-represented or
8 under-represented due to amplification bias, the number
9 of molecules comprising unique identifiers will also be
10 over-represented or under-represented, and the
11 quantification of the molecules can be corrected to
12 reflect this manner of bias."

13 Do you see that?

14 A Yes.

15 Q Chee discloses correcting for amplification
16 bias, correct?

17 MR. WUESTE: Object to form.

18 THE WITNESS: What Chee is -- what Chee is
19 proposing here is ways to understand what exactly was the
20 relative populations of DNAs that were synthesized --
21 again, his ROIs are DNAs that were being made -- and how
22 do I -- I want to continue with the right DNA, and I
23 don't want to continue with the wrong DNA, so I want to
24 ensure, what is the fraction of right versus wrong.
25 Okay?

1 So he's proposing that using the unique
2 identifiers and reading them, if the unique identifier --
3 if the amplification bias was happening post the addition
4 of the unique identifier -- that's the assumption here --
5 that he would be able to correct for that bias and
6 understand that 25 percent of his original population was
7 the right sequence versus maybe the final sequencing says
8 50.

9 So he is correcting for amplification bias in
10 this application. So yeah, I would agree.

11 BY MR. BROUGHAN:

12 Q So ignoring whether the source is natural or
13 synthetic DNA, you agree that Chee discloses correcting
14 for amplification bias, correct?

15 MR. WUESTE: Object to form.

16 THE WITNESS: He -- what Chee is proposing is a
17 method -- obviously, he needs to show that that method
18 works, but by just reading the unique identifiers, he is
19 proposing that that would allow him to correct for
20 amplification bias.

21 BY MR. BROUGHAN:

22 Q So Chee takes a sample, amplifies it --

23 MR. WUESTE: Object to form.

24 BY MR. BROUGHAN:

25 Q Let me start again.

1 Chee starts with a sample, amplifies it, and
2 then applies an error correction process to it, like
3 generating the consensus sequence?

4 A Can you show me where -- like, a figure or some
5 text where we can talk about this more in detail?

6 Q Look at Figure 7.

7 A Yeah, I was going to propose the same. Okay.

8 Q Chee starts with a sample of nucleic acids. We
9 can set aside the question of whether naturally
10 occurring --

11 A Fine. Fine. Nucleic acids in the sample.
12 That's fine.

13 Q Chee generates constructs from the nucleic acids
14 in the sample --

15 A Uh-huh.

16 Q "Yes"?

17 MR. WUESTE: Sorry. Dr. Puglisi, let him finish
18 the question before you answer.

19 MR. BROUGHAN: Thank you.

20 BY MR. BROUGHAN:

21 Q Chee then amplifies the constructs, correct?

22 A Correct.

23 Q Although it's not shown in Figure 7, Chee has
24 the error correction process where it will take
25 constructs with the same unique identifier and generate

1 the consensus sequence from that?

2 MR. WUESTE: Object to form.

3 BY MR. BROUGHAN:

4 Q Yes?

5 A I'm making an assumption that he's doing it. It
6 just says, "sequence determination of regions of interest
7 and unique identifiers," so I don't know what analysis is
8 being done here and what -- you know, how he's doing the
9 assembly of sequences of regions of interest. So the
10 last part is not explicit in Figure 7. Maybe it's in the
11 figure legend.

12 Q After amplification, Chee discloses the process
13 we looked at in column 14 for generating a consensus
14 sequence derived from multiple clonal copies of a
15 construct, correct?

16 MR. WUESTE: Object to form. Mischaracterizes
17 the document.

18 THE WITNESS: He disclosed that in that
19 paragraph, but this is a specific protocol and
20 specific -- I don't know what he's doing here. If one of
21 my students came and showed me this, I'd ask for the
22 details.

23 BY MR. BROUGHAN:

24 Q If you look at column 21 to 22.

25 A Column 21 --

1 Q Starts 21, line 58.

2 A Oh, okay. Now we're talking. Okay. 28,
3 figure -- 22?

4 Q Column 21, starting at line 58.

5 A Okay.

6 Q And then it spans over to column 22, line 2.

7 A Okay. Let me read this.

8 [Reviewing.]

9 Yes, now I understand. Thank you.

10 Q What do you understand the consensus sequences
11 707 to be?

12 A So based on what is said in this, okay, you have
13 pools containing an ROI and a unique identifier in 703.
14 Okay? Each one of those is a different pool. "These are
15 amplified to create pools containing identical
16 descendants of each construct 703."

17 I'm just having -- is 703 -- I can't -- 703 are
18 different -- I don't understand if they have the same
19 unique identifier or -- but I think they do. Okay? It's
20 really poorly written, "a unique identifier."

21 "The sequence is then determined 706 for the
22 pool of amplified constructs 705." So that's the --
23 okay.

24 "These sequences are optionally assembled to
25 create a consensus sequence."

1 Okay. So, again, repeat the question just so I
2 -- sorry. I was making sure I understood.

3 Q Give me a moment because I've lost track of the
4 question.

5 A Yeah.

6 Q So there's -- Chee creates "pools containing
7 identical descendants of each construct containing an ROI
8 and unique identifier."

9 Do you see that?

10 A "Identical descendants of each construct" --
11 pools -- I understand that, yeah. Okay.

12 Q That's like "multiple clonal" -- that's like --
13 you can use -- sorry. Strike that.

14 "Pools containing identical descendants of each
15 construct," that's another way of saying "multiple clonal
16 copies of the construct," right?

17 MR. WUESTE: Object to form.

18 THE WITNESS: Again, I'm just a little bit
19 confused about --

20 Okay. He's got a region of interest. Okay.
21 Takes a nucleic acid region -- a sample. Okay. And then
22 individual molecules are all tagged with a different
23 unique identifier? Is that what's going on?

24 "Associated with one or more amplification sites
25 and a unique identifier."

1 I'm just super confused. The language is not
2 helping us here because I would read this -- I read
3 this -- he's got a plural and a singular -- that there's
4 only one unique identifier being added to all the nucleic
5 acids, but I'm sure that's not what he's doing, but I
6 don't want to interpret it.

7 Okay. And then I'm getting -- everything here
8 is black, so is that the same unique identifier? Are
9 those different after the amplification? I'm assuming
10 not, but that's not what the figure says.

11 I know what you want to ask me, but the text is
12 not helping me answer that.

13 BY MR. BROUGHAN:

14 Q Right. Let's abandon Figure 7 for now, and
15 let's look at column 14, line 46 to 50.

16 Actually, let's start at line 42. It says,
17 "Multiple instances."

18 A [Reviewing.]

19 Q So Chee at this point has multiple clonal copies
20 of a construct, right?

21 A Yeah, I think it's important if we're going to
22 read Chee is to read the paragraph above because that's
23 the starting point. Okay?

24 So he's taking individual molecules, okay, and
25 they're being put onto beads and then amplified. All

1 right?

2 So, I mean, that's where the amplification is.
3 So you start with one molecule, and you amplify that
4 molecule. I think that's the key here. Okay?

5 And then he goes, "Okay, well, I'm going to read
6 this out with sequencing," and every sequencing platform
7 has its problems.

8 And then "Multiple instances of the same
9 molecule can be sequenced, and the ROI of an individual
10 parent construct can be identified by its unique
11 identifier, as molecules with identical identifiers arise
12 via amplification of the same original construct."

13 All right. In the -- in the lines 32 to 37
14 application of this, that would be from an original bead.
15 Okay? So that's where the clonal amplification -- so you
16 should be able to go from a unique identifier back to a
17 bead, okay, because that's where the DNA was born, on
18 that bead. Okay?

19 And then he's going, "Thus, a variation in the
20 sequence of a single copy of a construct most likely to
21 be a synthesis or sequencing error if it differs from a
22 consensus sequence derived from multiple clonal copies of
23 the construct, which are identified as identical by
24 descent with a shared unique identifier."

25 So if you get -- if the UM, the unique molecular

1 identifier, the unique identifier is the same, it means I
2 must have come from the same bead, but if I get a
3 different sequence, there's an error there.

4 That's the way I read this, which I think is the
5 same thing you're saying.

6 Q Maybe. Chee starts with a sample, whether it's
7 on a bead or not, creates the constructs, amplifies the
8 constructs, sequences them, and then for any constructs
9 that have the same unique identifier, it can create the
10 consensus sequence to correct for errors? Yes?

11 MR. WUESTE: Object to form. Mischaracterizes
12 the document. Calls for speculation.

13 THE WITNESS: Yeah, there's a consensus
14 sequence, which in many applications of Chee was
15 something he designed because he made the DNA, right? So
16 he knows what that target sequence is.

17 And he's trying to say, "Is there variation from
18 that consensus sequence? And if there's a variation, it
19 means I have an error somewhere, either in the sequencing
20 or in the synthesis, so I'm going to discard that."

21 That's what he's doing. All right? So he's
22 following the process that you're saying. Okay? But,
23 you know, where there's a consensus sequencing analysis
24 just depends on what he's trying to do.

25 And most of the time, he's trying to identify,

1 "Is this the right DNA that I designed, because I'm
2 trying to make the gene for hemoglobin, and I don't want
3 to have an error there."

4 And so the consensus sequence is what he
5 designed, and then he's looking at the individual reads
6 to understand if there's errors or not.

7 MR. WUESTE: Counsel, we've been going about an
8 hour. So whenever is a good time for a break, that's
9 fine.

10 THE WITNESS: I'm happy to keep answering.

11 MR. BROUGHAN: Why don't we take a break. I
12 think I -- yeah, let's take a break.

13 THE WITNESS: Okay.

14 (Recess taken from 1:50 p.m. to 2:06 p.m.)

15 BY MR. BROUGHAN:

16 Q If you turn to column 9 of Chee. If you read
17 the paragraph that starts at line 22.

18 A [Reviewing.]

19 Okay.

20 Q What is massively parallel sequencing?

21 A Massively parallel sequencing is what we were
22 calling earlier in the deposition next-generation
23 sequencing.

24 Q Chee discloses that its constructs with unique
25 identifiers can be used with next-generation sequencing.

1 Yes?

2 A He's discussing, yes, the application of his
3 technology with next-generation sequencing.

4 Q And when used in next-gen sequencing, the unique
5 identifiers can be used to determine that certain
6 molecules are descended from the same decent -- or
7 descended from the same original molecule?

8 A He's -- what Chee is using is using the unique
9 identifiers to say that the origin of that molecule that
10 got sequenced came from an individual molecule, again,
11 assuming the identifiers were designed correctly.

12 Q Chee says the unique identifiers can also --
13 sorry. Strike that.

14 Chee says that the unique identifiers can be
15 used to identify technical errors rather than real
16 differences in sequences, correct?

17 A That's what's written there, yes.

18 Q And that "a consensus sequence can be determined
19 using data from multiple molecules," meaning multiple
20 molecules with the same unique identifier, right?

21 MR. WUESTE: Object to form. Mischaracterizes
22 the document.

23 THE WITNESS: He's proposing an analysis that's
24 happening after the fact, that he would just do a --
25 instead of doing just a global consensus sequence, he's

1 doing a consensus sequence on a subset of molecules.

2 BY MR. BROUGHAN:

3 Q What subset?

4 A He says, "because molecules that are identical
5 by descent can be identified," okay -- I mean, it's not
6 really clear what he's proposing, so I guess I shouldn't
7 fill in my own interpretation of it.

8 But he's saying, "I should be able to get better
9 consensus sequencing from multiple molecules because I
10 can use the UMIs in some way," although the approach is
11 not really mapped out.

12 Q UMIs are universal --

13 A I'm sorry. The unique identifiers. Sorry.

14 Q So in this example in Chee, Chee would get a
15 sample, create the constructs, run it through the next-
16 generation sequencing workflow, which would include
17 amplifying the sample, putting it through the sequencer,
18 and getting sequence reads, correct?

19 MR. WUESTE: Object to form.

20 THE WITNESS: The -- what Chee is proposing is
21 to use the unique identifiers as a way to correct for
22 some of the problems in the parallel sequencing of this
23 time -- let's say 2009 -- which was discussed earlier,
24 which is error rates due to the sequencing technology and
25 also errors that are introduced in the amplification

1 process, which is not just amplification bias.

2 Next-generation sequencers used non-traditional
3 amplification methods. I'm trying to be general because
4 454 was different than Illumina.

5 But all sorts of problems about amplification
6 that are not just amplification bias, amplification
7 errors, and then sequencing errors. And what he's
8 proposing to do is to correct for some of those errors.

9 BY MR. BROUGHAN:

10 Q Could we look at -- I want to look at the next
11 paragraph in Chee, which goes from line 40 to 52.

12 A Uh-huh.

13 Q Can you take a moment to read that.

14 A [Reviewing.]

15 Okay. Yes.

16 Q Chee says that its methods can be used for
17 genomic sequencing, correct?

18 A Yes, that's what the first sentence states.

19 Q Chee says that its methods can be used to detect
20 rare sequence variants, correct?

21 A It claims to be able to detect rare sequence
22 variants, yes. That's what he's saying.

23 Q Chee can detect "minor allelic variant or
24 haplotypes in a sample containing DNA from multiple
25 individuals," correct?

1 MR. WUESTE: Object to form.

2 THE WITNESS: Again, I mean, this is what he's
3 broadly suggesting the technology might be able to do.

4 BY MR. BROUGHAN:

5 Q And Chee says that the -- "a specific
6 application of the methods of the invention is for
7 confirmation of polymorphisms and mutations," as an
8 example. Yes?

9 MR. WUESTE: Object to form.

10 THE WITNESS: That's what's written in the -- in
11 the text. I agree.

12 BY MR. BROUGHAN:

13 Q Detecting rare sequence variants, minor allelic
14 variations, polymorphisms, that's not synthetic biology,
15 correct?

16 A Could be from synthetic biology, but the
17 application here is -- DNA from individuals is assuming
18 the DNA is isolated from those individuals.

19 MR. BROUGHAN: Mark this as the next exhibit,
20 please. 1044.

21 (Exhibit 1044 marked for identification.)

22 BY MR. BROUGHAN:

23 Q The court reporter has handed you what's been
24 marked as Exhibit 1044. Okay. This is another variation
25 of Figure 5 that we prepared.

1 A So this is your preparation. This is not
2 something I've ever seen before; is that correct?

3 Q Correct.

4 A Okay. Just wanted to understand. Thought it
5 looked -- the font changed.

6 Q Yes, this "error correction" column is
7 different.

8 A Okay.

9 Q We inserted that "error correction" column.

10 A Okay. Great.

11 Q So on the left-hand side of the figure, there's
12 the original sample.

13 A Uh-huh.

14 Q Then there's amplification.

15 A Uh-huh.

16 Q And the beginning of each sequence, we've added
17 an additional base, the A, C, A, A, G.

18 Do you see that?

19 A Okay.

20 Q Okay. And then we've added this error
21 correction step in the middle. And then on the right,
22 this is the same from Figure 5.

23 A Okay.

24 Q Okay. After sequence reads are grouped by the
25 tag -- so 1011 in the red box -- that grouping goes to an

1 error correction step.

2 Do you see that?

3 A Yes.

4 Q Okay. And within the error correction step,
5 there's a process for generating a consensus sequence.

6 Do you see that?

7 A Okay.

8 Q And this looks similar to what we saw in
9 Bentley. Yes?

10 MR. WUESTE: Object to form.

11 THE WITNESS: I mean, the consensus call at that
12 position A, yes, that's similar to Bentley. Yeah, that's
13 what we saw. And for the T's. Assuming we're using that
14 methodology.

15 BY MR. BROUGHAN:

16 Q Yes.

17 Do you understand that this figure depicts how
18 Illumina contends Chee works?

19 MR. WUESTE: Object to form.

20 THE WITNESS: I don't -- I don't know what
21 Illumina contends about Chee. That sounds like a
22 legal --

23 BY MR. BROUGHAN:

24 Q You read Dr. Gabriel's report, declaration?

25 A Yes, I did.

1 Q Do you understand that this is how Dr. Gabriel
2 contends Chee operates?

3 A Could you show me exactly? Because I don't have
4 Dr. Gabriel's report in front of me. I'm forgetting
5 exactly her arguments.

6 Q Do you understand that this is how she contends
7 it works, or you do not understand that this is how she
8 contends it works?

9 MR. WUESTE: Object to form. Put the document
10 in front of him.

11 THE WITNESS: I can't say that I agree or
12 disagree without -- without recalling Dr. Gabriel's
13 document. You're proposing a detailed analysis of DNA
14 sequencing, a set of steps. As we saw in some of the
15 previous documents, the details of what is proposed is
16 really important.

17 BY MR. BROUGHAN:

18 Q So on the left-hand side, you see there's four
19 molecules in the original sample?

20 A I understand there's four molecules in the
21 original sample.

22 What I'm -- I'm going to tell you what I
23 understand, okay, which has nothing to do with
24 Dr. Gabriel for the moment, okay, because I would like to
25 see the document if I'm going to opine on Dr. Gabriel's

1 opinions.

2 Somehow after amplification -- amplification
3 doesn't just have a bias. It also has errors. So you
4 put errors in there. I'm trying to understand. That's
5 what the difference --

6 Q Yes, those are errors, correct.

7 A Okay. So I have errors. These are errors that
8 maybe happened in sequencing. Maybe they happened in
9 bridge amplification, which is the type of amplification
10 that occurred at this time period on an Illumina box, or
11 in the emulsion, you know, PCR that was happening in 454.

12 Okay. So you're getting an error introduced at
13 the amplification step. Okay? And then you did
14 sequencing rates with whatever technology. And now
15 you're going over to this error correction step that is
16 an extra step that you guys are adding. Okay.

17 Q And this error correction step generates
18 consensus sequences using sequence reads that have the
19 same identifier on them, same tag.

20 A So we have the same identifier. We bin them
21 all. And then you're doing a consensus sequence analysis
22 a la Bentley.

23 Q A la Bentley and a la Chee.

24 MR. WUESTE: Object to form. Mischaracterizes
25 the document. Mischaracterizes Chee. Calls for

1 speculation.

2 THE WITNESS: Yeah, again, this is kind of
3 invented, but okay. I --

4 BY MR. BROUGHAN:

5 Q And then --

6 A I agree that you're making a consensus analysis
7 of those three sequences in red and you're doing a
8 consensus call at that -- I agree that those are
9 consensus calls being made for each of the boxes.

10 Whether that's what Chee was proposing or
11 Gabriel and Bentley, you know, that's a different story.

12 Q After the error correction step, you have the
13 error-corrected sequence reads.

14 MR. WUESTE: Object to form.

15 THE WITNESS: Again, I don't even know if
16 that -- those are errors. Why do I know a priori?
17 You've added nucleotide variability to these two
18 sequences.

19 There's two sequences here in the original
20 sample, right? They've got -- those four molecules of
21 two different sequences got four different tags. Now I
22 do something, amplification, manipulation and sequencing.
23 And from the original molecule of 1011, I got two
24 sequences out.

25 Now, maybe that's a sequencing error, but I

1 don't know. Maybe there -- maybe there was variability
2 in the original sample.

3 So we're ascribing that to variability, some
4 sequencing error, but that could be actual -- you know,
5 some kind of low-abundance mutation, right, or -- it is a
6 mutation that is not represented in this figure.

7 So the figure -- the starting point of the
8 figure is confusing.

9 The only thing that's not confusing to me is
10 what you just said, that I -- I take three reads, and I
11 do consensus base call. Fine. I mean, that's -- any
12 POSA would have done that.

13 But, you know, this whole trying to put all
14 those pieces together into, "This is what Chee is saying
15 we're doing by this figure" is very misleading.

16 BY MR. BROUGHAN:

17 Q Would it help if I said that this was not -- if
18 we talked about this example without reference to Chee?

19 A You're happy -- I'm happy for you to talk about
20 it any way you want.

21 Q I'm just seeing if that would help with what
22 you're saying.

23 A Yeah.

24 Q All right. Do you agree that the error
25 correction shown in 1044 could be collapsing within the

1 scope of the '730 claim 1?

2 MR. WUESTE: Object to form. Calls for
3 speculation. Incomplete hypothetical.

4 THE WITNESS: What I would say is that what I
5 see in the red box is consensus sequencing of a
6 collection of reads.

7 BY MR. BROUGHAN:

8 Q Is consensus sequencing of a collection of reads
9 collapsing within the context of claim 1 of the '730
10 patent?

11 A Collapsing is a two-step process, where these
12 would have been sorted. So no, it's not the same thing.
13 This is standard consensus sequencing analysis.

14 Q Standard consensus sequencing analysis is not
15 the same thing as collapsing in claim 1 of the '730
16 patent?

17 A I think we've already discussed that.

18 Q Do you know Dr. Stacey Gabriel?

19 A I believe I met her, yeah. She's very good.

20 Q Okay. Met her a few times? Not close
21 colleagues?

22 A I don't know -- no. Maybe if I met her once at
23 some meeting.

24 Q Got it.

25 A She's younger than I am.

1 Q Sorry. I'm just making sure I don't have
2 anything else.

3 Do you know Jay Shendure?

4 A Jay Shendure? Yes, I do.

5 Q Shendure.

6 A I do. I know him better than Stacey Gabriel, if
7 that's of any use, that knowledge.

8 Q Did you know him in 2009?

9 A 2009? Probably -- no, I think I probably first
10 met him in 2011, '12.

11 MR. BROUGHAN: I don't have any further
12 questions at this time.

13 MR. WUESTE: If you could give me a couple
14 minutes. I'll see if I have any redirect.

15 MR. BROUGHAN: Do you want to take a break?

16 MR. WUESTE: Yes, please.

17 MR. BROUGHAN: Yeah.

18 (Recess taken from 2:25 p.m. to 2:32 p.m.)

19 EXAMINATION

20 BY MR. WUESTE:

21 Q Welcome back, Dr. Puglisi. I'd like you to turn
22 to Exhibit 1001, which is the '730 patent, first. I want
23 to direct your attention to the claims, so the last page.

24 A Yes.

25 Q Could you read the last limitation of claim 1,

1 the correcting step?

2 A "Correcting for error or bias introduced during
3 said workflow by collapsing target:differentiator tag
4 combinations observed more than once into a single
5 count."

6 Q And then read out claim 2, please.

7 A "The method of claim 1, wherein said correcting
8 step further comprises collapsing all sequence reads
9 comprising a same differentiator tag into a single read
10 before determining a consensus base-call for the target
11 nucleic acid molecule sequences."

12 Q And how do -- how does the last limitation of
13 claim 1 of the '730 patent read in comparison to claim 2
14 of the '730 patent affect your analysis of whether
15 collapsing is the same or different as a consensus
16 base-call?

17 MR. BROUGHAN: Object to form.

18 THE WITNESS: Again, could you repeat the
19 question? Sorry.

20 BY MR. WUESTE:

21 Q Sure.

22 A It's getting late.

23 Q When reading the last limitation of claim 1 of
24 the '730 patent next to claim 2 of the '730 patent, what
25 does that tell you about whether or not collapsing is the

1 same or different as determining a consensus base-call?

2 MR. BROUGHAN: Object to form.

3 THE WITNESS: Well, in claim 2, you know, you
4 are collapsing the reads, and then you're doing a
5 consensus base-call. So they're two independent steps.

6 BY MR. WUESTE:

7 Q Okay. And, now, if you could pull back up
8 Exhibit 1044, which was the diagram --

9 A This one?

10 Q -- Counsel closed on.

11 That's correct.

12 A This one.

13 Q That one.

14 A Okay.

15 Q And to be clear, had you seen this diagram
16 before?

17 A No, I did not. This is the first time.

18 Q In the error correction portion of Exhibit 1044,
19 what was your understanding of what the consensus steps
20 were referring to?

21 A What was happening in the consensus steps?

22 Q That's right.

23 A You're looking at all the reads, and again, as
24 we discussed earlier, at each position, you're analyzing
25 what was the nucleotide that the technology read out at

1 that position, and statistically, you're making a call
2 about what was the most likely right answer at that
3 position.

4 And this, we discussed in terms of Bentley.

5 Q Okay. And so is it your understanding that --
6 strike that.

7 Earlier, counsel asked you a question about
8 whether or not standard consensus sequencing was the same
9 or different from the collapsing step of claim 1 of the
10 '730 patent, right?

11 A Yes.

12 Q And when you were answering that question, was
13 your understanding of consensus sequencing analysis the
14 consensus base-call that you're describing here?

15 A Yes.

16 MR. WUESTE: No further questions.

17 MR. BROUGHAN: No questions.

18 THE REPORTER: On the record, could I get
19 transcript orders?

20 MR. WUESTE: Whatever the standard order is. I
21 don't think we need -- we don't need it any time soon.

22 MR. BROUGHAN: Yeah, like, three days. What is
23 the price cutoff? It's like three, five?

24 THE REPORTER: I don't know.

25 MR. BROUGHAN: Three is fine. We definitely

1 don't need it tomorrow. Whoever said that -- we're not
2 in that much of a hurry, but three days -- but we'll get
3 a rough today?

4 THE REPORTER: Do you want a rough?

5 MR. BROUGHAN: Yes.

6 THE REPORTER: No problem.

7 MR. WUESTE: I'll take a rough whenever you're
8 able to put it together.

9 (Off the record at 2:37 p.m.)

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C E R T I F I C A T E

Oral deposition of JOSEPH D. PUGLISI, PH.D., taken at
Sidley Austin LLP, Building One, 1001 Page Mill Road,
Suite 100, Palo Alto, California 94304, on Wednesday,
September 17, 2025, commencing at 9:14 a.m.

I, Debbie Leonard, Certified Shorthand Reporter
No. 14350 for the State of California, do hereby
certify that the aforesaid testimony was taken before me
at the time and place indicated; that said deponent was
by me duly sworn to tell the truth, the whole truth, and
nothing but the truth; that the testimony of said
deponent was correctly recorded in machine shorthand by
me and thereafter transcribed under my supervision with
computer-aided transcription; that the deposition is a
true and correct record of the testimony given by the
witness; that I am not disqualified as specified in Rule
28 of the Federal Rules of Civil Procedure; that the
adverse party was present; and that I am neither of
counsel nor kin to any party in said action, nor
interested in the outcome thereof.

WITNESS my hand and official seal this 19th day
of September, 2025.


Debbie Leonard, CSR, RDR, CRR
CA CSR NO. 14350

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