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Transcript of Paul T. Spellman, Ph.D.

Date: March 18, 2025

Case: 10X Genomics, Inc. -v- Bruker Spatial Biology, Inc. (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

Bruker EX2018.001

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2 -----
3 BEFORE THE PATENT TRIAL AND APPEAL BOARD
4 -----

5 10X GENOMICS, INC.,

6 Petitioner,

7 v.

8 BRUKER SPATIAL BIOLOGY, INC.,

9 Patent Owner,
10 -----

11 Case IPR2023-01300

12 U.S. Patent No. 11,473,142
13 -----

14
15 REMOTE DEPOSITION OF

16 PAUL T. SPELLMAN, Ph.D.

17 March 18, 2025
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21 Reported by: Susan S. Klinger, RMR-CRR, CSR

22 Job No. 576242

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March 18, 2025

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11:58 a.m.

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Remote Deposition of PAUL T. SPELLMAN, Ph.D.,

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held remotely before Susan S. Klinger, a

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Registered Merit Reporter and Certified Realtime

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Reporter of the State of Texas.

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E X H I B I T S

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

2 PAUL SPELLMAN, Ph.D.,

3 having been first duly sworn testified as follows:

4 EXAMINATION

5 BY MR. CHEUNG:

6 Q Dr. Spellman, please state your name and
7 address for the record?

8 A Paul Spellman, 10807 Rochester Avenue, Los
9 Angeles, California 90024.

10 Q Did you prepare for today's deposition?

11 A Yes.

12 Q And what did you do to prepare?

13 A Met with counsel, read documents that have
14 been introduced into this case already, went over
15 deposition transcripts of myself, read
16 declarations of myself and Dr. Sherman, et cetera.

17 Q Did you review any documents that are not
18 listed in your reply declaration in this case?

19 A I familiarized myself with basic science
20 studies. So I might have read a paper about the
21 exact mechanism of how something worked to refresh
22 my memory, but I did nothing, as to something I am

1 going to testify today, as to something I haven't
2 already commented on.

3 Q How long did you spend preparing for
4 today's deposition?

5 A I don't know exactly, more than 20 hours,
6 less than 100 hours.

7 Q When you met with counsel, who did you
8 meet with?

9 A Those present.

10 Q When did you have your meeting with
11 counsel?

12 A Over the past several weeks.

13 Q How many times?

14 A I believe on four separate occasions. It
15 may have been three, multiple times in some days.

16 Q How long were the meetings in total?

17 A I don't -- I don't have -- I would have to
18 check my billing records.

19 Q Less than 10 hours?

20 A Somewhere between 10 and 20 hours, I
21 believe.

22 Q And how long did you spend preparing your

1 reply declaration in this case?

2 A I would have to check my billing records
3 exactly since that was more than a month ago. The
4 exact time I think I included that in my ballpark
5 number of up to 100 hours, but...

6 Q Okay. And in preparing for today's
7 deposition, did you review your reply declaration?

8 A I did.

9 Q Did you review your first declaration in
10 this case?

11 A I did.

12 Q Did you find any of the opinions in your
13 first declaration to be incorrect?

14 A The reply declaration updates some of the
15 opinions based on Bruker's IPR positions and the
16 Board's construction of certain terms that weren't
17 available in my initial declaration. So those --
18 those opinions are in my reply declaration.

19 Q So any amendments that you would like to
20 make to your first declaration are present in your
21 reply declaration; is that right?

22 A I believe that that is correct.

1 Q Are there any opinions in your first
2 declaration that you disagree with in your reply
3 declaration?

4 A I maintained the positions held in my
5 first declaration given the IP -- my understanding
6 of Bruker's infringement position at the time and
7 my understanding of the terms as defined at the
8 time and that, I believe, is maintained in my
9 reply declaration.

10 Q So all of the opinions in your first
11 declaration remain unchanged; is that right?

12 A Given the I -- the infringement position
13 presented by -- by NanoString, now Bruker and my
14 understanding of the terms of the -- and the
15 claims as I interpreted them, those -- those
16 positions have not changed.

17 I have additional positions in my reply
18 declaration based on the IPR positions filed by
19 Bruker and the patent court, the IPR court's
20 construction of claim terms that are different
21 than I understood them to be that have been
22 updated. And so there is -- new opinions are in

1 my reply declaration.

2 Q Do you have any positions in this case
3 that are not included in your first or reply
4 declaration?

5 A I have not offered any opinions that are
6 not in my first or reply declaration.

7 Q Are there any opinions not in your first
8 or reply declaration that you want to offer now?

9 A No.

10 Q Dr. Spellman, are you familiar with
11 Illumina paired-end sequencing?

12 A Yes.

13 Q What is your understanding of Illumina
14 paired-end sequencing?

15 A Illumina paired-end sequencing is a
16 technology or set of technologies commercialized
17 by Illumina. It involves clonal amplification on
18 a solid substrate to create a set of molecules
19 that have specific orientations.

20 And because DNA polymerases extend DNA
21 synthesis in only one direction, one can sequence
22 from the set of molecules on the surface of a

1 Illumina array in one direction and generate high
2 quality data that is relatively short, typically
3 between 25 base pairs in length and is potentially
4 as long as 500 base pairs in length. The most
5 common length at the time of the patents in this
6 case would be about 150 base pairs in length or
7 perhaps 100 base pairs in length.

8 That synthesis happens in one direction.
9 And Illumina Technology has developed a process by
10 which either of the strands can be sequenced. And
11 so one can sequence either the -- what is
12 sometimes referred to as top or bottom strand or
13 first or second strand or plus or minus strand,
14 but always in the 5 prime to 3 prime direction.

15 So when one sequences in paired-end mode,
16 one sequences one molecule in one direction, and
17 its reverse complement molecule, which is a
18 separate molecule with a separate sequence in the
19 other direction. Also 5 prime to 3 prime, always
20 5 prime to 3 prime.

21 So Illumina sequencing in paired-end mode
22 sequences two independent but related sets of

1 molecules. And again, it doesn't sequence
2 individual molecules. The sensitivity of Illumina
3 sequencing is capable of detecting -- I don't know
4 the exact number of molecules on the surface, but
5 certainly not one, thousands if not millions of
6 molecules.

7 Q When you say Illumina sequencing in
8 paired-end mode sequences two independent but
9 related set of molecules, are you referring to a
10 double-stranded molecule where the first read
11 sequences one strand and the second read sequences
12 the complementary strand?

13 A My understanding of Illumina sequencing is
14 that is not that normal way it works. Illumina
15 sequencing, as I understand it, normally operates
16 from a single strand and creates a copy of that
17 strand later on to create the reverse complement.
18 And then again, sequences only a single strand by
19 removing the first strand.

20 So at no point is -- my understanding is
21 the sequencing utilizing a double-stranded
22 molecule. It is sequencing single-stranded

1 molecules, to the best of my understanding.

2 Q But the single-stranded molecule that is
3 sequenced on the first read and the
4 single-stranded molecule that is sequenced on the
5 second read in Illumina paired-end sequencing,
6 they are complementary to each other, right?

7 A They would be complementary if they were
8 bound to each other, but they are not.

9 Q And then would it be fair to say that the
10 two strands are not bound to each other but they
11 have a complementary sequence?

12 A For the -- I believe for the -- all of the
13 parts that are going to provide useful
14 information, they are exact reverse complements of
15 one another, but they, to the best of my
16 understanding, do not exist as a duplex during the
17 sequencing process.

18 Q Does Illumina paired-end sequencing
19 involve the use of two different adapters, one on
20 each end of the single-strand molecule that is
21 sequenced?

22 A Yes. Illumina maintains its ability to

1 sequence in both directions by encoding, I
2 believe, what are normally called p5 and p7
3 primers is the convention although it is arbitrary
4 and they're reverse complements encoded in the DNA
5 sequence. And those set the orientation and
6 preference in each round about which direction is
7 being sequenced.

8 Q So in Illumina paired-end sequencing, in
9 the first read would all of the molecules be bound
10 to the array via the p5 adapter while on the
11 second read all the molecules would be bound to
12 the array by the p7 adapter?

13 A I don't believe the Illumina sequencing
14 normally refers to its flow cells as arrays.
15 Later on they introduce patterned arrays although
16 I believe that would certainly be after many of
17 the patents-in-suit in this case. Although I
18 don't have the exact date, but certainly before
19 Frisen -- certainly after Frisen and I believe
20 after Stahl.

21 So flow cells for many -- for many years
22 were unpatterned arrays or unpatterned --

1 unpatterned processes that were not generally
2 referred to as arrays, my apology.

3 And I believe you are correct, that
4 normally one would sequence from the p5 and then
5 the p7 primers. It is -- again, it is arbitrary
6 and not terribly important which one goes first,
7 but it is ordered and Illumina could change those
8 at any time if they wanted to.

9 Q Okay. So in my understanding -- so under
10 Illumina paired-end sequencing, all of the
11 molecules intended to be sequenced on the first
12 read, all of the molecules would be attached to
13 the flow cell on one of the two adapters for that
14 first read. And then on the second read, all the
15 molecules would be attached to the flow cell via
16 the second adapter for that second read; is that
17 correct?

18 A I think it is a little more complicated
19 than that. There is -- there is the exact
20 chemistry is extremely complicated. And I don't
21 believe we have a reference to bring up in this
22 case right now to go over the exact mechanics of

1 its behavior, but it exists as several rounds.

2 And its chemistry has changed over time in
3 some capacities, but in general, one has a step in
4 which one performs Colony PCR to produce clusters.
5 Those clusters at the outset would be
6 double-stranded, but my understanding is that only
7 one of the two strands is retained and sequenced
8 and then later copied to make the second-strand
9 sequence occur.

10 So but -- but broadly speaking, I think
11 your characterization is reasonable. That in the
12 first round one of the strands is present, and in
13 the second round the other strand is present.

14 Q How is Illumina paired-end sequencing
15 different from Illumina single-read sequencing?

16 A Single-end sequencing would only sequence
17 one of the two strands. That is the primary
18 difference.

19 Q So is the difference between single-read
20 sequencing and paired-end sequencing that the
21 single-read sequencing essentially only performs
22 the first read of the paired-end sequencing

1 workflow and then it stops?

2 A Yes.

3 Q Do you understand that the Stahl method
4 employs Illumina paired-end sequencing?

5 A That is my recollection. I believe it to
6 be true.

7 Q Does the So-456 method employed Illumina
8 paired-end sequencing?

9 A I would stipulate that it would be
10 expected, but I would have to check to be sure.

11 Q Do you know if the So-456 method employs
12 the Illumina single-read sequencing?

13 A I would have to bring up the specification
14 to read it carefully.

15 Q Dr. Spellman, if you can go to the exhibit
16 links and bring up Exhibit 1016 which should be
17 Stahl paper?

18 (Exhibit 1016 discussed.)

19 A I do. Click on the second link in the
20 chat here?

21 Q It is my understanding that the last two
22 links should both work?

1 A And what exhibit am I looking at again?

2 Q 1016?

3 A Yes, Stahl.

4 Q Yes.

5 A Yes, I have it.

6 Q If you have that up, if you can go to the
7 supplementary materials page 7 and let me know
8 when you are there.

9 A I'm on page 7.

10 Q Okay. I'm going to direct you to the last
11 sentence on -- the last complete sentence on page
12 7 which reads, finished libraries were diluted to
13 4 nanomolar and sequenced on the Illumina NextSeq
14 platform using paired-end sequencing according to
15 manufacturer's protocol. Do you see that
16 sentence?

17 A Yes.

18 Q Do you understand paired-end sequencing on
19 the Illumina NextSeq platform to be a commonly
20 used next generation sequencing method in around
21 2016 when Stahl was published?

22 A The Illumina NextSeq platform was a -- and

1 I believe still is a supported platform for
2 Illumina sequencing and would have been reasonably
3 common at the time.

4 Q Okay. Do you see the sentence after that
5 which goes over to the next page which says,
6 Typically 31 or 51 bases were sequenced on read
7 one and 121 or 101 bases were sequenced on read
8 two. Do you see that?

9 A I do.

10 Q Do you have any reason to disagree with
11 that statement that read one was 31 or 51 bases
12 and read two was 121 or 101 bases?

13 A I have no reason to dispute their
14 statement.

15 Q Do you have an explanation why the number
16 of bases sequenced on read one and read two are
17 different?

18 A I have an understanding of that, yes.

19 Q And what is your understanding?

20 A It would imply that the read one is -- I
21 would need to check to be exactly sure, but the
22 information encoded in the product has barcode

1 information and other relevant library information
2 on one end from the extension product.

3 And then it will run into the poly(A) tail
4 sequence of the mRNA. And when it did that, it
5 would have less information. And depending on the
6 orientation of sequencing, which I would have to
7 check, it could be that they did not want to waste
8 sequence -- sequencing homopolymer runs of As, or
9 that they needed to sequence through the entire
10 homopolymer run of A by doing a longer sequence.

11 My belief is that it is the second model
12 that they are catching the location information
13 from the 31 or 51 bases. And then using the
14 second read to connect information about the
15 captured mRNA, but I would have to go back and
16 very closely map this architecture to the library
17 construction.

18 Q Is it your belief that the -- on read two
19 of 121 or 101 bases that that length is sufficient
20 to sequence through the poly(A) tail of the
21 molecule to other sequences?

22 A It would depend very closely, and that is

1 why I don't think it is modeled that way. I think
2 the first read is collecting information from the
3 location information, the shorter read, and then
4 the longer read is collecting information from the
5 mRNA. That would be my -- my understanding.

6 Q So your understanding is that the first
7 read of the 31 or 51 bases is the spatial barcode.
8 And that first read is shorter than the second
9 read, because the mRNA poly(A) tail is on the
10 other side beyond the 31 or 51 bases; is that
11 right?

12 MS. KHANDURI: Objection, form.

13 A I think that is the most likely without
14 doing a very deep mapping of exactly how it is
15 engineered.

16 Q Do you know whether the read length of an
17 Illumina paired-end sequencing performed on a
18 NextSeq platform changed or increased from 2016 to
19 2018?

20 A There have been changes to lengths on the
21 platforms over time. The lengths here are quite
22 atypical. I would have -- and so the exact

1 chronology of when read lengths have changed over
2 time I could not give you without reference.

3 They continually improved from the release
4 of Illumina machines circa 2005, 2007 until today.
5 Just last week there was an announcement of
6 paired-end 300 or even 500 base pair reads on the
7 X series sequencers.

8 Similarly MiSeq sequencers have long had,
9 I believe, 2 by 500 sequencing, so the technical
10 capabilities of various Illumina sequences have
11 changed over time.

12 Q Would it be fair to say that the maximum
13 read length of Illumina sequencers are
14 approximately 500 bases per read?

15 A It would depend on many factors and what
16 timeframe you're looking at. I don't know there
17 is an inherent limit to what an Illumina sequencer
18 is capable of. These are what is commercially
19 available today or have been commercially
20 available in the past.

21 Q Do you know whether in 2018 Illumina
22 sequencers were capable of sequencing more than

1 500 bases per read?

2 A I do not believe so. I don't believe
3 there was a commercial version of the Illumina
4 sequencer that would do that. An individual
5 investigator might alter the machine in some way
6 to achieve more than that, but it is -- but I
7 don't think there was a commercial kit that
8 allowed it.

9 Q What is the average length of a mRNA
10 molecule that can be found in a human tissue?

11 A MRNAs have enormous length variability
12 depending on lots of factors. The average human
13 protein is about 300 amino acids in length and
14 that corresponds to 900 base pair of coding
15 sequence.

16 Typical mRNAs in addition to the coding
17 sequence have a 5 prime and 3 prime untranslated
18 region, and then the poly(A) tail that is common
19 in the mammalian transcripts.

20 So together it is common to see total
21 transcript lengths of between 13 and 1,500 base
22 pairs with 1,500 base pairs being the most common

1 length cited for a typical transcript. However,
2 there are no -- these are for spliced transcripts.
3 There are -- unspliced transcripts are much, much
4 longer. It can be as -- and the largest human
5 proteins, I believe, are in the 10,000 amino acid
6 range meaning that their mRNAs are 30,000 base
7 pairs or more.

8 So the range is quite broad from
9 incredibly short, perhaps just a couple of hundred
10 base pairs in length or bases in length, to tens
11 of thousands. And if you are talking about
12 unspliced transcripts, I believe the titin TTN
13 gene is something like a million base pairs in
14 length unspliced.

15 Q Would you agree that each read of an
16 Illumina paired-end sequencing run is not able to
17 determine the sequence of an entire length of
18 mRNA?

19 A I'm not sure what the question is, because
20 that is not usually the goal of most people's
21 application of these sorts of technologies. But
22 if you're just asking if the typical mRNA is

1 longer than the total length of Illumina's
2 paired-end sequencing, the answer would be yes.
3 The typical mRNA is longer than the typical
4 lengths of paired-end sequencings, but that is not
5 usually the goal that people utilize.

6 Q When you refer to the goal that people
7 typically utilize, what do you mean?

8 A The amount of information one needs to
9 correctly detect the presence of an mRNA is very
10 different than sequencing the entire mRNA. And
11 therefore, one normally is providing something
12 like how often you detect transcript or the
13 surrogate as the surrogate for gene 1 or gene 2 or
14 gene 3 versus as a set of counts.

15 And the exact sequences are not the
16 recorded information, but rather the counts of how
17 many such things were found. It is not generally
18 necessary if one is measuring individual genes to
19 perform whole transcript sequencing. There are
20 applications and this is not one of them.

21 Stahl is not one of these applications in
22 which one is trying to detect various isoforms of

1 transcripts or -- in which case sequencing across
2 transcripts is useful or having extremely long
3 reads is useful, but Stahl does not do that.

4 Q In Stahl where read two is 121 or 101
5 bases, is that amount of sequence information
6 sufficient to determine the identity of the
7 transcript?

8 A In general, if the sequence being
9 generated is not a known repeat sequence,
10 something on the order of 20 base pairs of
11 sequence is generally considered to be genome
12 unique. A method like Stahl would probably map
13 reads rather than to the entire genome to catalogs
14 of known transcripts in which case shorter read
15 lengths could be likely useful again absent the
16 presence of repeats.

17 But for the majority if not the vast
18 majority of transcripts and genes, 100 base pairs
19 would be sufficient to catalog its detection.

20 Q So to clarify when this sequence of a
21 transcript where 100 base pairs is known from what
22 came from the 5 prime end of an mRNA, that 100

1 base pairs of information is sufficient to catalog
2 the detection of that transcript; is that right?

3 A I think you added a clause. I'm not sure
4 I understand why you added about the 5 prime end.
5 It would not actually matter where in the
6 transcript the information came from.

7 Q So in a method like Stahl when paired-end
8 sequencing is performed, the read is from the ends
9 of the molecules that are sequenced. 100 base
10 pairs of information is enough to match against a
11 database to determine the identity of that
12 transcript; is that right?

13 A In general, that would be the case.

14 Q Dr. Spellman, are you familiar with a
15 technique called in situ hybridization?

16 A Broadly speaking, yes.

17 Q Is in situ hybridization a method of
18 detecting the presence of a nucleic acid sequence
19 in a sample?

20 A It can be, yes.

21 Q Can northern blotting be used to detect
22 the presence of a nucleic sequence in a sample?

1 A Northern blotting is specifically limited
2 to mRNAs or RNAs, but it is -- the purpose is to
3 both detect and quantify the abundance of mRNAs or
4 RNA species.

5 Q Is that the same case for southern
6 blotting but for DNAs in a sample?

7 A Southern blotting is usually a little more
8 complicated, because the fragments in southern
9 blotting depending on the sample would -- could be
10 too long to process properly. And thus southern
11 blotting normally is coupled with some typically
12 enzymatic digestion to create fragments of
13 specific lengths. And southern blotting is a
14 routine method for DNA sequencing in some
15 contexts, for example, using restriction fragment
16 length polymorphisms.

17 These techniques have been largely
18 replaced by modern sequencing approaches, but
19 southern blotting would be a classic method for
20 detecting the abundance and presence of a DNA
21 sequence.

22 Q So southern blotting is a method for

1 detecting the abundance and presence of a DNA
2 sequence by detecting DNA fragments; is that
3 right?

4 A Yes. And it can also be used for
5 determining the sequence of a DNA fragment in
6 various clever contexts.

7 Q Can immunohistochemistry be used to detect
8 the presence and abundance of a nucleic acid
9 sequence in a sample?

10 A Immunohistochemistry would normally be
11 used to detect a protein sequence, but I'm sure
12 there is someone who has figured out how to do
13 with nucleic acid.

14 Q Is branched DNA a technique that can
15 detect the presence and abundance of a nucleic
16 acid sequence in a sample?

17 A I've heard the term. I'm not deeply
18 familiar with branched DNA as in the way you are
19 using it. So I can't answer that without at least
20 a reference to look at.

21 Q What is your understanding of what
22 branched DNA is?

1 A I've heard its use in several different
2 contexts, and I'm not prepared to give you a
3 definition because I don't know what one you are
4 using it as.

5 Q Would a person of skill in the art
6 consider in situ hybridization to be a sequencing
7 technique?

8 A Given the proper designed experiment, yes.

9 Q Would a person of skill in the art
10 consider northern blotting to be a sequencing
11 technique?

12 A Again, given the proper design of the
13 experiment in both of these cases, yes. And for
14 example, the common way to determine HLA genotypes
15 is not by DNA sequencing but by antibody binding
16 to proteins expressed from sequences to determine
17 their underlying genotypes.

18 In the case of RNA expression, the way of
19 using it to determine the sequence would be to
20 look at RNA isoforms, which would be untied to
21 their underlying sequences.

22 So if -- if one had the proper experiment

1 and the proper experimental design, these two
2 approaches would be quite straightforward to
3 determine the sequence of an underlying molecule
4 or derivatives or a parent set of molecules.

5 Q When you say determine the sequence of an
6 underlying molecule or derivatives, do you mean
7 determine the presence of a specific sequence in
8 the sample?

9 A In this case, it would do both. So again,
10 with the HLA genotyping example I gave, one would
11 detect the presence of protein isoforms that are
12 tied to specific genotypes. And so the detection
13 of the protein of isoform X or Y or Z would tell
14 you the genotype X or Y or Z.

15 Q So you're not contending that the specific
16 genotype is being determined de novo without a
17 reference to some pre-existing database, right?

18 MS. KHANDURI: Objection, form.

19 A That is arguable. I strongly suspect that
20 in the case of the HLA genotypes they were first
21 implied by the ability to classify and detect the
22 proteins. So -- so I'm not sure how to answer

1 that.

2 I think the blood compatibility group
3 detection was often done by protein. And you may
4 have had the underlying protein sequence or you
5 might not have. You might have only classified
6 them by their antibody scheme. So today, it would
7 be very common if one were doing this to do so by
8 reference to a database, but essentially all
9 sequencing at this point is done by reference to
10 databases.

11 Q Did you review Dr. Sherman's declaration
12 in this case?

13 A Yes.

14 Q If you can bring up Dr. Sherman's
15 declaration, which is Exhibit 2008.

16 (Exhibit 2008 discussed.)

17 A Yes, I have it open.

18 Q And if you can go to paragraph 46, are you
19 there?

20 A Almost.

21 Q Okay.

22 A Paragraph 46, yes.

1 Q Right. Do you see the diagram that
2 Dr. Sherman prepared regarding Stahl's workflow?

3 A Yes.

4 Q Do you disagree with Dr. Sherman's diagram
5 as a depiction of Stahl's workflow?

6 A As a schematic for a POSA to understand
7 the process, it is reasonably accurate. Although
8 specific details of the protocol are abstracted or
9 simplified. And so it would depend on whether or
10 not you are asking about an explicit thing or just
11 as a general concept. As a general concept, it is
12 reasonable.

13 Q Are there any discrepancies between
14 Dr. Sherman's diagram and Stahl's workflow?

15 A Again, as I tried to explain, I think the
16 exact mechanics are -- sorry, the rough mechanics
17 are correct. The exact way it plays out is
18 abstracted to a simplified level and some of the
19 important details are limited in this diagram.

20 Q Are there any abstracted or simplified
21 details that you can elaborate on now?

22 A One very abstract thing that I understand

1 I think, why Dr. Sherman did, but plays into parts
2 of the conversation we were just having is that
3 Dr. Sherman has shown the lengths of all the
4 molecules to be the same and that is not correct.

5 At various points molecules are
6 potentially incomplete or fragmented or shortened.
7 And as a consequence it is not -- the drawings
8 here in which every molecule is a complete copy of
9 the preceding ones are not required for Stahl and
10 they are actually unlikely to occur in Stahl in
11 many cases. In some cases they absolutely occur
12 as drawn.

13 Q Is there a fragmentation step in Stahl's
14 workflow?

15 A To the best of my recollection, there is
16 not, but I'm not -- I would have to check very,
17 very carefully to be sure.

18 Q What did you mean that at various points
19 molecules are potentially incomplete or fragmented
20 or shortened that is not represented in the
21 diagram?

22 A Well, very simply in the very first step

1 Sherman has shown complete synthesis of the mRNA,
2 and I don't believe Stahl has a requirement for
3 that.

4 Q So you mean that in the tissue sample in
5 the first step there may be incomplete mRNA
6 molecules, is that what you are referring to?

7 A Well, there could be incomplete mRNA
8 molecules themselves, but the second step of
9 synthesizing first-strand cDNA does not have to
10 extend all the way to the 5 prime end of the mRNA.
11 It could stop short of that.

12 Q Then would those incomplete first-strand
13 cDNAs continue to go through the rest of Stahl's
14 workflow?

15 A Yes.

16 Q Would those incomplete first-strand DNAs
17 be eventually sequenced?

18 A Very plausibly, yes.

19 Q And would the sequencing data that came
20 from those incomplete first-strand cDNAs be useful
21 for determining the presence and abundance of that
22 transcript?

1 A As long as they encoded unique information
2 about the mRNA, yes.

3 Q Stahl uses capture probes to capture any
4 mRNA with a poly(A) tail, right?

5 A That -- that is their goal, yes.

6 Q So any transcript in the tissue sample as
7 long as it is poly-adenylated it can be captured
8 by the capture probe?

9 A That -- that is the design of Stahl,
10 absolutely.

11 Q And the sequence on the 5 prime end of
12 these captured transcripts that is not known,
13 right?

14 MS. KHANDURI: Objection, form.

15 A Your question is whether or not the 5
16 prime end when one is sequencing from, in this
17 orientation the top, whether or not that
18 particular sequence is a known sequence or not; is
19 that correct.

20 Q No, let me clarify.

21 My question is when mRNA transcripts are
22 captured by the capture probes, at that point it

1 is not known which transcript has been captured,
2 right?

3 MS. KHANDURI: Objection, form.

4 A At the point of capture essentially all
5 mRNAs that are poly-adenylated are available for
6 capture, for collection. I think -- I think that
7 is what your question is, and that would be the
8 answer.

9 Q And each of the mRNAs that have been
10 captured they can each have different 5 prime
11 sequences because they are different transcripts,
12 right?

13 MS. KHANDURI: Objection, form.

14 A Amongst the mRNAs, there are estimated to
15 be about 100,000 isoforms across the genome,
16 perhaps more, perhaps less for poly-adenylated
17 transcripts, something in that ballpark. But in
18 any given tissue or cell type, the number is
19 generally considered to be quite a bit lower,
20 perhaps 10 or 20,000 transcripts with unique --
21 with -- and the number of unique 5 primes ends of
22 those transcripts would be even smaller perhaps, 5

1 to 10,000 commonly with any given cell type.

2 In this particular case, Stahl's mRNA may
3 or may not be complete, and the cDNA produced from
4 that mRNA may or may not be complete. And
5 therefore, both the 3 prime end of the attached
6 DNA/cDNA construct in step 2 can have different
7 ends even for the same parent mRNA.

8 Q Even with about 10,000 different
9 transcripts in a type of tissue, knowing the first
10 or any -- any sequence of about 20 bases is
11 sufficient to determine the identity of the parent
12 mRNA; is that right?

13 MS. KHANDURI: Objection, form.

14 A 20 base pairs to perhaps 30 base pairs
15 would normally be sufficient to identify the gene
16 that an mRNA was derived from. Over the past, you
17 know, 20 to 30 years there has been a substantial
18 separation between the idea of genes and
19 transcripts, because many genes have many
20 transcript isoforms. And it would be very
21 uncommon that 20 or 30 or even 100 base pairs of
22 mRNA sequence would uniquely identify a transcript

1 isoform, but in the vast majority of cases it
2 would identify the gene accurately.

3 Q I see. So knowing 20 to 30 base pairs of
4 an mRNA sequence is enough to identify the gene,
5 but 100 base pairs is not enough to determine the
6 specific isoform of a transcript?

7 MS. KHANDURI: Objection, form.

8 A Generally speaking, that is correct.

9 MS. KHANDURI: Can we take a break soon?

10 MR. CHEUNG: Oh, yeah, we have been have
11 been going for about an hour, sure. Let's take a
12 break.

13 (Recess, 1:03 to 1:14 p.m.)

14 Q Dr. Spellman, during the break, did you
15 speak with anyone about the substance of this
16 deposition?

17 A No.

18 Q If you can turn to page 3 of the
19 supplementary materials of Stahl. Are you there?

20 A Yes, I'm on page 3.

21 Q Do you see the heading Surface spatially
22 barcoded oligonucleotides followed by a sequence?

1 A Yes.

2 Q Is the sequence depicted here on page 3 of
3 the supplementary materials the 5 prime sequence
4 of the first-strand cDNA?

5 A Sorry, I'm not sure what your question is.

6 Q During the first reverse transcription
7 reaction in Stahl's workflow, the capture probe is
8 extended to result in the first-strand cDNA,
9 right?

10 A This oligonucleotide bound to the surface
11 would be extended by reverse transcriptase from
12 the VN sequence and continue onward into -- the
13 copying the mRNA onto the molecule.

14 Q So the sequence of the first-strand cDNA
15 starting on the 5 prime end is the sequence of the
16 surface bound oligonucleotide shown on page 3 of
17 the supplementary materials; is that correct?

18 A The figures shown in the Sherman model
19 that we were just looking at, the black sequence
20 is this sequence listed here. And this sequence
21 would then be incorporated into the final
22 first-strand DNA product that is a -- that we can

1 call the cDNA, if you like.

2 Q So you agree that the black portion of the
3 first-strand cDNA has the sequence of the capture
4 probe, yes?

5 A Yes. I think I testified to that already
6 that the -- that the conjugated oligonucleotide
7 bound at the 5 prime end by AmC6, and then
8 including these uracil region. And then the
9 specific sequence including the a teamer spatial
10 barcode that is not specified as well as a series
11 of partially patterned bases followed by the Oligo
12 (dT) partially pattern basis and then an
13 unpatterned base at the very 3 prime end.

14 I think that would be the 3 prime end
15 where it is listed as an N, would be the point of
16 extension by reverse transcriptase copying the
17 captured mRNA.

18 Q What is the sequence on the 3 prime end of
19 the first-strand cDNA?

20 A I believe it is described as the
21 conjugation chemistry. I would have to look up
22 what the AM stands for, but it is the attachment

1 point to the array. And then the 5 Us are not DNA
2 bases typically. I mean they might be deoxy uri,
3 I would have to check, but they're not canonical
4 DNA bases. They're the uracils used for the
5 cleavage reaction later on.

6 Q Dr. Sherman -- I mean, Dr. Spellman, I was
7 asking about the 3 prime end of the entire
8 first-strand cDNA. So the red portion of what is
9 depicted in Dr. Sherman's diagram.

10 A Would you like me to go back to the
11 Sherman declaration?

12 Q If it would be helpful for you, you can
13 bring that up. That was Exhibit 2008. The
14 diagram we were discussing is at paragraph 46.

15 A Yes, I'm there, so what is your question?

16 Q What is sequence of the first -- the 3
17 prime end of the first-strand cDNA or what is
18 depicted in red in that diagram?

19 A It would be the reverse complement of the
20 mRNA captured, bound and extended at the end of
21 the cDNA.

22 Q And when the second-strand cDNA is

1 synthesized, what is the sequence of the 5 prime
2 end of that second-strand cDNA?

3 A To the best of my ability to recall in the
4 Stahl method, the second-strand cDNA is
5 synthesized by random examers binding to what is
6 listed as the minus strand of the cDNA, and that
7 is commonly a random hexamer. And therefore, it
8 would be a random sequence six base pairs in
9 length that is in a mixture of oligonucleotides
10 used to hybridize and extend to make second-strand
11 DNA.

12 Q So random hexamers are used to prime the
13 synthesis of the second-strand cDNA; is that
14 right?

15 A That is my recollection.

16 Q So if random hexamers are used as primers
17 for synthesis of the second-strand cDNA, then does
18 that mean the second-strand cDNA formed from
19 copies of the same transcript can end up with
20 different sequences because of the use of the
21 random hexamers?

22 MS. KHANDURI: Objection, form.

1 A It would be expected, yes.

2 Q As you explained earlier, even though
3 these second-strand cDNAs can be slightly
4 different because of the use of random hexamers,
5 knowing the sequence of 20 to 100 base pairs would
6 be sufficient to determine the identity of the
7 transcript, right?

8 A I mean, I think what I said was the gene,
9 but not necessarily the transcript.

10 Q Right. The gene can be identified but not
11 necessarily the specific isoform of the
12 transcript, right?

13 A That is correct.

14 Q Do you see that at what has been labeled
15 step 6 of Dr. Sherman's diagram of Stahl's
16 workflow there is the addition of a ligation
17 adapter to the 3 prime end of the amplified RNA?

18 A Yes.

19 Q Do you agree that ligation adapters are
20 added to the 3 prime end of amplified RNA
21 molecules?

22 A Stahl's protocol depends at this step on

1 the ligation of an adapter to the 3 prime end of
2 amplified RNAs, yes.

3 Q And if you go back to Stahl as Exhibit
4 1016 and go to supplementary materials page 8.

5 A Yes.

6 Q Do you see that the sequence of the
7 ligation adapter is listed on that page?

8 A Yes.

9 Q Do you see that the sequence of the second
10 reverse transcription primer is also listed on
11 that page?

12 A I do.

13 Q Do you agree that the second reverse
14 transcription primer has -- is a reverse
15 complement of the ligation adapter?

16 A It is not complete, but yes, the start of
17 it is the same. I don't think it is complete, no.

18 Q Right. Do you agree that the second
19 reverse transcription primer has a reverse
20 complementary sequence to the ligation adapter
21 except for three nucleotides AGA?

22 A That appears correct without drawing it

1 out and being absolutely sure, but yes, that looks
2 correct.

3 Q So do you agree that during the second
4 reverse transcription reaction that takes place in
5 Stahl's workflow, the second reverse transcription
6 primer hybridizes to the sequence of the ligation
7 adapter?

8 A Yes, that is how the Stahl workflow is
9 designed. Just as a technicality, I believe there
10 is an additional C at the 3 prime end of the
11 ligation adapter that is -- that is also there,
12 but other than that, yes. It is dideoxy-C, so
13 that it doesn't extend, but it is a technical
14 detail.

15 Q If I could direct you one page up to page
16 7 of the supplementary materials in Stahl. Do you
17 see about the middle of the page there is a
18 sentence that states, a total reaction volume of
19 10 microliter containing 1XKAPA HiFi HotStart
20 ReadyMix 1X EVA green, 0.5 micromolar PCR InPE
21 1.0, 0.01 micromolar PCR InPE2.0, 0.5 micromolar
22 PCR index and 2 microliter purified cDNA were

1 amplified by qPCR with the following protocol.

2 Do you see that?

3 A Yes.

4 Q Do you agree that after reverse
5 transcription of the amplified RNA and
6 amplification reaction is performed that adds the
7 sequencing adapters InPE1.0, InPE2.0 and PCR
8 index?

9 A This specific reaction you are pointing to
10 is a -- is an efficiency step. So no, this
11 particular step is not part of the downstream
12 workflow. It is a step to measure how much of the
13 -- of the reverse transcribed product there is.

14 Q I'm going to direct you to the next
15 sentence which has, after determining the amount
16 of cycles needed based on the qPCR, the samples
17 were amplified in a total reaction volume of 25
18 microliters. Do you see that?

19 A Yes.

20 Q And then the following sentence starts
21 with the libraries and then continues on, do you
22 see that?

1 A Yes.

2 Q So do you agree that the amplification of
3 the sample to a total reaction volume of 25
4 microliters results in the library?

5 A No.

6 Q So when in Stahl's workflow when it refers
7 to the libraries were purified, what is the
8 libraries?

9 A Well, I think I'm being -- you misread the
10 sentence above, and -- and so it was not
11 grammatically correct.

12 If you are asking does the PCR that is
13 described in the sentence after determining the
14 amount continuing onward, does that result in a
15 PCR reaction that can then be carried forward into
16 the rest of the protocol, the answer is yes.

17 Q In the PCR reaction where samples are
18 amplified in a total reaction volume of 25
19 microliters, are the samples during that PCR
20 appended with the sequences of the PCR primer
21 InPE1.0, PCR primer InPE2.0 and PCR index primer?

22 A The question is a little complicated,

1 because it appears that in this step while PCR
2 would normally use one or two primers, in this
3 particular case there is a third primer.

4 Q Okay, let's take a step back.

5 During the PCR reaction where samples are
6 amplified in a total reaction volume 25
7 microliters, does that PCR reaction involve the
8 use of three primers which are PCR primer InPE1.0,
9 PCR primer InPE2.0 and PCR index primer?

10 A Okay. Yes, I've worked out how the
11 primers relate to one another. The reaction uses
12 all three primers, yes.

13 Q Let's talk specifically about this
14 amplification reaction. During this amplification
15 reaction, do you agree that PCR primer InPE2.0
16 binds to the sequence on the amplified RNA
17 corresponding to the ligation adapter?

18 MS. KHANDURI: Objection, form.

19 A I think it would be more accurate to say
20 that PCR primer InPE2.0 binds to DNA copies of the
21 ligation adapter after the first-strand of PCR has
22 occurred.

1 Q Do you mean the first cycle of PCR has
2 occurred?

3 A Yes. In this particular application,
4 there is only one DNA strand going into PCR,
5 whereas, it is common in PCR to have
6 double-stranded DNA. But as I understand it, the
7 first -- the only strand going into this is the
8 product of the second reverse transcription primer
9 as a cDNA. And so the input into the PCR is not
10 an RNA molecule, but only the cDNA molecule which
11 is single stranded.

12 So I was trying to be more precise in
13 describing that PCR primer InPE2.0 would bind to
14 the second strand of the cDNA being manufactured
15 here in the reverse complement orientation to the
16 ligation adapter.

17 Q I see, yeah, okay. Thanks for that
18 clarification.

19 So in the first cycle of the amplification
20 reaction, the single-stranded cDNA becomes
21 double-stranded due to the PCR primer InPE1.0; is
22 that right?

1 A Yes, that would be correct.

2 Q And then on the second cycle of that
3 amplification reaction, then the PCR primer
4 InPE2.0 can hybridize to the copy of the cDNA that
5 was generated in the first cycle; is that right?

6 A Yes. In cycle 2 both PCR primer InPE1.0
7 and PCR primer InPE2.0 now have reverse complement
8 sequence to bind -- sequences to bind to and both
9 reactions can occur.

10 Q And does the PCR index primer bind to the
11 same strand that the PCR primer InPE2.0 bind to
12 during the cycles of amplification?

13 A Yes. Once there is sufficient amount of
14 product containing the GTG ACT PCR primer InPE2.0
15 present, then the PCR index primer can bind to its
16 reverse complement through the same set of
17 sequences, which appear to be 13 or so bases long.

18 Q So the product of the amplification
19 reaction after all the cycles are completed, does
20 that product when compared to the single-stranded
21 cDNA at the start of the amplification reaction,
22 does the end product have the extended sequence of

1 PCR primer InPE1.0 on one end and the tail
2 sequence of the PCR index primer on the other end?

3 MS. KHANDURI: Objection, form.

4 A In broad -- I mean, I think, I might have
5 phrased it a little differently, but -- but the --
6 all of the products that are produced will have
7 primer -- PCR primer InPE1.0 on one 5 prime end of
8 a strand and PCR index primer on the other 5 prime
9 end of the reverse complement strand.

10 Q And to clarify, the end of the product
11 with the sequence of the PCR index primer is the
12 end that corresponds to where the ligation adapter
13 was added to the amplified RNA?

14 MS. KHANDURI: Objection, form.

15 A That appears to be correct, yes.

16 Q So the tail sequence of the PCR primer
17 InPE1.0 is essentially added to the end of the
18 molecule corresponding to the spatial barcode?

19 A I would have to draw it out to be sure.

20 Q If I can point you back at the diagram at
21 paragraph 46 of Exhibit 2008.

22 A No, I understand what you are saying. I

1 just have to -- that diagram does not include PCR
2 primer InPE1, InPE2 or the index primer, and so I
3 would to draw it out to be sure.

4 Q Right, but do you have the diagram in
5 front of you?

6 A I currently have the Stahl supplement. I
7 understand that the diagram shows the ligation
8 adapter 1N, but I would have to draw it out to be
9 sure this is the -- this is the detail oriented
10 task.

11 Q But you agree that the tail of the PCR
12 index primer after the amplification reaction is
13 essentially added to the end of the molecule with
14 the ligation adapter, right?

15 MS. KHANDURI: Objection, form.

16 A The sequence GTGACTGGAGTTC is
17 complementary to the 3 prime end of the ligation
18 adapter absent the dideoxy-C at the end of the
19 ligation adapter. So it is consistent with it
20 binding at the same places, that end of the second
21 reverse transcription primer adding on the
22 sequences CAAG blah blah blah XXX.

1 Q So the sequence of the PCR primer InPE1.0
2 that would be added to the opposite end of that
3 molecule before amplification reaction, right?

4 MS. KHANDURI: Objection, form.

5 A That appears correct.

6 Q So looking at just the 5 prime sequence,
7 so one end of the product has that PCR primer
8 InPE1.0, the AATGATAC and so forth. And the other
9 end, when you are looking at the 5 prime, has the
10 PCR index primer sequence of CAAGCAGAA and so
11 forth, right?

12 A That would appear to be correct, yes.

13 Q And when this amplification product with
14 the sequences we have just described added on,
15 when that is loaded on to the Illumina NextSeq
16 platform, does reading from the end with the
17 sequence of the PCR primer InPE1.0 correspond to
18 read one of Illumina paired-end sequencing?

19 A I would have to check the primer
20 sequences.

21 Q Do you know whether sequencing that
22 amplification product where the sequence of the

1 PCR index primer is attached to the flow cell
2 corresponds to read one of the Illumina paired-end
3 sequencing workflow?

4 MS. KHANDURI: Objection, form.

5 A I can read through the Stahl reference to
6 tell you which one is which if you like. I
7 suspect it is described, otherwise I would have to
8 look it up in another reference.

9 Q But you agree that reading from one end of
10 the molecule would correspond to read one and
11 reading from the other end would correspond to
12 read two of a paired-end sequencing workflow?

13 MS. KHANDURI: Objection, form.

14 A The final molecules on the sequencer and
15 their orientations would naturally flow in the way
16 you have described. The exact mechanics of
17 individual molecules binding to the flow cell and
18 being sequenced on the flow cell I think are being
19 abstracted by the question, but the -- the overall
20 concept as described is correct.

21 Q But sitting here today, you are not
22 certain which side of the molecule is read one and

1 which side is read two; is that right?

2 MS. KHANDURI: Objection, form.

3 A I would have to go through the Stahl
4 reference in close detail and then cross index it
5 against other references in the case. I know that
6 the p5 and p7 sequences are provided in other
7 documents.

8 Q One side of these amplified reaction
9 products would correspond to what you refer to as
10 a p5 sequence and the other end would correspond
11 to a p7 sequence; is that right?

12 A That would be the normal Illumina
13 workflow, yes.

14 (Exhibit 1055 discussed.)

15 Q If you can bring up Exhibit 1055, which
16 should be your reply declaration in this case?

17 A Yes, I have 1055 up.

18 Q Okay. If I can direct you to paragraph
19 34, let me know when you are there.

20 A Yes, I'm at 34.

21 Q Do you see the first sentence where you
22 state, as explained in my first declaration, the

1 first-strand cDNAs (the DNA products of claim 1's
2 steps (c) and (d) are the entire molecules
3 comprising the sequence of the capture probe and
4 the sequence of the synthesized DNA.

5 Do you see that sentence?

6 A Yes.

7 Q You don't disagree with that sentence, do
8 you?

9 A No.

10 Q If I can direct you to paragraph 68 of
11 your declaration. Let me know when you are there.

12 A Yes.

13 Q I will direct you to the last sentence of
14 paragraph 68. You have a similar sentence, and I
15 quote, and, as explained in my first declaration,
16 the first-strand cDNAs (the DNA products of claim
17 1's steps (c) and (d)) are the entire molecules
18 comprising the sequence of the capture probe and
19 the sequence of the synthesized DNA.

20 Do you see that?

21 A Yes.

22 Q You don't disagree with that sentence, do

1 you?

2 A No.

3 Q Is it your opinion that in your first
4 declaration you identified the first-strand cDNAs
5 in Stahl, the entire strand including the capture
6 probe and the synthesized cDNA as the DNA products
7 of claim 1's steps (c) and (d)?

8 MS. KHANDURI: Objection, form.

9 A Under the initial infringement position
10 and my understanding of the -- of the terms at the
11 time, I believe that that is correct.

12 Q So at this time, is it your understanding
13 that the first-strand cDNAs in Stahl, the entire
14 strand including the capture probe and the
15 synthesized cDNA is the DNA products of claim 1's
16 steps (c) and (d)?

17 A I'm going to go to my copy of my
18 declaration, if that is okay. It is clean.

19 Q Yeah, that is fine.

20 A So under claim construction in paragraph
21 -- in paragraph 6 through, I believe, 11, I have a
22 longer conversation about the synthesis products

1 of claim 1 and the DNA products that are the
2 endpoint. And under the initial infringement
3 positions and my initial interpretations of the
4 claims as written, the paragraph 68 statement here
5 is correct. Given Bruker's IPR positions and the
6 Board's construction of the synthesis step, I have
7 an alternate set of conclusions based on those
8 positions -- claim construction conditions.

9 Q So in your first declaration where you
10 explained that the first-strand cDNAs are the
11 entire molecules comprising the sequence of the
12 capture probe and the sequence of the synthesized
13 DNA as the DNA products of claim 1's step (c) and
14 (d) is based on your initial interpretation of the
15 claims as written; is that right?

16 MS. KHANDURI: Objection, form.

17 A And the infringement position of
18 NanoString at the time.

19 Q And in your reply declaration, has your
20 interpretation of the claims and the infringement
21 position of Bruker changed from when you prepared
22 your first declaration?

1 A When I prepared my declaration, Bruker's
2 IPR position was unavailable to me. Additionally
3 the Board's claim construction of the term
4 synthesis in claim C -- in claim 1, (c) and (d)
5 was unavailable to me. And I've updated and
6 expanded my interpretations and opinions based on
7 additional guidance provided by the Court and
8 others so far.

9 Q But you maintain the positions stated in
10 your first declaration, right?

11 A Absent the Court's -- absent the Court's
12 claim construction on the term -- on claim -- on
13 the steps (c) and (d) of claim 1, I believe that
14 my interpretation of the claims as written and the
15 infringement position as applied is appropriate.

16 Q Is the Board's claim construction on the
17 synthesizing term different from the
18 interpretation you applied in your first
19 declaration?

20 A Reading from page 5 of my reply, the Board
21 interpreted synthesizing DNA products as follows:
22 We interpret "synthesizing DNA products"

1 consistent with its usage in claim 1 as amplifying
2 the collected plurality of oligonucleotides
3 released after application of a force from the
4 location of the sample using primers that have, 1,
5 have binding sites on the collected
6 oligonucleotide and, 2, contain
7 location-identifying, identifying nucleic acid
8 sequences that are incorporated into the DNA
9 product upon synthesis.

10 Continuing on, we apply this construction
11 and interpret synthesizing DNA products not to
12 require direct replication of the first cDNA
13 strand and only the strand to create the end
14 product as patent owner urges.

15 Because of that, that is a different
16 interpretation of what the claim appears to read
17 in plain and ordinary language, and therefore, I
18 have provided both opinions using what I
19 interpreted as the plain and ordinary language in
20 conjunction with the infringement position of
21 NanoString at the time in my first declaration and
22 now updated based on the IPR positions taken by

1 Bruker as well as the Board's claim construction
2 on -- on this step.

3 Q In your reply declaration, is it correct
4 to say you have presented two positions, one based
5 on the plain and ordinary language in conjunction
6 with the infringement position of NanoString at
7 the time in your first declaration and the second
8 position is the one based on the IPR positions
9 taken by Bruker as well as the Board's claim
10 construction on the synthesizing step?

11 A I think I said it best in the reply
12 declaration itself, but that sounds like an
13 accurate summary of my positions in my reply
14 declaration.

15 Q If I can direct you to paragraph 125 of
16 your reply declaration.

17 A Yes, I'm at paragraph 125 of my hard copy.

18 Q Do you have any notes in your hard copy of
19 the reply declaration?

20 A I do not. It is a clean copy that I
21 printed myself.

22 Q Do you see the first sentence in paragraph

1 125 which ends with the phrase, "with the
2 resulting first-strand cDNAs (DNA products of
3 steps (c) and (d) of claim 1) incorporating
4 spatial barcodes"?

5 A Yes.

6 Q So is it your opinion in your first
7 declaration that the first-strand cDNAs in So-456,
8 is the claimed DNA products of steps -- claim 1(c)
9 and 1(d)?

10 A As I believe it very clearly states there,
11 I would -- I would agree with that statement that
12 in paragraph 125 I identify the reverse
13 transcribes molecule as -- as the -- as the DNA
14 products of claim 1.

15 Q And similar to the case with Stahl, do you
16 present two positions on -- two positions on --
17 one based on your initial interpretation of the
18 claim terms along with NanoString's infringement
19 contentions and a second position based on the
20 Board's construction and Bruker's IPR position?

21 A That is correct. I had neither Bruker's
22 IPR position nor the Board's claim construction at

1 the time of writing my initial opinion, and so I
2 have also used those claim constructions to
3 provide opinions.

4 Q If you can bring up paper 25, that would
5 be the Board's decision on instituting IPR in this
6 case. Let me know when you have it up?

7 A Yes.

8 Q Have you reviewed this document?

9 A I believe that I did.

10 Q If I can direct you to page 21.

11 A Yes, I'm on page 21.

12 Q Okay. Do you see the last paragraph of
13 page 21 that spills over to the next page that
14 starts at, we interpret synthesizing DNA products.
15 Do you see that?

16 A I do.

17 Q I believe the beginning of this paragraph
18 is what you cite in your reply declaration that
19 you read off earlier; is that right?

20 A That looks correct, yes.

21 Q Is there any part of the Court's
22 construction here in this paragraph for construing

1 synthesizing a first plurality and second
2 plurality of DNA products by performing a
3 synthesis reaction that you disagree with?

4 A We're starting at the bottom of page 21
5 and going downward?

6 Q Yes, just that paragraph starting at the
7 bottom of 21 and spilling over to the first half
8 of page 22?

9 A So ending with Federal Circuit 2003; is
10 that correct?

11 Q Correct, yes.

12 A This seems like a reasonable position.

13 Q And you stated earlier that you applied
14 the Board's construction here in your -- the
15 alternate position in your reply declaration; is
16 that right?

17 A I believe that's correct.

18 Q And moving onto the next paragraph on page
19 22, so the one that says -- it starts with, our
20 interpretation on the record before us is
21 consistent with the specification disclosure
22 stated above and so forth. Do you see that

1 paragraph?

2 A Yes.

3 Q Do you agree with the Board's explanation
4 of its construction as stated here in this
5 paragraph of the claim term synthesizing a first
6 plurality and second plurality of DNA products by
7 performing a synthesis reaction?

8 A Which specific phrase are you pointing to?

9 Q Well, there is only one sentence in this
10 paragraph, so the entire sentence. That the
11 Board's construction is consistent with the
12 specifications disclosure stated above, and also
13 consistent with patent owner's infringement
14 contentions where patent owner identifies
15 synthesizing DNA products as covering a multistep
16 amplification process resulting in a DNA product
17 containing location-identifying nucleic acid
18 sequences.

19 Is there any part of that sentence that
20 you disagree with?

21 A I have no basis to disagree with the
22 Board's interpretation here.

1 Q Do you see that as support for that
2 sentence the board cites to Exhibit 1022,
3 specifically Step 1, permeabilization and reverse
4 transcription, step 2, second-strand synthesis and
5 denaturization and step 3, probe release and
6 extension?

7 A I see that.

8 Q Do you see that the Board identified these
9 three steps in NanoString's infringement
10 contentions as support that patent owner
11 identified a multistep amplification process
12 resulting in a DNA product containing
13 location-identifying nucleic acid sequences?

14 A The Board is using the infringement
15 position, I believe, to -- to make that
16 determination of mapping, if I understand it
17 properly.

18 Q Do you agree with the Board's
19 interpretation?

20 A I'm not sure that I think the Board is
21 limiting the multistep amplification process to
22 just the steps 1, 2 and 3 as given the

1 infringement contentions, but is using steps 1, 2
2 and 3 as the basis for understanding the
3 infringement contentions.

4 And so perhaps I would suggest that the
5 Board's ultimate interpretation would depend on
6 more than steps 1, 2 and 3, but I would have to
7 consider that more deeply.

8 Q Do you disagree with the Board's
9 interpretation?

10 A I would have to consider that more deeply.

11 Q Do you see that citation the Board
12 referred to is page 9 of 12 of Exhibit 1022 for
13 steps 1, 2 and 3?

14 A Yes.

15 (Exhibit 1022 discussed.)

16 Q Can you bring up Exhibit 1022 and go to
17 page 9?

18 A 9 as marked or 9, true 9?

19 Q That is a good question. Let's --

20 A 9 as marked is blank, so I'm assuming it
21 is true 9. No, now I'm not sure.

22 Q Yeah, I think it is the smaller 9 and not

1 -- or it looks like it is also marked page 18
2 like, page 18 of the PDF?

3 A Yes, I'm there.

4 Q Do you see that step 1 refers to a
5 permeable ligation and reverse transcript step in
6 the Visium Fresh-Frozen product?

7 A I do.

8 Q Do you see that at the end of step 1, the
9 product is a spatially barcoded full-length cDNA
10 from poly-adenylated mRNA on the slide?

11 A Yes.

12 Q And step 2 is a second-strand synthesis
13 and denaturing step, do you see that?

14 A Yes.

15 Q And the end of step 2 is a denatured cDNA
16 molecule that is transferred off of the captured
17 area?

18 A Step 2 is a second-strand synthesis
19 followed by a denaturation and transfer to a
20 corresponding 2, yes.

21 Q Do you agree that the Board found that
22 Bruker identified the second-strand cDNA in the

1 Visium Fresh-Frozen product as the claimed DNA
2 product?

3 A That is my understanding.

4 Q Do you understand that Dr. Sherman
5 proposed a construction for the claim term
6 synthesizing a first plurality and second
7 plurality of DNA products by performing a
8 synthesis reaction?

9 A Yes.

10 Q If you can bring up Exhibit 2008, which is
11 Dr. Sherman's declaration, and go to paragraph 35.

12 A Okay, I'm at paragraph 35.

13 Q Do you see that Dr. Sherman's construction
14 of the claim term synthesizing a first plurality
15 and second plurality] of DNA products while
16 performing a synthesis reaction, is that it should
17 have its plain and ordinary meaning?

18 A I do see that, yes.

19 Q Do you agree that the claim term
20 synthesizing a first plurality and second
21 plurality of DNA products by performing a
22 synthesis reaction should have its plain and

1 ordinary meaning?

2 A I discuss this in paragraph 12 and further
3 in my reply declaration, and no, I do not.

4 Q Do you see the last sentence in that
5 paragraph where Dr. Sherman states, a POSA would
6 not have had difficulty interpreting this claim
7 term?

8 A I do see that, yes.

9 Q Do you agree that a POSA would not have
10 had difficulty interpreting this claim term?

11 A I think that Dr. Sherman has failed to
12 recognize that the infringement positions of
13 Bruker, the IPR positions of Bruker and the
14 Board's definition are harmonizing together to
15 identify an interpretation of this element that is
16 far beyond the plain and ordinary meaning of the
17 terms.

18 Q So is it your opinion that the
19 synthesizing claim term should not have its plain
20 and ordinary meaning?

21 A As I've stated, the claim term must be
22 considered in the context of the infringement

1 positions minimally, which the patent owner's --
2 sorry, the IPR position taken by Bruker and the
3 Board, and therefore, harmonizing those yields an
4 interpretation of the language that is not the
5 plain and ordinary language absent interactions
6 between that and other elements of the claim -- of
7 other elements of the patent, other claims of the
8 patent, my apologies.

9 MS. KHANDURI: Counsel, can we take a
10 break now?

11 MR. CHEUNG: Yes, that is fine. Let's
12 take a break.

13 (Recess, 2:29 to 2:39 p.m.)

14 Q Dr. Spellman, during the break, did you
15 speak with anyone about the substance of this
16 deposition?

17 A No.

18 Q Before the break, we were talking about
19 claim construction of the synthesizing step. In
20 your declaration, either the first declaration or
21 your reply declaration, do you offer your
22 construction of the synthesizing claim term?

1 MS. KHANDURI: Objection, form.

2 A I have a fairly lengthy discussion in my
3 initial declaration or, I'm sorry, a short
4 discussion in my initial declaration about claim
5 construction given my understandings, and then --
6 and then whether or not there is controlling
7 definitions.

8 And then I used those interpretations in
9 context of -- in my initial declaration, the
10 infringement positions of NanoString and my reply
11 declaration I used the Board's construction of
12 this term as well.

13 Q So what is your interpretation of the
14 claim term, synthesizing a first plurality and
15 second plurality of DNA products by performing a
16 synthesis reaction?

17 A In my initial declaration, I used the
18 plain and ordinary definition and the infringement
19 position of NanoString at the time to understand
20 steps (c) and (d) synthesizing a plurality by
21 performing a synthesis reaction. And then it goes
22 on, that uses the plurality of oligonucleotides

1 collective step (a), and in that context I
2 understood that the synthesis reaction should be
3 direct, directly utilizing the oligonucleotides.

4 There is an additional clause on including
5 the identifier and I rendered an opinion on that
6 individually. And that is the end of steps (c)
7 and (d).

8 Q Is the interpretation in your initial
9 declaration beyond the plain and ordinary meaning
10 of the term?

11 A It is in conjunction with the infringement
12 position of NanoString at the time.

13 Q So is your interpretation of the
14 synthesizing claim term in your initial
15 declaration the plain and ordinary meaning of the
16 term?

17 MS. KHANDURI: Objection, form.

18 A I will reiterate that it is in the context
19 of NanoString's infringement position.

20 (Exhibit 1044 discussed.)

21 Q I'm going to direct you to paragraph 27 in
22 Exhibit 1044, your first declaration in this case.

1 A Paragraph 27?

2 Q Yes.

3 A Yes.

4 Q And do you see that you state that, I
5 understand that in an IPR, patent claim terms are
6 given their ordinary and customary meaning as
7 understood by a POSA at the time of the invention
8 in view of the patent's specification and its
9 prosecution history. Do you see that?

10 A Yes.

11 Q So my question is is it your
12 interpretation of the language of the synthesizing
13 step the ordinary and customary meaning as
14 understood by a POSA at the time of the invention
15 in view of the patent's specification and its
16 prosecution history?

17 A I believe I've answered this question, and
18 I believe the answer that I gave was that it is in
19 context of the infringement position of NanoString
20 as well as the plain and ordinary meaning and
21 customary understanding of a POSA at the time.

22 Q So to clarify, so your interpretation of

1 the synthesizing claim step is the plain and
2 ordinary meaning in context of the infringement
3 position of NanoString; is that right?

4 A At the time, yes.

5 Q And your interpretation of the
6 synthesizing claim step is that also applied in
7 your reply declaration?

8 A Those elements of my interpretation of the
9 claims prior to the Board construction and the
10 previous IPR position of Bruker goes under the
11 infringement interpretations are -- are the plain
12 and ordinary meaning in the context of Bruker's
13 infringement interpretations as I state in my
14 reply declaration.

15 Q I'm going to direct you to your reply
16 declaration, if you can go to paragraph 12.

17 A Yes, I'm at paragraph 12.

18 Q Is it your opinion that the synthesizing
19 step in claim 1 includes amplifying?

20 A In the context of the specification, the
21 claims and Bruker's infringement positions, yes.

22 Q Is it your opinion that a POSA would find

1 that the word synthesizing is equivalent to
2 amplifying?

3 A Given the infringement positions, the use
4 of the term amplifying, and the -- and the
5 references throughout the specification, I believe
6 that they would understand that synthesizing is a
7 sub -- that amplifying is a form of -- sorry, that
8 synthesizing includes amplifying.

9 Q Is it your opinion that a POSA would
10 understand synthesizing to include amplifying but
11 not that the two are equivalent?

12 A In paragraph 13 of my reply, I note that
13 the Board accurately understands that synthesis
14 reactions using an oligonucleotide as a template
15 are a copying reaction, and I believe that POSA
16 would recognize that as well. And that the first
17 round of a copying reaction is the first step of
18 an amplification reaction. It produces additional
19 molecules that are reverse complements of the --
20 of the initial molecule, and thus, you have more
21 material than you had after the synthesis reaction
22 started.

1 Q So would a POSA understand that if a
2 synthesis reaction was not templated then it would
3 not be a form of amplification?

4 A That is a good question. I don't think it
5 matters, because in this case the synthesis
6 reactions are templated.

7 Q Can you provide an opinion now on whether
8 a POSA would understand that a non-templated
9 synthesis reaction would include or not include
10 amplification?

11 MS. KHANDURI: Objection, form, relevance.

12 A I'm not sure about the question and I
13 think it would be up to the POSA and the specific
14 context under which they're considering things,
15 but in general an amplification reaction should
16 take -- using nucleic acid, should take a small
17 amount of the nucleic acid and produce more of the
18 nucleic acid and it could switch back and forth
19 between DNA and RNA as appropriate.

20 Q So a POSA would not consider a synthesis
21 reaction without a template to be an amplification
22 reaction even though more of the nucleic acid is

1 being produced?

2 MS. KHANDURI: Objection, form, relevance.

3 A Well, I think it is not more, it is that
4 there is any. A synthesis reaction without a
5 template has nothing to start with. Amplification
6 being copying or replication, copies of nothing
7 are nothing. So I think a POSA would, depending
8 on context, probably not view that as an
9 amplification reaction. All of this is in context
10 of the specification and the -- and the
11 infringement positions by NanoString.

12 Q Do you understand that the Board issued a
13 preliminary construction of the claim term
14 identifying the first plurality of DNA products
15 and the second plurality of DNA products
16 synthesized in step (c) and step (d) by
17 sequencing?

18 A Yes.

19 Q I am going to direct you to paper 25 and
20 please go to page 28.

21 A Page 28, yes.

22 Q Do you see the Board's construction in the

1 first complete paragraph of page 28?

2 A I do.

3 Q Is there any part of the Board's
4 construction of the claim term identifying the
5 first plurality of DNA products and the second
6 plurality of DNA products synthesized in step (c)
7 and step (d) by sequencing that you disagree with?

8 A Given the infringement positions, the IPR
9 positions taken by Bruker, I do not disagree with
10 this construction. I think it is reasonable.

11 Q Did you apply the Board's construction of
12 the claim term identifying the first plurality of
13 DNA products, the second plurality of DNA products
14 synthesized in step (c) and step (d) by sequencing
15 in the opinions in your reply declaration?

16 A In my reply declaration, when utilizing
17 the Board's claim construction, I use the Board's
18 claim construction as -- as described in paragraph
19 19, page 9 of my reply declaration locating the
20 specific analyte within the tissue sample by
21 correlating the DNA product using the
22 location-identifying nucleic acid sequences.

1 Q I will direct you to the next paragraph on
2 page 28 of paper 25, which has -- which states
3 accordingly, for purposes of this decision, we
4 applied this construction and interpret
5 synthesizing DNA products not to require direct
6 replication of the first cDNA strand and only this
7 strand to create the end product as patent owner
8 urges.

9 Do you see that paragraph?

10 A I do.

11 Q Do you agree with the Board's
12 interpretation of its construction of the
13 synthesizing DNA products claim term?

14 A Given the IPR position, the infringement
15 position, I do not disagree with this.

16 Q Do you understand that Dr. Sherman
17 proposed a construction for the claim term
18 identifying the first plurality of DNA products
19 and a second plurality of DNA products synthesized
20 in step (c) and step (d) by sequencing?

21 A I do.

22 Q If you can bring up Exhibit 2008 and go to

1 paragraph 26?

2 A Yes.

3 Q Do you see that Dr. Sherman's opinion on
4 the construction of the identifying a first
5 plurality [and second plurality] of DNA products
6 by sequencing, term is stated here in paragraphs
7 26 through 29?

8 A I do.

9 Q Do you see that Dr. Sherman's construction
10 for the identifying claim term is that it should
11 have its plain and ordinary meaning?

12 A I do.

13 Q Do you agree that the claim term
14 identifying the first plurality of DNA products
15 and second plurality of DNA products synthesizes
16 step (c) and step (d) by sequencing should have
17 its plain and ordinary meaning?

18 A I think the concern is that Dr. Sherman is
19 using the plain and ordinary meaning not in the
20 context of the litigation at hand, not in terms of
21 the IPR position and not in terms of the
22 infringement positions and that the Board's

1 construction is attempting to resolve potential
2 issues between those topics, and thus, I favor the
3 Board's construction.

4 Q So is it your opinion that Dr. Sherman's
5 construction using the plain and ordinary meaning
6 is not in the context of this case, not in terms
7 of Bruker's IPR position and not in terms of the
8 infringement positions?

9 A In paragraph 21 of my reply declaration I
10 highlight how Dr. Sherman disagrees with the
11 Board. And I note that he specifically complains
12 that any method of determining the identity of DNA
13 products that does not involve sequencing. The
14 issue is that Dr. Sherman is attempting to lock in
15 the concept of direct determination of the DNA
16 sequencing failing to recognize the extremely long
17 history in molecular biology of indirect methods
18 that are incredibly useful and common.

19 And as a consequence, his comment that any
20 method of determining the identity of DNA products
21 does not involve sequencing is inherently
22 incorrect. That any method of determining the

1 identity of DNA products is sequencing. And so
2 the idea that one must do things in a direct
3 manner is anathema to molecular biologists when a
4 better method that may be indirect is available.

5 So determining the sequence of a DNA
6 product is something that can be done directly or
7 indirectly and it is inappropriate. And a POSA,
8 in my opinion, would not read it in a limiting
9 context.

10 Q Is it your opinion that determining the
11 sequence of a DNA product either directly or
12 indirectly is considered sequencing?

13 A Yes.

14 Q And is it your opinion that you disagree
15 with Dr. Sherman's construction that the
16 identifying step should have its plain and
17 ordinary meaning is that sequencing by indirect
18 methods is excluded?

19 MS. KHANDURI: Objection, form.

20 A I prefer the Board's construction, because
21 it makes clear that the interpretation of the
22 experiment is done by, as the Board says, locating

1 the specific target analyte within the tissue
2 sample by correlating the DNA product using the
3 location-identifying nucleic acid sequences.

4 Q Is the Board's construction of the
5 identifying claim term of correlating --
6 correlating using the location-identifying nucleic
7 acid sequences, is that the plain and ordinary
8 meaning of the claim term.

9 MS. KHANDURI: Objection, form.

10 A In the context of litigation at hand, the
11 infringement position taken by NanoString, the
12 IPR -- the IPR positions taken by Bruker, I
13 believe that the Board's construction is a more
14 accurate interpretation of the plain and ordinary
15 meaning of the claim as written.

16 Additionally I will point out, as I said
17 in paragraph number 21, Dr. Sherman disagrees with
18 the Board, because it allows any method of
19 determining the identity of DNA products. That is
20 sequencing. Determining the identity of DNA
21 products is sequencing the DNA products. And it
22 -- as the Board, I think, has properly understood,

1 it does not need to be direct.

2 Q What do you mean when you say "direct"?

3 A One can perform DNA sequencing by directly
4 taking a molecule and sequencing that and only
5 that molecule. One can perform sequencing by
6 amplifying that molecule, and then amplifying that
7 molecule again in sequencing many, many copies
8 together to get sufficient signal to determine the
9 sequence of that molecule. One can put that
10 molecule or copies of that molecule through a
11 nanopore. One can hybridize that molecule or
12 copies of that molecule to an array.

13 In each of those forms, there might be
14 advantages in altering the nature of the DNA to
15 achieve some other factor, so that the
16 determination of its sequence is more useful, more
17 targeted, more informative.

18 And the intermediate steps one might
19 choose to do so are myriad. And a POSA would
20 understand that any method that allow you to
21 sequence the DNA, to determine the sequence of the
22 DNA, whether it was direct or indirect and gain

1 the information one wanted from it, is appropriate
2 in this claim.

3 Q When you say indirect method of
4 sequencing, are you referring to any method of
5 determining a sequence with an intermediary step?

6 A I'm describing any set of intermediary
7 steps with any set of analytes that allow one to
8 determine the sequence. So Affymetrix arrays had
9 routinely been used for determining sequences by
10 hybridization. They would almost certainly use an
11 RNA intermediary to achieve that.

12 The -- the -- many of the nanopore
13 sequences that are currently on the market produce
14 molecules that are not nucleic acid. The Roche,
15 for example, just released a new one that makes
16 something completely different that is a
17 non-natural -- it is an analog of a nucleotide,
18 but it is something completely different and uses
19 that in conjunction with a nanopore.

20 But fundamentally a POSA would want to
21 know what is the sequence of my DNA molecule and
22 understandably does not care how one achieves

1 that. One could do it by restriction enzymology.
2 There are technologies to do sequencing by -- by
3 electrostatic interactions. There are hundreds of
4 ways at this point to sequence -- to obtain the
5 sequence of the DNA molecule, and none of it has
6 to be direct.

7 Q So the examples you describe Affymetrix
8 array and the nanopore and Roche products, are
9 those all examples of indirect methods of
10 sequencing?

11 A The Affymetrix array I described would
12 definitely be indirect in that a DNA product would
13 have been turned into RNA and the RNA would have
14 been sequenced, so the DNA product would not be
15 sequenced directly.

16 The Roche method I just described is a
17 little trickier, because it would take DNA as
18 input. But the thing that was actually assessed
19 for sequence is a non-canonical nucleotide system.
20 It is certainly not DNA. It is called sequencing
21 by expansion. And that molecule is fed through a
22 nanopore, which detects voltages. So the actual

1 process of sequencing happens by detecting
2 something that is not DNA and determining its
3 sequence.

4 So the process by which one takes a DNA
5 molecule and then gets sequence that corresponds
6 to it, has, as I said, probably hundreds of
7 methods that are appropriate in specific
8 situations. And the technology is under constant
9 evolution.

10 Q Which methods do you consider to be direct
11 methods of sequencing?

12 A The only method that I would consider
13 truly direct sequencing would be single molecule
14 sequencing. There are a few different versions of
15 that that have been commercialized.

16 Q So you would not consider the Illumina
17 paired-end sequencing to be a method of direct
18 sequencing?

19 A Not particularly, no. It has certain
20 features that are implicitly indirect. The
21 molecules that are utilized and are necessary to
22 work are not those molecules that are put into the

1 system. And some of the molecules that are
2 sequenced are only copies, reverse complement
3 copies of the initial molecules put in.

4 Q Would you consider Sanger sequencing to be
5 a method of direct sequencing?

6 A Sanger sequencing is fairly complicated.
7 The method that I would call direct sequencing at
8 its purest would be an instrument from Helicos
9 that bound individual molecules to the surface and
10 using a very complicated total internal reflection
11 microscope, sequenced individual bases of that
12 molecule one at a time.

13 Another technology that I would consider
14 direct sequencing is the current PacBio
15 instruments and the previous generations of the
16 PacBio instruments in which a double-stranded DNA
17 molecule is ligated into a circle creating what
18 they call a smart bell.

19 And that individual unadulterated molecule
20 is fed into the sequencer and its individual
21 sequence is determined. The nanopore sequencers
22 could in some applications also be direct DNA

1 sequencing depending on how they're utilized and
2 how the library construction is performed. I
3 think they -- I believe they often are. I have
4 the most experience with the PacBio platform.

5 Sanger sequencing as a direct method may
6 be considered -- it probably falls into the same
7 line as Illumina, because in this particular case
8 Sanger sequencing takes a single DNA product
9 rather than a plurality of products, creates many
10 independent copies of them so that one has
11 substantial material and then performs aggregate
12 pooling sequencing of all of those molecules in
13 parallel such that one has to have a clonal
14 population of fragments that one has considered
15 and constructed and then create a whole panel of
16 derivative molecules that end at specific bases.

17 So I think some practitioners of the art
18 would consider it direct, but it is not direct
19 sequencing of individual molecules. It is -- it
20 is direct -- it is partially direct sequencing of
21 very, very large numbers of copies of molecules
22 collectively, but at what point does one determine

1 the sequence of an individual molecule.

2 Q Do you understand that Dr. Sherman
3 proposed an alternative construction for the
4 identifying claim term where he adds the phrase
5 "wherein the sequence of a DNA product and the
6 sequence of the location-identifying nucleic acid
7 sequences are determined via sequencing onto the
8 Board's construction"?

9 A I do.

10 Q Do you agree with Dr. Sherman's
11 alternative construction?

12 A I prefer the Board's construction inasmuch
13 as I believe the Board -- that the relevant
14 component is -- is the first part of the phrase
15 looking at page 9 of my reply declaration,
16 locating the specific target analyte within the
17 tissue sample by correlating the DNA product using
18 the location-identifying nucleic acid sequences.

19 Dr. Sherman, I note in paragraph 21 of my
20 reply, any method of determining the identity of
21 DNA products is allowed, according to the Board's
22 interpretation and I believe that that is correct.

1 I believe that any method of determining the
2 identity of DNA products is sequencing.

3 And as a consequence I don't feel the need
4 to involve the additional phrase. And I don't
5 actually think the sentence "any method of
6 determining the identity of DNA products that does
7 not involve sequencing" is internally consistent,
8 because determining the identity of DNA products
9 is -- is sequencing.

10 So you don't need the extra clause on
11 there. And so if one is using the
12 location-identifying nucleic acid sequences, and
13 the DNA products, the specific target analytes one
14 has achieved this process.

15 Q So would it be fair to say that you don't
16 disagree with Dr. Sherman's alternative
17 construction it is just that you find the
18 additional phrase unnecessary?

19 MS. KHANDURI: Objection, form.

20 A That is correct.

21 Q I want to direct you to paragraph 56 of
22 your reply declaration.

1 A Yes.

2 Q Do you see the second sentence in
3 paragraph 56 where you state, the Board's
4 interpretation and encompasses sequencing
5 molecules that are different from the first-strand
6 (and second-strand) cDNA's due to, e.g., addition
7 of adapters and index sequences?

8 A I do.

9 Q Your opinion is that the Board's
10 interpretation encompasses sequencing molecules
11 that are different from the first-strand and
12 second-strand DNAs due to the addition of adapters
13 and index sequences, correct?

14 A I used -- for example, I don't think that
15 is a limiting set of things that can be altered in
16 the first and second-strand DNAs.

17 Q Are there additional differences from the
18 first-strand and second-strand cDNA's under the
19 Board's interpretation besides the addition of
20 adapters and index sequences?

21 MS. KHANDURI: Objection, form.

22 A We went through a number of examples in

1 Stahl in which there are adapters added and
2 potentially removed. Additionally in Stahl we
3 went through shortening processes where the first
4 strand and the second strand might be shorter than
5 the initial corresponding molecules. That aligns
6 very well with the enzymatic fragmentation that I
7 understand happens in Visium Fresh-Frozen when
8 they construct full length cDNAs.

9 So in my opinion, the process of turning
10 an initial mRNA in this case into useful
11 information in no way requires that the complete
12 mRNA be maintained or that once constructed an
13 mRNA stays at the same length.

14 So in addition to the addition of adapters
15 and index sequences, I believe that as long as the
16 -- in this case, as long as useful information
17 about the gene expression can be identified, that
18 the conditions have been met.

19 Q So under the Board's interpretation, the
20 differences that are encompassed between the first
21 and second-strand cDNA includes the addition of
22 adapters, the addition of index sequences, the

1 removal of adapter sequences, the short -- and the
2 shortening of one strand from the other. Are
3 there any other differences that are encompassed?

4 MS. KHANDURI: Objection, form.

5 A In my opinion, any modification for
6 example, turning from DNA into RNA or turning from
7 DNA into some expansion that can be sequenced on
8 the new Roche expansion sequencer or alteration of
9 the chemistry to improve some component.

10 In the case of bisulfite sequencing, the
11 treatment of nucleic -- DNA nucleic acids with
12 bisulfite reagent that removes cytosine residues
13 unless they have been methylated so that one can
14 detect methylated cytosines.

15 All of these are modifications that could
16 be useful in the right context and they are
17 non-limiting. All that matters is that one has
18 sequence that corresponds to -- one has inferred
19 the sequence of the DNA products so that one can
20 make a useful conclusion about the abundance in
21 this case of transcripts and their location.

22 Q Is it your opinion that the Board's

1 interpretation encompasses sequencing any molecule
2 that is downstream from the first-strand or
3 second-strand cDNA as long as the sequence
4 molecule retains the spatial barcode and a
5 sequence that allows its identity to be inferred?

6 A Pretty close. I would say that as long as
7 the identity of the spatial barcode and the
8 identity of the collected oligonucleotide in this
9 case, by the infringement position we mean mRNAs
10 can be inferred.

11 Q So as long as any -- well, strike that.

12 So as long as the molecule that is
13 sequenced allows the identity of the spatial
14 barcode and the identity of the collected
15 oligonucleotides to be inferred that is
16 encompassed by the Board's interpretation?

17 A Reading the Board's construction, locating
18 the specific target analyte within the tissue
19 sample by correlating the DNA product using the
20 location-identifying nucleic acid sequences, I
21 believe that that is correct.

22 Q I'm going to direct you to paragraph 32 in

1 your reply declaration.

2 A Yes.

3 Q Is it your opinion that Stahl meets the
4 synthesizing steps (c) and (d) of claim 1 because
5 Stahl's method includes synthesizing first-strand
6 cDNAs via reverse transcription?

7 A Can you repeat the question?

8 Q Is it your opinion that Stahl meets the
9 synthesizing steps (c) and (d) of claim 1 because
10 Stahl's method includes synthesizing first-strand
11 cDNA's via reverse transcription?

12 A You have truncated my statement in my
13 reply declaration. Using the captured
14 poly-adenylated mRNAs as templates, with the
15 resulting first-strand cDNAs incorporating spatial
16 barcodes.

17 And this is in context of the original
18 infringement positions from NanoString and the
19 specification and the claims.

20 Q So is it your opinion that Stahl teaches
21 the synthesizing steps (c) and (d) of claim 1,
22 because Stahl's method includes synthesizing

1 first-strand cDNAs via reverse transcription using
2 the captured poly-adenylated mRNAs as templates
3 with the resulting first-strand cDNAs
4 incorporating spatial barcodes?

5 A You are reading from my reply declaration,
6 which I do not disagree with. And you are leaving
7 out the statement that this is under Bruker's
8 infringement interpretation. But other than that,
9 I stand by my declaration, my original declaration
10 and my reply declaration.

11 Q Are you referring to the, "under Bruker's
12 infringement interpretation" in the title of this
13 section?

14 A In paragraph 32 of my reply declaration,
15 the paragraph begins, as explained in my first
16 declaration, under Bruker's infringement
17 interpretation, that is not a title. That is --
18 that is explaining why Stahl teaches these steps
19 under this particular infringement position.

20 Q By "under Bruker's infringement
21 interpretation," are you referring to your
22 interpretation of Bruker's infringement

1 contentions?

2 A At the time of my initial declaration,
3 yes.

4 Q And as we discussed, your opinion on that
5 has not changed, right?

6 A I stand by the conclusions given the
7 initial -- my initial interpretation of the
8 infringement position, the claims as issued, the
9 specification that goes with those claims, and the
10 infringement position. This is an internally --
11 it is -- it is not in consideration of the Board's
12 position or the IPR position taken by Bruker.

13 Q I'm going to direct you to paragraph 37 of
14 your reply declaration.

15 A Yes, I'm at paragraph 37 of the reply.

16 MS. KHANDURI: We need to take a break.

17 THE WITNESS: Could we go another 15
18 minutes and then have lunch?

19 MS. KHANDURI: Sure.

20 Q Do you see the first sentence of paragraph
21 37 where you state, although Bruker's infringement
22 contentions for claim 1's steps (c) and (d) also

1 cite Visium FF's "step 2 Second Strand Synthesis &
2 Denaturation," a POSA would understand that
3 Visium's FF's step 2 does not mean claim 1's steps
4 (c) and (d). Do you see that statement?

5 A I do.

6 Q So is it your testimony that a POSA would
7 understand that Visium Fresh-Frozen's step 2 does
8 not meet claim 1's step (c) and (d)?

9 A I go on to discuss that the Fresh-Frozen
10 product from Visium does not meet the requirements
11 of (c) and (d), because the second-strand
12 synthesis uses the first-strand cDNA's templates
13 rather than the collective oligonucleotides.

14 And if a POSA were to read a synthesis
15 reaction as a single synthesis reaction to both
16 meet the template requirement and the
17 incorporation requirement, then this would be
18 incorrect.

19 Q Sorry, did you say correct or incorrect?

20 A My final word was incorrect.

21 Q By incorrect you mean that a POSA would
22 understand that Visium Fresh-Frozen's step 2 does

1 not meet claim 1's steps (c) and (d), right?

2 A If one -- that is correct, as long as the
3 a single synthesis reaction must meet both
4 template and incorporation requirements. The
5 Board, in its construction, says that that is not
6 necessary. So under the Board's interpretation, I
7 can reach a different conclusion.

8 Q But under your opinion as described here
9 in paragraph 37, a POSA would understand that a
10 single reaction must meet both the template
11 requirement and incorporation requirement of claim
12 1's steps (c) and (d), right?

13 A I believe that's correct.

14 Q Is it your understanding that infringement
15 contentions are understood from the perspective of
16 a POSA?

17 A I believe that is correct. One has to map
18 the infringement contentions to individual claim
19 elements, and that in determining whether or not
20 any individual claim element met the limitation
21 that would be done in the context of a POSA.

22 Q And as we discussed you understand that

1 the Board has its own construction of the
2 synthesizing claim term in steps (c) and (d) of
3 claim 1, right?

4 A That is correct.

5 Q Do you understand that claim terms are
6 understood from the perspective of a POSA?

7 A In my discussion of claim construction at
8 the beginning of each of my declarations, there
9 are many things that a POSA would utilize, one of
10 which -- there are many things that happen in
11 construing claim terms, but yes, from the point of
12 view a POSA is one of those things.

13 Q Is it your understanding that the Board's
14 claim construction of the synthesizing step is how
15 the Board views a POSA to understand the claim
16 term?

17 A My understanding is that the Board's
18 construction is dependent upon the infringement
19 position, the IPR position of Bruker, the plain
20 and ordinary meaning of the terms as read by a
21 POSA, the specification as presented in the patent
22 and I believe that is it, but I could check.

1 Q Is it your understanding that the Board's
2 claim construction of the synthesizing step does
3 not take into account the perspective of a POSA?

4 A I don't think I said that. I think I said
5 it does take into perspective the opinion of a
6 POSA, but not exclusively.

7 Q Let turn for the record to paragraph 50 of
8 your reply declaration. Let me know when you are
9 there.

10 A I'm at paragraph 50.

11 Q Do you see near the end of that paragraph
12 you state, and Stahl's second-strand cDNA's are
13 that the "DNA products" of steps (c) and (d) of
14 claim 1 under the Board's and Bruker's IPR
15 constructions?

16 A Yes.

17 Q By "under the Board's construction," you
18 are referring to the Board's construction that
19 we've been discussing throughout, right?

20 A Correct.

21 Q And when you say "under Bruker's IPR
22 constructions," are you referring to Dr. Sherman's

1 proposed construction for the synthesizing term?

2 A No. I believe I'm referring to the IPR
3 constructions that Bruker took after I filed my
4 original declaration and that went into the
5 Board's overall determination of claim
6 construction here.

7 Q So when you say by "under Bruker's IPR
8 constructions," you are not referring to the
9 proposed constructions by Dr. Sherman?

10 A Earlier in the paragraph I do refer to
11 that as well.

12 Q Right, I just want to clarify when you say
13 under Bruker's constructions, are you referring to
14 Dr. Sherman's proposals or the construction like
15 you mentioned that Bruker took but that are not
16 Dr. Sherman's constructions?

17 A I believe I generally referred to it as --
18 this is language that I don't believe I used very
19 often in the document. Normally -- normally I
20 referred to Bruker's previous IPR position or
21 Bruker's previous IPR interpretation. In here I'm
22 talking construction, so I would have to think

1 more carefully about whether or not I'm referring
2 specifically to that or also to Dr. Sherman's
3 proposed definition. I can spend time doing that
4 if you like.

5 If we could take a break within the next
6 five minutes, please.

7 Q Sure. I can represent to you that when I
8 do a search of the document for "Bruker's IPR
9 constructions" it shows up three times as similar
10 language, but I'm unable to find any definition of
11 -- and that is why I want to -- you to clarify
12 what you're referring to for Bruker's IPR
13 constructions?

14 A Absolutely I can understand that. And my
15 response was that I will have to read all the
16 sections that you have identified and think about
17 them to try to clarify that for you.

18 MR. CHEUNG: Okay. Why don't we take our
19 lunch break now.

20 (Recess, 3:52 to 4:29 p.m.)

21 Q Dr. Spellman, during the break, did you
22 speak with anyone about the substance of this

1 deposition?

2 A No.

3 Q I want to direct you to paragraph 54 of
4 your declaration. Let me know when you are there.

5 A I'm at paragraph 54.

6 Q Okay. Did you see the phrase in paragraph
7 54, wherein the sequencing library was constructed
8 from the amplified copies of second-strand cDNAs?

9 A Yes.

10 Q Do you see the next phrase which states,
11 which themselves were generated downstream from
12 the first-strand cDNAs reverse transcribed from
13 the collected target mRNAs. Do you see that?

14 A I do.

15 Q By which themselves were generated
16 downstream from the first-strand cDNAs.

17 Do you mean that the synthesis of the
18 second-strand cDNAs was the next subsequent
19 reaction after synthesis of the first strand
20 cDNAs?

21 A Can you repeat the question?

22 Q In that paragraph when you state, which

1 themselves were generated downstream from the
2 first-strand cDNAs, do you mean that the synthesis
3 of the second-strand cDNAs was the next reaction
4 after synthesis of the first-strand cDNAs?

5 A Yes.

6 Q So by downstream, you just mean that the
7 synthesis of the second-strand cDNA occurs after
8 the synthesis of the first-strand cDNA, right?

9 A That's correct.

10 Q I want to direct you to paragraph 60 of
11 your -- of your reply declaration.

12 A Yes.

13 Q Do you see the first sentence where you
14 state that, Dr. Sherman mischaracterizes those
15 methods which he states that Stahl's workflow
16 implements...stranded RNA sequencing or
17 strand-specific RNA sequencing to ensure that the
18 strand specificity of the target mRNA is
19 maintained as the sequence of the RNA is
20 determined so that information on strand origin is
21 not lost during sequencing. Do you see that?

22 A I do.

1 Q Is it your opinion that Stahl does not
2 implement stranded RNA sequencing or
3 strand-specific RNA sequencing?

4 A I state exactly the opposite. I state in
5 -- for one, strand preservation is an inherent
6 feature of Stahl's method, so it inherently does
7 it.

8 Q So is it your opinion that Stahl's
9 workflow does implement stranded RNA sequencing or
10 strand-specific RNA sequencing?

11 A But it does not do so to ensure that the
12 strand specificity of the target mRNA is
13 maintained blah blah blah.

14 I'm not objecting to the first part of
15 Sherman's statement, I'm objecting to it to the
16 ensure clause.

17 Q So is it your opinion that stranded RNA
18 sequencing or strand-specific RNA sequencing does
19 not ensure that the strand specificity of the
20 target mRNA is maintained as the sequence of the
21 RNA is determined so that information on strand
22 origin is not lost during sequencing?

1 A Perhaps it is a little convoluted, but the
2 way I interpret Sherman's statement was that -- I
3 interpreted his statement to imply that one
4 specific strand was important rather than its
5 reverse complement. And that that was somehow a
6 critical feature is maintaining the plus strand or
7 the minus strand, when in reality all that was
8 required was knowing which primer was on which
9 end.

10 So it has nothing to do with the sequence
11 or the direction of the sequence. It has to do
12 with the -- the sequences attached at the -- at
13 the ends of the molecules. And since the -- since
14 the encoded information is a function of the
15 poly(A) tail as well as the reverse transcription
16 from the primer or, sorry, the IVT primer and the
17 capture and the -- and the location identifier
18 primer, all those are at one end of the poly(A) of
19 the molecule.

20 So you don't care which strand is which as
21 long as you can identify which one has that
22 feature. It doesn't matter if you sequence the

1 positive or the negative strand. They're always
2 going to come out in a certain orientation. So my
3 objection to Sherman's characterization is around,
4 like, keeping track of which strand was which.
5 You don't have to do it, it is inherent.

6 Q Let me see if I can summarize that
7 correctly. So your opinion is that because of
8 Stahl's workflow where the captured molecules have
9 a poly(A) tail on one end and there is the in
10 vitro transcription primer on the other end, which
11 will lead to the sequenced product having known
12 but different adapters on both ends so that when
13 you sequence a POA can tell the orientation of
14 the original mRNA. Is that a fair
15 characterization?

16 A That is fair. I think you made a small
17 technical detail that is not important. But the
18 key difference here is in addition -- in relation
19 to unstranded RNA seq, which was common at this
20 time or a bit before in which one does cDNA
21 double-stranded cDNA ligates on adapters in an
22 unoriented manner and then PCRs them. And then

1 one does not know which strand was the transcribe
2 strand.

3 But because this process is strand
4 anchored, one can always figure it out from which
5 primer is on which end. But that is not true in
6 unstranded protocols, but it is inherent in the
7 way they have done it here.

8 A regular RNA seq protocol makes cDNA from
9 across the entire molecule, and then makes
10 second-strand across the entire molecule, not just
11 at the 3 prime end. And therefore, when you --
12 and then it ligates on the same linkers on to both
13 sends, so there is no way to tell which strand was
14 which. That was the standard unstranded method
15 that was commonly used in Illumina's RNA seq
16 experiments.

17 It is not common anymore, because this is
18 relatively straightforward. There are other
19 stranded methodologies that require this anchoring
20 information, but this is inherently stranded
21 because of the way it captures things.

22 My description there is in strand

1 orientation in Stahl is not maintained by which
2 strand is sequenced, but rather by knowing the
3 orientation of sequencing that occurs, that is
4 correct, so you can draw that.

5 Q I just want to understand. So in the
6 unstranded RNA seq methods, would -- would the
7 POSA not be able to determine the, I guess,
8 strandedness from -- similarly from the poly(A)
9 tail?

10 A In most RNA seqs don't use poly(A) tail
11 extensions. The standard RNA seq experiment
12 before this time, before the time of Stahl, did
13 reverse transcription with random Hexamers, not
14 with Oligo(dT), therefore, they created cDNA
15 across the entire molecule of mRNA not just from
16 the 3 prime end.

17 Q I see. So because the traditional RNA seq
18 approach was to use random hexamers to perform the
19 reverse transcription, there is no guarantee that
20 a poly(A) tail would be captured in every --

21 A It was almost never --

22 Q -- tran --

1 A It was basically never captured, so you
2 never had an anchoring orientation.

3 Q I see, okay.

4 Would it be fair to say, then, that every
5 RNA sequencing approach that uses a poly-dT
6 sequence to hybridize to the poly(A) tail of an
7 mRNA is inherently a stranded RNA sequencing
8 approach?

9 A No, because you can -- you could do it in
10 another way where you -- where you made long --
11 made cDNA and then fragmented it, because if the
12 cDNAs are longer than the sequencer can handle, it
13 is common to shorten the fragments up and then you
14 would cleave off the poly(A) tail. And sequencing
15 the poly(A) tail has very little information in
16 it, because it is redundant across molecules.

17 So it is not -- there are ways to do it
18 and maintain strand information, it just requires
19 more effort. And when RNA seq was invented, it
20 did not -- most people didn't bother. I would say
21 stranded RNA seq is the standard today, but it was
22 not the standard in, say, 2010 to 2012. By 2016 I

1 think it was pretty common to maintain stranded
2 information, but I would have to -- I don't think
3 I have done a comprehensive literature review.

4 Q So in standard RNA sequencing approaches,
5 even if a poly-dT sequence is used to hybridize to
6 the poly(A) tail to an mRNA, the mRNA molecule may
7 be fragmented before putting on a sequencer and
8 that would -- that would lead a POSA to lose track
9 of which strand came from the mRNA?

10 MS. KHANDURI: Objection, form.

11 A Roughly speaking that is correct. A POSA
12 needs to know what they're keeping on their
13 molecules, so that they can keep track of
14 molecules. Stahl -- the structure of Stahl
15 because of the anchoring sequences that are
16 incorporated during -- and it is required not just
17 to keep the poly(A) tail but also the
18 location-identifying sequence at that end, right.
19 So you can't cleave off that end, because then you
20 lose your identifying sequence.

21 So there is a lot of stuff in Stahl that
22 makes this stranded behavior inherent.

1 Q Do you know approximately how long a
2 poly(A) tail on mRNA is?

3 A It's highly variable. It can be as short
4 as 20 or 30 base pairs in length, it can be as
5 long as a couple of hundred base pairs in length.
6 The design in Stahl favors extension near the --
7 at the beginning of the poly(A) tail, if you look
8 at -- if we were to look again at the oligos
9 utilized, you will see they have a string of Ts
10 and then a V and then an N.

11 And the VN is an anchor sequence that is
12 -- the V is not a T, and the N is any base. And
13 so it is -- it would tend to favor hybridizing and
14 anchoring the Oligo(dT) at the first two bases
15 that are not T or the second to the last base that
16 is not T, and then the first base could be a T or
17 any other base.

18 So it is -- it is a mix of -- so it tends
19 to favor, but given the very long lengths of
20 poly(A) tails it is not impossible that it could
21 anchor, bind and extend off the poly(A) tail as
22 well.

1 Q Is there an advantage of Stahl's workflow
2 compared with a modified version of Stahl's
3 workflow wherein after the second-strand cDNA
4 synthesis that double-stranded DNA is amplified
5 with sequencing adapters and sequenced?

6 MS. KHANDURI: Objection, form.

7 A I'm not sure I quite understand your
8 question. I think I do, but I think I'm going to
9 ask you to clarify it a little more completely.

10 Can you describe the -- it's Stahl versus
11 something else? Can you make -- can you be more
12 specific about what the Stahl something else,
13 what -- what the something else is?

14 Q The comparison I'm trying to make is if
15 you follow the beginning first few steps of
16 Stahl's workflow, so you generate a first-strand
17 cDNA, and then you generate the second-strand
18 cDNA. And then at that point you immediately
19 proceed to append like Illumina sequencing
20 adapters to the ends and then directly put it on a
21 sequencer.

22 A Yes. In principle that could be done and

1 there would be advantages to that version versus
2 the in vitro transcription version of Stahl. It
3 would depend on a variety of factors as to which
4 one was more favorable to do. And arguably at
5 some level it is, like, what techniques the POSA
6 prefers. They are both compatible methods to take
7 a cDNA that is a double-stranded cDNA and turn it
8 into something that could later be put on a
9 sequencer.

10 So they're both -- they're both
11 practicable. It is certainly -- there is nothing
12 to stop you from doing that. There are things you
13 would have to change in the protocol to do so. So
14 for example, with random hexamer priming, you
15 won't have full length second double-stranded DNA,
16 so you would have to clean up the extra tail. You
17 would have to do blunt end ligation, which many
18 people don't really love to do. You would have to
19 probably do some size selection, right, you need
20 some size selection in there.

21 So there are a variety of pretty
22 straightforward steps that would have been to be

1 manipulated to -- to move from the
2 second-strand -- the second-strand,
3 double-stranded material, that second-strand to an
4 Illumina sequences library. It is not just a
5 single ligation reaction that has to be done, but
6 it is totally -- it is totally within the art in
7 my opinion.

8 The IVT itself, I suspect the reason Stahl
9 liked it is because it is a linear amplification
10 and they're used to it. You know, Stahl --
11 everyone has techniques that they prefer, and
12 they're not necessarily an indictment of another
13 method. They're just different.

14 So in -- if I had to guess at Stahl's
15 motivation for the IVT they liked the linear
16 amplification component of the IVT. Perhaps they
17 weren't as comfortable with single or the
18 multiplex PCR steps that one has to do with
19 Illumina libraries or they wanted to limit the
20 number of cycles for some reason. They clearly do
21 them later on, so it is not totally clear to me
22 what is -- what is stopping them.

1 Q Can you explain what is the linear
2 amplification component of the IVT?

3 A In vitro transcription takes a
4 double-stranded DNA molecule that has the proper
5 sequences embedded in it and using an RNA
6 polymerase makes hundreds or thousands of tens of
7 thousands of copies -- of RNA copies of one of the
8 strands. So that is -- that is the aRNA. That is
9 amplified RNA and it is linear, because it mostly
10 corresponds to the number of molecules you put
11 into. There is no exponential component to it.

12 Q So when you refer to linear amplification,
13 you're talking about that the amount of product at
14 the end of amplification is a linear progression
15 recycle rather than an exponential increase in the
16 products?

17 A Yes. I mean, linear amplification doesn't
18 have cycles. You just run it for a certain amount
19 of time, but -- and that is another reason,
20 like -- but that is not a big difference, like,
21 that is not a big deal. It just doesn't undergo
22 exponential amplification like PCR.

1 You can get a lot of increase, right, you
2 could get a 1,000 or maybe even a million fold
3 increase if you do it really well, but it is -- it
4 is linear rather than -- you will never hit an
5 exponential phase.

6 Q But the -- as we were discussing, if Stahl
7 was to be modified so that the double-stranded
8 cDNA product or the double-stranded cDNA after the
9 second-strand cDNA and that continues forward
10 where I believe you mentioned there is -- needs to
11 be a blunt end ligation of adapters and such, when
12 that product is eventually sequenced, the -- the
13 strand will still be able to be determined due to
14 the poly(A) tail that would be carried forward
15 through the steps, right?

16 MS. KHANDURI: Objection, form.

17 A Yes. The poly(A) tail and the -- and the
18 location-identifying sequence are on one end as
19 well as primer sequences that are on that end as
20 well. So there are sequences that are anchored at
21 one end and will always be there that would allow
22 you to maintain stranded information.

1 Q If I can direct you to paragraph 76 of
2 your reply declaration.

3 A Yes.

4 Q Is it your opinion that Stahl's
5 second-strand cDNAs are used as templates to
6 generate a library of molecules with added
7 adapters for Illumina paired-end sequencing?

8 A I think that is an accurate summary of
9 what is in paragraph 76, yes.

10 Q Do you see where you used the phrase, the
11 molecules comprising the sequence of the
12 second-strand cDNAs?

13 A Yes, I see that sentence.

14 Q Okay. By the molecules comprising the
15 sequence of the second-strand cDNAs, are you
16 referring to the cDNAs that were reverse
17 transcribed from the amplified RNA?

18 A Yes. In this paragraph, I'm referring to
19 -- the second-strand cDNAs now refers to
20 second-strand cDNAs of aRNA. Oh, sorry, no, my
21 apologies.

22 In this paragraph the second-strand cDNAs

1 still are the DNA products of claim 1 and the PCR
2 molecules now contain parts of the cDNA molecules
3 of the -- of the products of claim 1 after the
4 aRNA step.

5 Q So you're saying that in Stahl's method
6 the cDNAs generated after the amplified RNA step
7 are the molecules that are used as templates to
8 generate a library of molecules with added
9 adapters for Illumina NextSeq paired-end
10 sequencing, right?

11 A No, that is what I was clarifying. The
12 second-strand cDNAs there refers to the DNA
13 products of claim 1. At the very beginning -- the
14 original second-strand cDNAs, the product at the
15 very end, those molecules comprise the sequence of
16 the second-strand DNAs, and are then -- and the
17 derivative molecules that are downstream copies of
18 those molecules are utilized as -- as in a PCR
19 reaction to -- to generate the library of
20 molecules that will then be sequenced on the
21 Illumina sequencer with the added adapters.

22 Q But so the molecules that undergo the

1 reaction to add adapters for Illumina NextSeq
2 paired-end sequencing, those molecules are
3 downstream copies of the second-strand cDNAs,
4 right?

5 A That's correct.

6 Q I would like to direct you to paragraph
7 88.

8 A Yes.

9 Q Do you see in the last sentence of
10 paragraph 88 where you state, therefore,
11 solid-phase second-strand synthesis in Stahl would
12 satisfy claim 5?

13 A Yes.

14 Q And so your opinion is that solid-phase
15 second-strand synthesis in Stahl satisfies claim
16 5, right?

17 A That is correct.

18 Q Do you agree that first-strand cDNA
19 synthesis in Stahl does not satisfy claim 5?

20 A I have only identified the second-strand
21 synthesis based on my review of my reply
22 declaration as the -- as the solid-phase synthesis

1 that meets the limitation of claim 5.

2 Q So do you agree that synthesis of the
3 first-strand cDNA does not satisfy claim 5?

4 A I don't think I have rendered an opinion
5 on that.

6 Q So you have no opinion now on whether
7 first-strand cDNA synthesis satisfies claim 5?

8 A I don't believe I have rendered an opinion
9 on that.

10 Q But I'm asking a different question.

11 Do you have an opinion sitting here today
12 on whether first-strand synthesis satisfies claim
13 5?

14 A I would have to think about that more.

15 Q So you're not prepared to render an
16 opinion today; is that right?

17 A I believe that is correct.

18 Q Do you agree that without modifying Stahl
19 so that the second-strand cDNA synthesis takes
20 place in solid-phase, Stahl does not satisfy claim
21 5?

22 MS. KHANDURI: Objection, form.

1 A Claim 5 requires that there is a
2 solid-phase synthesis reaction to occur. And
3 under the infringement positions, as I understood
4 them, at the time of my initial declaration Stahl
5 did not meet the infringement position alignment
6 with the Fresh-Frozen Visium product.

7 Under the Board's interpretation of
8 Bruker's IPR position, the second-strand synthesis
9 is the -- is consistent with the DNA product of
10 claim 1, and therefore, does occur in solid-phase
11 as -- as described in the specification of the
12 '142 patent.

13 Q Do you agree that without modification,
14 synthesis of the second-strand cDNA in Stahl
15 occurs in solution?

16 A In Stahl the second-strand cDNA occurs in
17 solution, that is correct.

18 Q So do you agree that without modification
19 Stahl's workflow does not meet claim 5?

20 A As discussed in Section B starting on page
21 38, claim 5 is obvious over Stahl, but it is not
22 anticipated over Stahl in my -- in my reply

1 declaration, and that opinion is also rendered in
2 my original declaration.

3 Q So I want to confirm your opinion that
4 Stahl does not meet claim 5 if Stahl is not
5 modified, right?

6 A The second-strand synthesis, if that is
7 required to meet the solid-phase limitation of --
8 of the claim, would have to occur on the solid
9 substrate. And I have an extensive discussion as
10 to why that would be reasonable in Section B.

11 Q Do you agree that performing the
12 second-strand synthesis in solid-phase is a
13 modification of Stahl's method?

14 A Yes, in so -- yes.

15 Q I want to direct you to paragraph 90 of
16 your reply declaration.

17 A Yes.

18 Q Do you see the last sentence of this
19 paragraph where you state, I also provided several
20 notable examples of solid-phase amplification
21 approaches that would have guided a POSA's routine
22 modifications to Stahl's workflow.

1 Do you see that?

2 A I do.

3 Q And do you see that you cite four
4 exhibits, Exhibit 1005, 1017, 1042, and 1049?

5 A Yes, from -- yes.

6 Q Do you know whether the notable examples
7 of solid-phase amplification approaches described
8 in those four exhibits perform stranded RNA
9 sequencing?

10 (Exhibits 1005, 1017 1042 and 1049 discussed.)

11 A I'm going to open Exhibit 1005.

12 Q Okay.

13 A And I'm going to open Exhibit 1042, and
14 Exhibit 1049.

15 So at least in 1005, 1017 and 1049, which
16 are Frisen -- now I've forgotten again what 1017
17 is and Fu, they all create initial orientations
18 that would local allow on to keep track of strand.

19 Q What do you mean that they create initial
20 orientations that would allow one to keep track of
21 strand?

22 A Because the first primer placement is

1 containing some piece of information that can only
2 go -- that can only enter the system through the
3 reverse transcription reaction, they will all
4 maintain orientation information about which
5 strand was the -- was the strand that was the
6 template for reverse transcription which allows
7 you to keep track of strand and its information.

8 Q Are you saying that similar to your
9 opinion on Stahl the methods in Exhibit 1005,
10 1017, and 1049 inherently keeps track of the
11 strands?

12 A Correct.

13 Q Next I will direct you to paragraph 101 of
14 your reply declaration?

15 A Yes.

16 Q Do you see here where you state that the
17 double-stranded cDNA could be released from the
18 array to perform RNA amplification and then also
19 alternatively the double-stranded cDNA could be
20 maintained on the array to perform RNA
21 amplification on the array for library
22 preparation?

1 A Yes.

2 Q So is it your opinion that Stahl's method
3 can be modified so that the cleavage step takes
4 place after the synthesis of the second-strand
5 cDNA?

6 A Alternatively there could be no cleavage
7 step and one could simply melt off the
8 second-strand cDNA. Either one of those is a
9 reasonable modification.

10 Q Both of these modifications will require
11 changing the cleavage step as it is in Stahl's
12 workflow, right?

13 A The first one would move it to after
14 second-strand synthesis, so it wouldn't require a
15 change in the cleavage step. It would require a
16 change in the second-strand synthesis step. The
17 other modification is not to perform cleavage at
18 all, and melt off. So I would not describe a
19 modification -- like, not doing something is a
20 modification of a step. I mean, sort of it is,
21 but not really.

22 Q So the first modification here is that the

1 timing of the cleavage step is modified from
2 before second-strand cDNA synthesis to after
3 second-strand cDNA synthesis, right?

4 A That would be possible, and as explicitly
5 suggested in Frisen.

6 Q That is the modification you are
7 discussing in the first sentence in paragraph 101,
8 right?

9 A Yes.

10 Q And then the second modification you
11 discussed in paragraph 101 is skipping the
12 cleavage step all together, right?

13 A Correct. Well, the second -- the first
14 sentence is modifying the method of release so
15 that you perform the release after the
16 second-strand. And that could either be by using
17 the cleavage method of user enzyme or melting.

18 The second paragraph of 10 -- the second
19 sentence of paragraph 101 is discussing using the
20 RNA amplification in solid-phase as well, which
21 would -- then you would not release the
22 double-stranded DNAs at all.

1 Q I see. So the first sentence here
2 includes -- the modification in the first sentence
3 here includes both changing the timing of the
4 cleavage step or skipping the cleavage step and
5 using denaturation?

6 A Correct.

7 Q And is it your opinion that either of
8 these modifications described here in paragraph
9 101 satisfies claim 5?

10 A Under the infringement contentions of
11 Bruker and the Board's statements, yes.

12 Q Did you discuss the modification or the
13 alternative modification described here in
14 paragraph 101 in your first declaration?

15 A I discussed moving the second-strand
16 synthesis to solid-phase in my initial
17 declaration, yes.

18 Q Where in your first declaration did you
19 discuss moving the second-strand synthesis to
20 solid-phase?

21 A In my discussion of claim 5, starting on
22 page 83.

1 Q Can you be more specific? Where in your
2 first declaration you discuss that the
3 double-stranded cDNAs in Stahl can be modified so
4 that they're released from the array to perform
5 RNA amplification in solution?

6 A In paragraph 171 a POSA would have known
7 that second-strand cDNA synthesis and library
8 amplification can be performed on Stahl 2016's
9 array. For example, Stahl's authors suggested
10 that their spatial detection method using a
11 barcoded array can include second-strand cDNA
12 synthesis and library amplification on the array
13 onto which the tissue was immobilized. So one or
14 both of them.

15 Q So that is --

16 A I don't limit it.

17 Q So does paragraph 171 of your first
18 declaration encompass the two modifications that
19 you describe in paragraph 101 of your reply
20 declaration?

21 A The entire section of my original
22 declaration starting on -- starting on page 83,

1 claim 5, continuing onward discusses the
2 modifications and benefits of -- and motivation to
3 combine of such processes. So it is not limited
4 to just the paragraph 171.

5 Q But does paragraph 171 encompass the
6 modifications described in your reply declaration
7 paragraph 101?

8 MS. KHANDURI: Objection, form.

9 A Sorry, I'm not sure I understand the
10 question.

11 Q In paragraph 171 where you state that a
12 POSA would have known that the second-strand cDNA
13 synthesis and library amplification can be
14 performed on Stahl's 2016's array, i.e.,
15 microscope slide, does that include the
16 modification to Stahl's method, the two that you
17 describe in paragraph 101 of your reply
18 declaration?

19 MS. KHANDURI: Objection, form.

20 A Does it describe it, is that what your
21 question is?

22 Q Is it included?

1 A I don't know what you mean by "included."

2 Q When you say a POSA would have known to
3 make that modification in paragraph 171 of your
4 first declaration, is what a POSA known how to do
5 the two modifications you list out in paragraph
6 101 of your reply declaration?

7 MS. KHANDURI: Objection, form.

8 A I think so, but I'm not sure I understand
9 the question. So I'm not 100 percent sure I can
10 give you a positive answer, because I really don't
11 fully understand the question.

12 Q In your first declaration when you state
13 that a POSA would have known that the
14 second-strand cDNA synthesis and library
15 amplification can be performed on Stahl 2016's
16 array, what are the modifications to Stahl's
17 workflow that a POSA would have known to do?

18 A The second-strand cDNA synthesis would be
19 the solid-phase synthesis of second-strand as
20 described in paragraph 101. And the library
21 amplification of the aRNA by in vitro
22 transcription is -- corresponds to the sentence in

1 101, alternatively the double-stranded cDNAs could
2 be maintained on the array to perform RNA
3 amplification on the array for library
4 preparation.

5 So I believe they map to those two steps
6 as you're describing them, but I'm not sure if
7 there is something else deeper in your question.

8 Q So in your first declaration when you
9 refer to library amplification, you are referring
10 to the in vitro transcription step that generates
11 amplified RNA; is that right?

12 A That is my recollection. I could go
13 through and read it very carefully if you like.

14 Q That library amplification that you
15 referred to in paragraph 171 does not refer to the
16 amplification reaction step involving the PCR
17 primer InPE1.0, PCR primer InPE2.0, and PCR index
18 primer, right?

19 A That is correct. There -- the in vitro
20 transcription done in paragraph 171 as described,
21 the RNAs would be untethered from the surface due
22 to the transcription process, and they would

1 diffuse into solution. So the -- I am
2 intrinsically talking about the RNA transcription
3 step alone there.

4 There might be a way to anchor those again
5 in some other manner, but I'm not -- I don't
6 believe I'm describing it there. It is certainly
7 not suggested in Frisen that I know of.

8 Q Next I want to direct you to paragraph 116
9 in your reply declaration.

10 A Yes, paragraph 116.

11 Q Do you see the last sentence in that
12 paragraph where you state that, second,
13 Dr. Sherman mischaracterizes Frisen's cited
14 paragraph which is just one instance disclosed in
15 Frisen's where large amounts of RNA in the sample
16 allow direct sequencing of second-strand cDNAs
17 without amplification. No teaching in Frisen
18 should be viewed as exclusionary to other
19 teachings.

20 Do you see that?

21 A Yes.

22 Q And do you see Frisen that you cite there

1 Exhibit 1017, page 13, lines 1 through 8?

2 A Yes.

3 Q Can you bring up Exhibit 1017 and go to
4 page 39, lines 1 through 8?

5 A I will need a break pretty soon.

6 Q Let me finish this question and we can
7 take a break.

8 A I'm on page 13, lines 1 through 8, yes.

9 Q Do see that page 39, lines 1 through 8
10 describes what -- what you refer to as one
11 instance in the paragraph 116 that we looked at in
12 your reply declaration?

13 A Okay.

14 Q Is there any other teaching in Frisen
15 besides this one instance here in page 39, lines 1
16 through 8 that -- that tells a POSA that a
17 second-strand cDNA should be synthesized on the
18 array?

19 A If you go to my original declaration in
20 paragraph 171, Exhibit 1017, page 12, 9 to 11 it
21 states, as will be described in more detail below
22 second-strand cDNA synthesis my optionally take

1 place on the array or it take place in a separate
2 step after the release of first-strand.

3 Paragraph 38 page -- column 20 to 23, the
4 step of second-strand DNA, for example, cDNA
5 synthesis may take place in situ on the array,
6 either as a discrete step of second-strand
7 synthesis, for example, using random primers as
8 described in more detail below or in the initial
9 step of an amplification reaction. And then page
10 39, 28 -- a long section on page 39, that
11 continues all the way to page 43. I don't think I
12 need to read it unless you really want me to.

13 Q Is it your understanding that three
14 citations that you just went through are teachings
15 in Frisen that the second-strand cDNA can be
16 performed on the array?

17 A Yes.

18 Q Okay. Let's take a break.

19 (Recess, 5:32 to 5:43 p.m.)

20 Q Dr. Spellman, during the break, did you
21 speak with anyone about the substance of this
22 deposition?

1 A No.

2 Q I want to direct you to paragraph 120 of
3 your reply declaration.

4 A Yes.

5 Q Do you see -- well, the first sentence in
6 this paragraph where you say, Sherman again,
7 applies an inappropriate narrow construction to
8 the terms amplification and solid phase, which as
9 construed in this litigation means "the synthesis
10 of a nucleic acid from a template using a primer"
11 and "where one product is bound to a solid
12 substrate" and so on.

13 Do you see that sentence?

14 A Yes.

15 Q Does -- does synthesis of a nucleic acid
16 from a template using a primer refers to the term
17 amplification?

18 A If one goes to the '142 patent, there is a
19 controlling definition of solid-phase
20 amplification in this litigation, and so it uses
21 that language.

22 Q My question is, in that phrase, does what

1 is in quotes, the synthesis of a nucleic acid from
2 a template using a primer refer to the term
3 amplification?

4 A Given the Board's decision on what
5 synthesis means, that synthesis is amplification,
6 I believe it does, yes.

7 Q And then so does the second quote, where
8 one product is bound to a solid substrate refer to
9 solid-phase?

10 A Correct.

11 Q Can you identify for me where these two
12 quotes are from?

13 A In my discussion of claim 5 in my original
14 declaration in paragraph 166, according to the
15 '142 patent solid-phase amplification refers to
16 any nucleic acid amplification reaction carried
17 out on or in association with a solid support such
18 that all or a portion of the amplified products
19 are immobilized on the solid support as they are
20 formed.

21 And then -- and then the second part, I
22 think, is my summarization of the Board's position

1 that synthesis of a nucleic acid meets the
2 requirement -- using a template, meets the
3 requirement of amplification given -- given the
4 grounds in the Board's construction of the
5 synthesis step of (c) and (d). And I believe it
6 is also based on the infringement position of
7 Bruker in the litigation.

8 Q Where does the exact phrase, the synthesis
9 of a nucleic acid from a template using a primer,
10 where does that phrase appear?

11 A I believe it is in quotes, so that it is
12 separated, not that it is a quote of the -- the
13 Court. It is an interpretation of the construed
14 claims given the -- given the litigation history,
15 the IPR position from Bruker and the District
16 Court's interpretation of the synthesis clause of
17 (c) and (d).

18 I don't -- I don't believe it lines up to
19 a correct an exact quote somewhere. I believe it
20 is offset in quotes so as to be clear what it
21 means.

22 Q I see. So the two phrases in quotes

1 there, which is the synthesis of a nucleic acid
2 from a template using a primer, and the second
3 quoted phrase, where one product is bound to a
4 solid substrate, that is not an exact quote, but
5 your interpretation of what the terms
6 amplification and solid-phase mean in this case;
7 is that right?

8 A Correct. In contradiction to clonal
9 amplification with linked primers, which is how
10 I'm ascribing Sherman's characterization of
11 solid-phase amplification. So those three quotes
12 are sort of distinct positions of things that
13 could be described, and they're in quotes to keep
14 them sort of intellectually separate is my
15 recollection.

16 Q I see. So right -- so the three phrases
17 in -- in quotations they're in paragraph 120 of
18 your reply declaration, these are your
19 interpretation of the three concepts and not exact
20 quotes found anywhere?

21 A I believe that's correct.

22 Q Later on in paragraph 120 do you see where

1 you talk about that in this context there are
2 multiple reasons -- multiple valid reasons for
3 paralellization, for example, gaskets that created
4 multiple reaction chambers were routinely used to
5 segment different parts of an arrays in parallel
6 to perform downstream reactions, (e.g.,
7 second-strand synthesis) rather than extracting
8 material from the array. Do you see that?

9 A I do.

10 Q Can you explain what gaskets that created
11 multiple reaction chambers have to do with Stahl?

12 A Yes, I believe I can.

13 Q Did you -- can you do so? Can you
14 elaborate?

15 A I'm pulling Stahl up, sorry.

16 Is it possible for me to download Stahl?
17 I don't believe my search function works within
18 Stahl.

19 Q If you have another way of getting the
20 Stahl. What is in the exhibit is the exhibit that
21 10x filed in this case.

22 A Yeah. No, I can download it from here, I

1 see that now.

2 Q Yeah.

3 A So in Stahl you will see that on page 8 of
4 the supplementary materials, probably the third --
5 second sentence down, when the method refers to
6 separate wells, these wells are created on the
7 glass slide by using a rubber mask to separate the
8 surface into reaction compartments.

9 That rubber mask, the other term it is a
10 gasket. And that rubber mask allows us to segment
11 the array into multiple addressable features.

12 Q Are you in the section titled Outline of
13 the Spatial Transcriptomics workflow, is that what
14 you are referring to?

15 A Correct. Rubber mask is a synonym for
16 gasket.

17 Q So in paragraph 120 of your reply
18 declaration when you refer to gaskets, are you
19 referring to these rubber masks that allow for
20 para -- paralellization?

21 A Yes. So you will see that in the
22 discussion of rubber masks, to separate the

1 surface into reaction compartments I described it
2 as gaskets that created multiple reaction
3 chambers, but they're identical concepts.

4 So a POSA would know about these, Stahl
5 and Frisen know about these. They're well used in
6 had the art. And there are any reason to engage
7 in doing something on a solid surface allows you
8 to do this sort of sub-compartmentalization.

9 Q Do these gaskets or rubber masks allow
10 multiple reactions to take place on the same
11 slide?

12 A That is one use for them, yes.

13 Q In paragraph 120 of your reply
14 declaration, when you refer to the gaskets
15 creating multiple reaction chambers to allow for
16 paralellization, is that what you are referring
17 to?

18 A Yes, it is exactly what I say. Used to
19 segment different parts of arrays in parallel to
20 perform downstream reactions.

21 Q So the paralellization that you are
22 describing in paragraph 120 of your reply

1 declaration is performing Stahl's workflow on
2 multiple samples at the same time; is that right?

3 A That would be a terrific use for this
4 technology. That is not -- far from the only one,
5 but that would be a great use.

6 Q Is what I described an example of the
7 paralellization that you referred to in paragraph
8 120?

9 A That would be an example, yes. It could
10 also be that you wanted to barcode different parts
11 of the sample with different barcodes that would
12 allow you to do it in parallel. It would also --
13 there is a very large number of things you might
14 achieve by treating different parts of the surface
15 differently.

16 Q So the paralellization refers to different
17 surfaces that can be used simultaneously with the
18 use of the gaskets; is that accurate?

19 A Normally it would be one surface that you
20 then sub-compartmentalize to do reactions in
21 different ways or for different behaviors, so that
22 you are doing things in parallel on the same

1 surface, but either with different samples in
2 different subregions or it could be that you just
3 want to treat each independent one slightly
4 differently.

5 Maybe you are doing optimization, and so
6 you want to do, you know, 100 different reactions
7 100 -- with slightly different conditions to see
8 which one might work best. There is tons of
9 reasons you might do this.

10 Q Next I want to direct you to paragraph 144
11 of your reply declaration.

12 A Paragraph 144, yes.

13 Q Do you see the first sentence you have
14 there, which ends with the phrase "under Bruker's
15 infringement contentions"?

16 A Yes.

17 Q What is Bruker's infringement conditions
18 -- contentions for conditions that release the
19 plurality of oligonucleotides from the first
20 location and second location of the tissue sample?

21 A You are asking what are Bruker's
22 infringement contentions; is that right?

1 Q What do you understand Bruker's
2 infringement contentions to mean for -- here where
3 you state that the conditions that release the
4 plurality of oligonucleotides from the first
5 location and second location of the tissue sample?

6 A Yes. Primarily that Bruker's infringement
7 contentions hold that -- that the first and second
8 location release can be simultaneous as -- as --
9 rather than ordered or serial or something like
10 that.

11 Q So here when you state that in your first
12 declaration you explained that the conditions that
13 released that claim term is under Bruker's
14 infringement contentions, you mean that multiple
15 locations are -- or the first and second location
16 are simultaneously released; is that right?

17 A That's correct. I can go back to my
18 original declaration as well. There is a longer
19 discussion in paragraphs 207 and 208 in my
20 original declaration, but I think that -- that
21 target how this happens, but I think this specific
22 infringement position of Bruker, that clause alone

1 is -- has something to do with multiple location
2 released simultaneously.

3 Q So you see that in paragraph 207 and 208
4 of your first declaration it doesn't mention
5 Bruker's infringement contentions, right?

6 A I do see that, yes.

7 Q I want to get your opinion on what it
8 means here.

9 A Yes.

10 Q Are you saying in paragraph 144 your reply
11 declaration that --

12 A Sorry, I would like to point out that the
13 end of paragraph 206 does -- in my original
14 declaration, does say according to NanoString's
15 interpretation, so just as a side note.

16 Q 206.

17 A The previous paragraph 206 does note.

18 Q I see. In your reply declaration are
19 you -- is it your opinion that meeting Bruker's
20 infringement contentions is sufficient to show
21 anticipation?

22 A No, I don't think that is correct. I

1 think you have to look at my original declaration
2 in all the paragraphs noted there, 207, 208, and
3 then -- and then looking at Stahl itself in the
4 various different paragraphs in Stahl. Is 1005
5 Stahl? Sorry, I don't have them memorized. No,
6 Stahl is not -- 1005, hold on.

7 Q 1005 is --

8 A 1005, is So, apologies.

9 So then looking at the various sections of
10 So.

11 We've been on Stahl so long I just thought
12 we were on Stahl still.

13 Q No problem.

14 I will direct you to paragraph 146 of your
15 reply declaration, so two paragraphs down.

16 A Yes.

17 Q Do you see that at the top of page 68 you
18 list a few examples of what you say are
19 appropriate treatments such as thawing,
20 sectioning, immobilization, de-paraffinization
21 de-crosslinking and/or permeabilization?

22 A Yes.

1 Q Are these methods that you listed out here
2 are they expressly disclosed in So-456?

3 A If we go to So-456, we would go to
4 paragraph 152. So starting on the top of page 30
5 of So, paragraph 151, a flow diagram of an
6 embodiment of a spatial detection analysis in a
7 tissue sample, so this is setting the context.
8 Method 200 is not -- can include but is not
9 limited to preparing a sample for analysis.

10 In some embodiments that includes a FFPE
11 tissue section onto a slide. Other examples
12 include fresh-frozen, fresh tissue, et cetera.

13 And then in paragraph 154 I also list that
14 link there in my primary declaration. At step
15 220, the target nucleic acid in the tissue section
16 is transferred onto an array so that the nucleic
17 acid expressly must leave the tissue to join the
18 array so that there is -- that has to happen in
19 order for this to work.

20 And the continued details in there. And
21 some embodiments target nucleic acids that are
22 transferred to the mRNA, which would be the

1 relevant one for this point.

2 And then there is also a reference to
3 paragraph 308. And in paragraph 308, the tissue
4 sample comprised a plurality of mRNA molecules
5 that are in contact with the capture array and so
6 the tissue sample has these mRNA molecules and
7 then they need to bind to the array. So these
8 various sections identify movement of the mRNA to
9 the solid surface array for capture.

10 In paragraph 146 of my reply I point to --
11 I point to a variety of different places including
12 the reference 1016, which is Stahl, about how --
13 how to move the -- move the material from the
14 tissue onto the -- onto the surface.

15 And that -- and that in the case of Stahl,
16 this would be an obvious approach. And then I
17 also note that in my original deposition frozen
18 tissue just simply thawing it would release target
19 mRNAs as the cells breakdown and their membranes
20 let things out.

21 Q So your opinion is that appropriate
22 treatments such as thawing, sectioning,

1 immobilization, de-paraffinization,
2 de-crosslinking and/or permeabilization, these are
3 methods that were routine in the art?

4 A Indeed although they're referenced in
5 Stahl, Stahl invented none of those methods.

6 Q So you agree that So-456 does not
7 explicitly state these appropriate treatments such
8 as the thawing, sectioning, immobilization, the
9 paraffinization, the crosslinking, and/or
10 permeabilization in the text?

11 A As I mentioned, there are several sections
12 in So-456 that describe the various processes that
13 can happen to prepare -- that the tissue sample is
14 prepared for analysis, and then material is
15 transferred to the array. And I described those
16 to you just now.

17 Q In the sections in So-456, they don't
18 mention thawing, correct?

19 A I don't see a reference to thawing in So.
20 Extensive reference to frozen tissue -- several
21 references to frozen. Paragraph 152 and paragraph
22 125 describe frozen samples. And obviously a

1 frozen sample is incapable of releasing RNA so
2 that if -- if you were going to release it one
3 would have to thaw it.

4 Q In various sections of So-456 that you
5 cite to they don't explicitly state the
6 de-paraffinization, correct?

7 A I do not see an explicit reference to
8 de-paraffinization in So.

9 Q Is there an explicit reference to
10 de-crosslinking in So-456?

11 A I don't believe so.

12 Q Is it your opinion that sectioning a
13 tissue sample is a condition that releases target
14 oligonucleotides in the sample?

15 A It could be.

16 Q As you mentioned, if a sample is frozen,
17 then sectioning that frozen sample without thawing
18 would not release target oligonucleotides from the
19 sample, right?

20 A No. And given that So states that the
21 mRNAs are captured on the array, it is implicit
22 that the thawing has happened.

1 Q So is it your opinion that the various
2 appropriate treatments that you have listed in
3 paragraph 146 of your reply declaration that were
4 routine in the art would be implicitly performed
5 by a POSA when they practiced the method of
6 So-456?

7 MS. KHANDURI: Objection, form.

8 A Yes, I also think it would be obvious to
9 make the modifications if necessary.

10 Q I want to direct you to paragraph 166 of
11 your reply declaration. Let me know when you are
12 there.

13 A Yes.

14 Q And do you see the last sentence of that
15 paragraph where you state, So-456 then uses the
16 second-strand cDNA as templates for amplification
17 to generate cDNA sequencing libraries as explained
18 above. Do you see that?

19 A I do.

20 Q So is it your opinion that the
21 second-strand cDNA in So-456 is used as templates
22 for amplification to generate cDNA sequencing

1 libraries?

2 A Can you repeat the question?

3 Q Is it your opinion that the second-strand
4 cDNAs in So-456 is used as templates for
5 amplification to generate cDNA sequencing
6 libraries?

7 A That is what is stated in paragraph 166
8 and I agree with that.

9 Q I will direct you back to paragraph 50
10 your reply declaration.

11 A Yes, I'm in paragraph 50.

12 Q Do you recall earlier I asked you about
13 what Bruker's IPR constructions mean at the end of
14 that paragraph?

15 A Yes.

16 Q Can you tell me now what you mean when you
17 say, it is under Bruker's IPR constructions?

18 A I believe I meant Bruker's previous IPR
19 positions, apologies. I believe it is the Board's
20 IPR construction and Bruker's IPR positions,
21 previous IPR position.

22 Q Can you turn to paragraph 135 of your

1 reply declaration? Do you see that the last
2 sentence of paragraph 135 also refers to Bruker's
3 IPR constructions?

4 A I do.

5 Q Is it the same case that the reference
6 there to Bruker's IPR constructions is referring
7 to Bruker's previous IPR position?

8 A And the Board's construction, yes.

9 Q And I want to direct you to paragraph 140?

10 A Yes, the same there as well.

11 Q Right. That is what I was going to ask,
12 okay. Great. No more questions from me.

13 MS. KHANDURI: Okay. So give us about 20,
14 25 minutes.

15 (Recess, 5:22 to 5:50 p.m.)

16 MS. KHANDURI: We do not have any
17 questions for Dr. Spellman. Thank you, Dr.
18 Spellman for your time today.

19 (Deposition adjourned at 5:50 p.m.)

20
21
22

1 CERTIFICATE OF SHORTHAND REPORTER

2 I, Susan S. Klinger, a Registered Merit Reporter
3 and Certified Realtime Reporter of the State of
4 Texas, do hereby certify:

5

6 That PAUL T. SPELLMAN, Ph.D., the witness
7 whose deposition is hereinbefore set forth, was duly
8 sworn by me before the commencement of such
9 deposition and that such deposition was taken
10 virtually and is a true record of the testimony
11 given by such witness.

12

13 I further certify that the adverse party,
14 10X GENOMICS, INC., was represented by counsel at
15 the deposition.

16

17 I further certify that the deposition of
18 PAUL T. SPELLMAN, Ph.D., occurred virtually, on
19 Tuesday, March 18, 2025, from 11:58 a.m. to 5:50
20 p.m.

21

22

1 I further certify that I am not related to
2 any of the parties to this action by blood or
3 marriage, I am not employed by or an attorney to any
4 of the parties to this action, and that I am in no
5 way interested, financially or otherwise, in the
6 outcome of this matter.

7
8 IN WITNESS WHEREOF, I have herunto set my
9 hand on the 20th of March, 2025.

10
11 
12

13 Susan S. Klinger, RMR-CRR, CSR

14 Texas CSR 6531, Exp: 10/23/25

15 California CSR 14487, Exp: 11/30/25
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