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Transcript of Paul T. Spellman, Ph.D.

Date: November 7, 2024

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

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

NanoString EX2009.001

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

- - - - - x
10X GENOMICS, INC., :
Petitioner, : Case No. IPR2023-01300
v. :
BRUKER SPATIAL : U.S. Patent No.
BIOLOGY, INC., : 11,473,142
Patent Owner. :
- - - - - X

Deposition of PAUL T. SPELLMAN, Ph.D.
Conducted Virtually
Thursday, November 7, 2024
11 a.m. EST

Job No.: 559863
Pages 1 - 125
Reported by: Debra A. Whitehead

1 Deposition of PAUL T. SPELLMAN, Ph.D., conducted
2 virtually.

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5 Pursuant to notice, before Debra Ann Whitehead,
6 E-Notary Public in and for the Commonwealth of
7 Virginia.

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20 ALSO PRESENT:

21 DOMINIC ADAMS, A/V Technician

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C O N T E N T S

EXAMINATION OF PAUL T. SPELLMAN, Ph.D.	PAGE
By Mr. Cheung	6

EXHIBITS MARKED IN TODAY'S SESSION
(Attached to the Transcript)

DEPOSITION EXHIBIT	PAGE
Exhibit 2007 Article, Advances in Ligase- Based Nucleic Acid Amplification Technology for Detecting Gene Mutations: A Review, by Li, et al.	37

EXHIBITS MARKED IN PRIOR SESSIONS
(Not attached)

DEPOSITION EXHIBIT	PAGE
Exhibit 1002 Declaration of Paul T. Spellman, Ph.D. in IPR2023-01298	19
Exhibit 1005 International Patent Application WO 2017/019456 A2	103
Exhibit 1016 Article by Stahl, et al.	69

1	EXHIBITS MARKED IN PRIOR SESSIONS - CONTINUED		
2	DEPOSITION EXHIBIT		PAGE
3	Exhibit 1043	U.S. Patent 11,473,142 B2	18
4	Exhibit 1044	Declaration of Paul T.	11
5		Spellman, Ph.D. in	
6		IPR2023-01300	
7	Exhibit 1050	October 2003 Article by	97
8		John-Francois Mercier, et al.	
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P R O C E E D I N G S

PAUL T. SPELLMAN, Ph.D.,

having been duly sworn, testified as follows:

MR. CHEUNG: Concord Cheung from Weil,
Gotshal & Manges, appearing for patent owner.

MS. KHANDURI: Pratibha Khanduri from
Sterne, Kessler, Goldstein & Fox, on behalf of
10X, the petitioner. Also on behalf of 10X,
Robert Greene Sterne and David Holman, from Sterne
Kessler.

EXAMINATION BY COUNSEL FOR PATENT OWNER
BY MR. CHEUNG:

Q Dr. Spellman, good morning.

A Good morning.

Q Can you state your name and address, for
the record.

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

Q Did you prepare for today's deposition?

A Yes.

Q What did you do to prepare?

A Read relevant documents and met with

1 attorneys.

2 Q How long did you spend in total preparing
3 for today's deposition?

4 A Probably about 30 hours.

5 Q Did you meet with counsel to prepare for
6 your deposition today?

7 A Yes.

8 Q Who did you meet with?

9 A Counsel present, and Gaby Longforth I
10 believe is her surname?

11 Q When did you meet with counsel?

12 A Over the past several weeks.

13 Q And did you spend, did you say, 30 hours
14 with counsel?

15 A No, I don't -- that would have included
16 my reading documents as well.

17 Q How long did you spend on your own
18 preparing?

19 A I don't -- I can't tell you exactly.
20 Somewhere between ten and 15 hours.

21 Q And how much time did you spend preparing
22 your declaration in this case?

1 A I couldn't tell you exactly. It's over a
2 year ago.

3 Q Can you give a ballpark? Is it more than
4 ten hours?

5 A Oh, yes.

6 Q More than 20 hours?

7 A I believe so.

8 Q Fifty hours?

9 A That's the most reasonable estimate that
10 I couldn't be certain. I'd have to check my
11 billing records.

12 Q So sitting here today, you think you
13 spent around 50 hours preparing your declaration.
14 Is that right?

15 A It's a pretty typical number for these,
16 yes.

17 Q How long did you spend with counsel
18 specifically to prepare for your deposition today?

19 A Something around 15 hours.

20 Q Did you review the patent at issue in
21 this case, the '142 patent?

22 A Yes.

1 Q Did you review Exhibit 1005 that you
2 referred to in your declaration as So 456?

3 A I reviewed So, yes.

4 Q Did you review Exhibit 1016 that refer to
5 in your declaration as Stahl 2016?

6 A Yes.

7 Q Did you review Exhibit 1017 that you
8 referred to in your declaration as Frisen?

9 A Yes.

10 Q Did you review Paper Number 25, the Board
11 Institution Decision?

12 A Not closely, if I did.

13 (Clarification by the court reporter.)

14 Q And those documents reviewed, you're
15 familiar with the substance of those documents?

16 A Key parts of them, absolutely, you know,
17 but, yes.

18 Q Have you previously been an expert in
19 patent cases?

20 A Yes.

21 Q How many cases have you been an expert
22 in?

1 A About ten.

2 Q Have you been deposed in these cases?

3 A Yes.

4 Q How many times would you say you have
5 been deposed?

6 A A similar number.

7 Q Have you previously been an expert in
8 district court cases?

9 A Yes.

10 Q Have you previously been an expert in
11 IPRs?

12 A Yes.

13 Q Are you familiar with the different parts
14 of a patent?

15 A Yes, I believe so.

16 Q Are you familiar with independent and
17 dependent claims?

18 A Yes.

19 Q Are you familiar with claim construction
20 in the context of patent law?

21 A As a -- as a practitioner of the art,
22 yes.

1 Q Did you offer any opinions on claim
2 construction in this case?

3 A I have a copy of my declaration that has
4 not been marked up.

5 On Paragraphs 55 of my declaration I
6 discuss claim construction.

7 MR. CHEUNG: Dominic, can you bring up
8 Exhibit 1044.

9 (Exhibit 1044, previously marked, not
10 attached.)

11 MR. CHEUNG: Can you go to Paragraph 55.

12 Q Dr. Spellman, is this the paragraph you
13 were referring to?

14 A Sorry, I said -- I thought I said Page
15 55. If I said Paragraph 55, I'm sorry, I was
16 referring to Paragraph 97.

17 MR. CHEUNG: Can we go to Page 55,
18 Paragraph 97.

19 Q Is this your only opinion on claim
20 construction in this case?

21 A My declaration is my testimony, and the
22 entire declaration is my testimony regarding claim

1 construction and other topics.

2 Q Regarding claim construction, can you
3 tell me which claims you have construed?

4 MS. KHANDURI: Objection. Form.

5 A From the -- in this case I examined the
6 patents of the '142 in context of the
7 specification, and interpreted those in context of
8 the infringement position from what is now Bruker,
9 and applied that logic to prior art to determine
10 whether or not the claims were valid.

11 Q Are there any specific claim terms in the
12 '142 patent where you opine that they have a
13 meaning that is not plain and ordinary?

14 A As described here in Section 97, at a
15 minimum I am using the NanoString interpretation
16 of infringement to guide my interpretation of the
17 claims.

18 Q Can you identify any claim terms where
19 you applied these, what you called NanoString's
20 interpretations?

21 A As I've said, the entire document is my
22 testimony.

1 Q Are you familiar with how claims are
2 interpreted?

3 A Yes.

4 Q You have identified Paragraph 55 -- or
5 Page 55, Paragraph 97, as including your claim
6 construction opinion.

7 Is there anywhere else in your
8 declaration where you have opined that any claim
9 terms should be given something other than their
10 plain and ordinary meaning?

11 A As I've explained, Mr. Cheung, the entire
12 document is my testimony.

13 Q Can you be any more specific about that?

14 A I'd be happy to read it aloud to you,
15 sir.

16 Q Sitting here today, do you believe that
17 any claim terms should be given anything other
18 than their plain and ordinary meaning?

19 A Under Paragraph 97, at a minimum I am
20 interpreting the claims in the context of
21 NanoString's infringement positions. In addition,
22 the entire document is my testimony.

1 Q What terms have you identified that
2 should be given something that is not their plain
3 and ordinary meaning? If there are any such
4 terms, please identify them now.

5 A They are --

6 MS. KHANDURI: Objection. Form.

7 A They are present in my declaration.

8 Q Where are they in your declaration?

9 A Would you like me to read you the entire
10 declaration?

11 Q No. I would like you to point me to the
12 specific page and paragraph.

13 A Sure. On Page 2, Paragraph 7, I identify
14 that the Stahl reference is to be used as an
15 anticipatory and obvious reference under the
16 challenged claims as they are interpreted by
17 NanoString.

18 Similarly, on Page 3 at the end of
19 Paragraph 7 I also identify the Claims 1 to 4 and
20 6 to 13 of the '142 are under NanoString's
21 interpretation of the infringement positions --
22 sorry, under NanoString's infringement positions.

1 In Paragraph 8 I also identify that the
2 claims are to be interpreted under the
3 infringement positions of NanoString. And again
4 at the end of Paragraph 8, again under
5 NanoString's interpretation of the infringement
6 positions.

7 In Paragraph 9, the discussion of Frisen
8 and solid-phase amplification.

9 Q Dr. Spellman, in these claims you've just
10 identified, are there any claim terms in those
11 claims that you're aware of for which you believe
12 NanoString applied a definition that is different
13 from its plain and ordinary meaning?

14 MS. KHANDURI: Objection. Form.

15 A I have been asked to evaluate the '142
16 validity in the context of prior art based on the
17 interpretation of the infringement positions from
18 NanoString.

19 Q Dr. Spellman, can you turn to Paragraph
20 27 in your declaration.

21 A Yes.

22 Q Do you see where you state that patent

1 claim terms are given their ordinary and customary
2 meaning as understood by a POSA at the time of the
3 invention?

4 Do you see that?

5 A Yes.

6 Q So I'm asking you, are there any claim
7 terms where that ordinary and customary meaning
8 does not apply?

9 MS. KHANDURI: Objection. Form.

10 A Following that sentence, I also identify
11 that the patent explicitly defines a claim term in
12 the specification, the patent definition controls,
13 for example.

14 Q That was not my question.

15 Are there any terms in the claims you're
16 aware of for which you believe NanoString applied
17 a definition that is different from the plain and
18 ordinary meaning?

19 MS. KHANDURI: Objection. Form.

20 A The plain and ordinary meaning is in
21 context of the specification and in context of, in
22 this case, the infringement positions as I

1 evaluated it.

2 Q Are there any claim terms, specific words
3 in the claims, where the plain and ordinary
4 meaning does not apply?

5 A My declaration is my testimony, so all of
6 the contents of my declaration are included. And
7 I can continue going through and identifying
8 sections that influence the interpretation of the
9 plain and ordinary meaning, if you'd like.

10 Q Dr. Spellman, that wasn't responsive to
11 my question.

12 Are there any specific claim terms you
13 can identify now, sitting here today?

14 MS. KHANDURI: Objection. Form.

15 A My declaration is my testimony.

16 Q Dr. Spellman, I still don't think that
17 was responsive. We will move on from now. But if
18 you keep giving me nonresponsive answers, we're
19 going to have a problem today. Okay? Let's move
20 on to another topic.

21 Are you familiar with the Doctrine of
22 Plain Differentiation?

1 A I'm not sure that I am.

2 Q You understand that the '142 patent has
3 independent and dependent claims?

4 A Can you please bring up the '142 claims.

5 MR. CHEUNG: Please bring up Exhibit
6 1043.

7 (Exhibit 1043, previously marked, not
8 attached.)

9 MR. CHEUNG: And the claims should be on
10 the last page of the file. So if you can zoom in
11 to the bottom half the page.

12 A Yes, what's the question?

13 Q Do you see that there are independent and
14 dependent claims in this '142 patent?

15 A I see Claim 1 as an independent claim,
16 and all the other claims is dependent upon Claim
17 1.

18 Q Do you understand that Claims 2 through
19 13 are narrower in scope than Claim 1?

20 A Yes.

21 Q Are you familiar with inherency in patent
22 law?

1 A I have a discussion of inherency in my
2 declaration.

3 MR. CHEUNG: Dominic, can you bring up
4 Exhibit 1002.

5 MS. KHANDURI: Objection. Scope.
6 (Exhibit 1002, previously marked, not
7 attached.)

8 MR. CHEUNG: Please go to Paragraph 35.

9 MS. KHANDURI: Objection. Scope.
10 Foundation.

11 Q Dr. Spellman, this is your declaration in
12 a related IPR. Please review Paragraphs 35
13 through 37.

14 A Sorry, which IPR case was this?

15 Q This is your declaration in the IPR of
16 the related '689 patent.

17 A Okay.

18 Q Sitting here today, do you disagree with
19 any portions of these paragraphs?

20 A I haven't reviewed it, and I believe this
21 is under advice of counsel. I'm not an attorney.

22 Q Okay. If you'll go to Paragraph 35 in

1 your declaration for this case.

2 A Yes, I have it in front of me.

3 Q Is there anything in Paragraph 35 that
4 you disagree with?

5 A My declaration is my testimony. I have
6 not identified any material errors.

7 Q Is there anything in Paragraph 36 you
8 disagree with?

9 A I haven't identified any errors.

10 Q Is there anything in Paragraph 37 you
11 disagree with?

12 A Again, I have not identified any errors
13 in my declaration.

14 Q And is there anything in Paragraph 38
15 that you disagree with?

16 A Same answer.

17 Q In your declaration in this case, are
18 there any claim elements where you relied upon
19 inherency?

20 MS. KHANDURI: Objection. Scope.
21 Relevance.

22 A Which case are you referring to?

1 Q Your declaration for the '142 patent.

2 A My declaration is my testimony. I can
3 read it to you, if you'd like.

4 Q Sitting here today, can you recall if
5 there are any claim elements where you relied on
6 it being inherently present?

7 A My declaration is my testimony.

8 Q Dr. Spellman, you reviewed your
9 declaration before coming here today. Correct?

10 A Correct.

11 Q And you spent a significant amount of
12 time preparing for today's deposition. Correct?

13 A I prepared for today's deposition.

14 Q So you prepared about 30 hours, you told
15 me earlier.

16 Is that right?

17 A Something on that order.

18 Q Now, can you direct me to any paragraph
19 in your declaration where you invoked inherency to
20 meet a claim element?

21 A My declaration is my testimony,
22 Mr. Cheung.

1 Q Dr. Spellman, that is nonresponsive. I
2 need you to tell me if you invoke inherency in
3 your declaration for the '142 patent?

4 A I'll read --

5 MS. KHANDURI: Objection. Form.

6 Q Dr. Spellman, I'm going to ask again.
7 Are there any claim elements where you invoked
8 inherency to meet the claim?

9 MS. KHANDURI: Objection. Form.

10 A The declaration is my testimony. I'm
11 happy to ask -- answer a question about the
12 declaration specifically.

13 Q Dr. Spellman, I'm asking you about the
14 contents of your declaration.

15 A Indeed, it is more than 150 -- almost 150
16 pages long, and you're asking me to memorize
17 specific sections and answer you in a memorization
18 test, and I won't do that, sir.

19 Q Dr. Spellman, you prepared for around 30
20 hours for today. Correct?

21 A Yes.

22 Q And then you spent approximately 50 hours

1 preparing your declaration. Correct?

2 A That was more than a year ago, sir.

3 Q So, and you can't tell me anywhere in
4 your declaration if you invoked inherency in any
5 portion of it.

6 Is that right?

7 A Mr. Cheung, my declaration is my
8 testimony. I'm happy to review it for you and go
9 over it. You're asking me to identify specific
10 section of a 150-page document from memory, and I
11 won't do it.

12 Q Dr. Spellman, you have your declaration
13 in front of you. You are welcome to do a search.

14 I just need a yes or no, did you invoke
15 inherency for any claim element or not.

16 MS. KHANDURI: Objection. Form.

17 A Yes. And I was reading my declaration,
18 and then you stopped me.

19 Q Dr. Spellman, go ahead and take some time
20 to review.

21 Dr. Spellman, do you have an electronic
22 copy of your declaration that we provided?

1 A I do not, no.

2 MR. CHEUNG: Counsel, is there a reason
3 you did not share the exhibit with Dr. Spellman?

4 MS. KHANDURI: Yes, there is a reason.
5 Because it includes -- we can discuss offline, if
6 you like. But, yes, there is a reason.

7 MR. CHEUNG: Counsel, everything in the
8 file that was sent over was on the public docket
9 for this IPR.

10 MS. KHANDURI: Yes, but not everything
11 was -- but not everything -- not all the documents
12 that you sent us were reviewed by Dr. Spellman in
13 preparing his declaration.

14 MR. CHEUNG: Counsel, I don't think
15 that's relevant. You should have shared the files
16 with Dr. Spellman.

17 MS. KHANDURI: We can share it now.

18 MR. CHEUNG: Now we're just wasting time
19 on the record.

20 Q Dr. Spellman, do you have your
21 declaration now?

22 A Yes, it arrived in the chat.

1 Q Now, can you open it and perform a search
2 and let me know if there were any claim elements
3 where you invoked inherency?

4 MS. KHANDURI: Objection. Form.

5 A The specific words "inherent" or
6 "inherency" do not appear to be present anywhere
7 other than in Section 35, 36, 37.

8 Q You mean paragraphs, right, Dr. Spellman?

9 A Yes.

10 Q So based on that, can you confirm,
11 sitting here today, that you are not relying on
12 inherency for any claim elements in your
13 declaration?

14 MS. KHANDURI: Objection. Form.

15 A I'm not an attorney, and I do not know
16 whether or not it needs to be labeled as such in
17 the explicit manner that you've identified.

18 My declaration is my testimony, and all
19 of its contents I agree with.

20 Q Dr. Spellman, you can confirm that the
21 word "inherency," "inherently," or any form of the
22 word, does not appear outside of Paragraphs 35 to

1 38.

2 Is that correct?

3 A Based on my search of the PDF, the
4 document does not include those words, to the best
5 of my ability to identify.

6 Nonetheless, the entire document is my
7 testimony.

8 Q Dr. Spellman, do you understand the
9 concept in patent law of a person of ordinary
10 skill in the art?

11 A Yes.

12 Q Please turn to Paragraph 25 of your
13 declaration.

14 A Yes.

15 Q Is this your definition of a person of
16 ordinary skill in the art as it relates to the
17 '142 patent?

18 A It is my understanding, yes.

19 Q Are you an expert in spacial detection of
20 a target analyte in a tissue sample?

21 A I believe I meet the definition of a POSA
22 in at least.

1 Q So to confirm, you're testifying that you
2 are someone of ordinary skill in the art as to the
3 '142 patent.

4 Is that right?

5 A I at least meet the definition of a POSA.

6 Q Are you familiar with methods for spacial
7 detection?

8 A Yes.

9 Q Did you prepare your declaration from the
10 viewpoint of a person of ordinary skill in the
11 art?

12 A Yes.

13 Q And directing you back to your definition
14 of a POSA.

15 Do you agree that a person of ordinary
16 skill in the art would be familiar with methods
17 and techniques in molecular biology, genetics, and
18 genomics?

19 A The text actually says "bioinformatics"
20 on my page. But, yes. I think. Maybe -- maybe
21 there is a second section where it has a similar
22 phrasing.

1 Q Are you familiar with DNA synthesis?

2 A Yes.

3 Q Would person of ordinary skill in the art
4 understand what a DNA synthesis reaction is?

5 MS. KHANDURI: Objection. Form.

6 A I think a person of ordinary skill in the
7 art would understand what DNA synthesis was, and
8 that there are a large number of reactions capable
9 of meeting the definition of a DNA synthesis
10 reaction.

11 Q In the context of nucleic acids, can you
12 provide some examples of a synthesis reaction?

13 MS. KHANDURI: Objection. Form.

14 A A far-from-limiting set of DNA synthesis
15 reactions include the use of a nucleic acid
16 polymerase such as reverse transcriptase or RNA
17 polymerase or DNA polymerase to synthesize either
18 homopolymers, templated polymers, nontemplated
19 polymer sequences.

20 From the point of view of a chemistry,
21 there would be a set of reactions that meet the
22 definition of DNA synthesis that are in vitro

1 synthesis of molecules by, for example,
2 phosphoramidite chemistry.

3 There is a very long list of things that
4 would meet the criteria of DNA or nucleic acid
5 synthesis.

6 Q Are you familiar with DNA amplification?

7 A Yes.

8 Q Is there a difference between a DNA
9 synthesis reaction and a DNA amplification
10 reaction?

11 A The first step of a DNA amplification
12 reaction is a DNA synthesis reaction. So it would
13 depend on context quite often.

14 Q Would a person of ordinary skill in the
15 art understand the term "synthesis" and
16 "amplification" differently?

17 A It would be dependent upon the context of
18 the language utilized.

19 Q Let's put it this way: Are there
20 synthesis reactions that are not amplification
21 reactions?

22 A Yes.

1 Q Can you provide an example?

2 A The trivial one of using phosphoramidite
3 chemistry to make a chain of nucleic acids from
4 scratch.

5 Q Can you think of any other examples?

6 A That would always meet the criteria of
7 never being -- that would never meet the criteria
8 of being an amplification step? I'd have to think
9 a long time about that.

10 Q How about, are there any amplification
11 reactions that are not synthesis reactions?

12 MS. KHANDURI: Objection. Form.

13 A I don't know that I've ever thought about
14 the question deeply, so I'm not sure I'm prepared
15 to render an opinion on that.

16 Q Do you have any belief one way or the
17 other whether amplification reactions and
18 synthesis reactions are exclusive of each other?

19 MS. KHANDURI: Objection. Form.

20 A What do you mean by "exclusive"?

21 Q Where you can have amplification
22 reactions that are not synthesis reactions.

1 MS. KHANDURI: Objection. Form.

2 A I can't think of any.

3 Q Are you familiar with PCR?

4 A Yes.

5 Q Are you familiar with the reagents that
6 are used to perform PCR?

7 A Yes.

8 Q What is the purpose of PCR?

9 A PCR, as defined in the Mullis invention,
10 would allow targeted amplification of a specific
11 region of DNA using oppositely pointed primers.

12 So the purpose of PCR is to allow a
13 practitioner of the art to create many copies of a
14 small segment of DNA using specific DNA sequences
15 as end stops.

16 Q Is DNA synthesized during PCR?

17 A Yes.

18 Q Is DNA amplified during a PCR?

19 A Generally, yes.

20 Q Are there circumstances where DNA is not
21 amplified during PCR?

22 A I am sure that someone has done something

1 clever once to create a situation where it may not
2 happen.

3 Q Can you provide more details?

4 A No, I don't believe I can.

5 Q During PCR, what is being amplified?

6 MS. KHANDURI: Objection. Form.
7 Foundation.

8 A In the very specific use of the term in
9 the context of Kary Mullis's invention of PCR, the
10 DNA sequence that is between two reverse
11 complementary -- sorry, two primers, one of which
12 is on the reverse complement strand of the other,
13 and in some applications other sequences that are
14 either intentionally or unintentionally amplified
15 simultaneously.

16 Q Is the molecule being amplified during
17 PCR referred to as a template?

18 A That would be a common thing to do, yes.

19 Q What is your understanding of what a
20 template in the context of PCR is?

21 A When one is designing a PCR to -- so
22 backing up a step.

1 PCR is a very broad process that is used
2 in nearly all of molecular biology circa 2015.
3 And in that context it is used widely to achieve
4 all sorts of things.

5 For example, it is not uncommon to do PCR
6 with random primers, where the -- where DNA
7 molecules are amplified more or less
8 indiscriminately using random sets of primers that
9 amplify them or -- but to answer the question more
10 broad -- more specifically, the template is the
11 thing being amplified.

12 Q Is the PCR product referred to as an
13 amplicon?

14 A It is one name that it's referred to, but
15 far from the only one. It is possible to have
16 many amplicons. So it's not a -- it's not a
17 strict definition from a PCR reaction circa 2015.

18 Q When would a person of ordinary skill in
19 the art have known -- first known about PCR?

20 A My recollection is that PCR in the Kary
21 Mullis version is published circa 1982 is my
22 recollection. Could be a little later than that.

1 And iterative improvements to PCR occurred for --
2 to today.

3 So the use of PCR would have been
4 widespread certainly by the early 1990s, and
5 derivative processes that add refinement and
6 extensions to the original idea continue to this
7 day.

8 Q Does the PCR product have the same
9 sequence as the template?

10 MS. KHANDURI: Objection. Form.

11 A The PCR product is double-stranded in
12 most implementations, although there are versions
13 of PCR where one is clever enough to remove one of
14 the two stands. And the first copy of the PCR
15 reaction is actually the reverse complement to a
16 portion of the template that may extend beyond the
17 internal -- the targeted amplicon.

18 The final, in a traditional PCR reaction,
19 of which again there are probably at this point
20 thousands of derivatives. But in the Kary Mullis
21 version of the PCR, the final molecule would
22 consider -- would be considered to be a duplex DNA

1 sequence with one of the strands having exactly
2 the same sequence as the initial template.

3 However, PCR is well known to have
4 errors, and so there are a whole series of things
5 that can happen where the final sequence might not
6 be identical.

7 Further, the primer sequences themselves
8 don't have to match the template perfectly. And
9 so you can change the sequence at the primer sites
10 quite effectively. I don't know how much detail
11 you want me to go into.

12 But I'm saying that shortly -- generally,
13 yes, but there are lots of variations where it
14 would be not.

15 Q So barring any errors, the amplicon will
16 have one strand that matches the sequence of the
17 template and the reverse complement together as a
18 double-stranded product.

19 Is that right?

20 MS. KHANDURI: Objection. Form.

21 A In most versions, not counting the
22 primers themselves, that would be correct.

1 Q Does the primers in the PCR reaction bind
2 to the template?

3 A In the Kary Mullis version, absolutely,
4 yes. And to the first and second derivative
5 rounds of PCR amplification.

6 Q Does the polymerase bind to the template?

7 MS. KHANDURI: Objection. Form.

8 A I'm not sure I would use the word "bind,"
9 but it's not an unreasonable use of the term.

10 Q Is the template a substrate of the
11 polymerase?

12 A Yes.

13 Q Are there methods of DNA synthesis that
14 do not involve primers?

15 A Yes.

16 Q Can you provide an example?

17 A Well, going back to the synthesis of
18 oligonucleotides by phosphoramidite chemistry, for
19 example.

20 Q Have you heard of ligase chain reaction?

21 A Yes.

22 Q Based on your understanding, how does

1 ligase chain reaction work?

2 A I'd have to bring it -- if you have a
3 picture of it, I can explain it to you. But I
4 can't explain it off the top of my head.

5 MR. CHEUNG: Dominic, can you bring up
6 the document marked Tab A. Please mark this
7 document as Exhibit 2007.

8 (Exhibit 2007 marked for identification
9 and is attached to the transcript.)

10 MS. KHANDURI: Can we flip through the
11 document before Dr. Spellman answers the question?
12 And can we also get a copy.

13 MR. CHEUNG: Please drop the document in
14 the Zoom chat.

15 MS. KHANDURI: Is it supposed to be 1028,
16 Exhibit 1028? The one that we got in the chat?

17 MR. CHEUNG: No. The document is
18 named -- the document name is Tab A.

19 A I have received Tab A, I'm downloading
20 it.

21 Yes, I have tab -- I have Advances in
22 Ligase-Based Nucleic Acid Amplification Technology

1 For Detecting Gene Mutations: A Review, open.

2 MS. KHANDURI: Hold on. Let me review
3 the document first.

4 Okay. Go ahead. Thank you.

5 Q Dr. Spellman, if you could turn to the
6 second page of the article and review the middle
7 on the right-hand side where it starts saying,
8 "Ligase chain reaction"?

9 A Are we looking at Figure 1?

10 Q Right. The paragraph to the right just
11 above Figure 1.

12 A Yeah.

13 Q Is this consistent with your
14 understanding of ligase chain reaction?

15 MS. KHANDURI: Objection. Relevance.

16 A I haven't read it in detail yet, but I
17 can spend the time to do so if you'd like.

18 Q Sure. Please do that. It's just one
19 paragraph.

20 A Oh, I'll need to read the context around
21 it as well. I'll need to start at the beginning.

22 Q Dr. Spellman, let me direct you to Figure

1 1.

2 A Sorry. I'm reviewing the document. Do
3 you need me to not review the document?

4 Q How long do you think you will need?

5 A I don't know. I haven't -- I've never
6 read this document before.

7 Q Dr. Spellman, we don't have time for you
8 to read the whole document. Let me just direct
9 you to Figure 1.

10 A Oh, no. I have the right to read the
11 whole document, sir.

12 Q Dr. Spellman, please just do as I
13 instruct.

14 A Yes.

15 Q Does Figure 1, does this refresh your
16 recollection of what ligase chain reaction is?

17 MS. KHANDURI: Objection. Relevance.

18 A I'd have to think about it.

19 Are you asking me to read the document to
20 put this figure in context? For example, this
21 figure --

22 Q No.

1 A This figure --

2 Q Dr. Spellman, just based on your
3 understanding of ligase chain reaction, does it
4 involve primers?

5 MS. KHANDURI: Objection. Form.
6 Relevance. Scope.

7 A I object to this figure. It has no
8 legend at all. It has a simple schematic diagram
9 depicting --

10 Q Dr. Spellman, I am asking you based on
11 your own understanding of ligase chain reaction,
12 and not in context of this figure.

13 MS. KHANDURI: Counsel, please let the
14 witness finish his answers before you start asking
15 him another question.

16 Objection. Relevance. Scope.

17 A Counsel, I -- I can review this and
18 answer your questions about ligase chain reaction.
19 Or I can tell you that I can't explain it without
20 review, as I've already testified.

21 Q Dr. Spellman, based on your
22 understanding, does ligase chain reaction involve

1 primers?

2 MS. KHANDURI: Objection. Scope.

3 Relevance.

4 A I don't know what you mean, sir.

5 Q Dr. Spellman, you are an expert in this
6 field. Correct?

7 A Yes.

8 MS. KHANDURI: Objection. Form.

9 Q So based on your understanding, does
10 ligase chain reaction involve primers?

11 MS. KHANDURI: Objection. Scope.

12 Relevance.

13 A In my uses of ligation for amplification,
14 for example in our work on molecular inversion
15 probes which use ligase to -- as a step in the
16 amplification step, it would depend very heavily
17 on what you mean by the word "primer."

18 Q Do you have an understanding of what a
19 primer is?

20 A Depending on the use of the term, a POSA
21 may or may not attribute the word "primer" to any
22 DNA, RNA, oligonucleotide sequence that is

1 complementary to another strand.

2 The primer in its most original context
3 is generally specific to DNA polymerases.
4 However, I am sure that people of ordinary skill
5 in the art in the literature use primer in many
6 other contexts.

7 But the original use of the term "primer"
8 is to distinguish between DNA polymerases that are
9 template-derived and extend off of an existing
10 oligonucleotide sequence.

11 So, but the term "primer" has taken on
12 lots and lots of different meanings in lots and
13 lots of different contexts.

14 Q Based on that original understanding and
15 meaning of primers, does ligase chain reaction
16 involve primers?

17 MS. KHANDURI: Objection. Form. Scope.
18 Relevance.

19 A It would depend on how a person of
20 ordinary skill is -- of the art is using the term.

21 Q Based on that original understanding of
22 the term primer as you just described, does ligase

1 chain reaction involve the use of primers?

2 MS. KHANDURI: Objection. Relevance.

3 Scope.

4 A Ligase chain reaction, to the best of my
5 knowledge, if it is only using ligase as the basis
6 for completing copies, would not technically use a
7 primer in the -- in the use of the term, with DNA
8 polymerase.

9 Q In the '142 patent, is the term "primer"
10 used according to the original understanding of
11 the term that you just gave?

12 MS. KHANDURI: Objection. Form.

13 A In the specification of the '142?

14 Q Yes.

15 A Oh, I'd have to read it in detail. It's
16 quite long.

17 Q So sitting here today, you're not able to
18 give an opinion one way or the other of how the
19 word "primer" is used in the specification.

20 Is that correct?

21 MS. KHANDURI: Objection. Form.

22 A Let me go to my declaration for a moment.

1 MS. KHANDURI: And, Counsel, after this
2 question can we have a break? It's been an hour.

3 MR. CHEUNG: Yeah, that's fine.

4 A Can you repeat your question?

5 Q In the '142 patent, is the term "primer"
6 used according to the original understanding of
7 the word "primer" that you gave?

8 MS. KHANDURI: Objection. Form.

9 A Minimally one -- it encompasses the use
10 of reverse transcriptase rather than DNA
11 polymerase and the use of a primer for reverse
12 transcription.

13 But I only evaluated the '142 in this
14 case in the context of the '142 claims. So I am
15 not prepared to render an opinion on all the other
16 ways they might have used primer in the
17 specification.

18 If you'd like to examine specific ones,
19 I'd be happy to do so.

20 MR. CHEUNG: Okay. Let's take a break
21 now. Let's go off the record.

22 (A recess was taken.)

1 BY MR. CHEUNG:

2 Q Dr. Spellman, have you heard of rolling
3 circle amplification?

4 A Yes.

5 Q Based on your understanding, how does
6 rolling circle amplification work?

7 A Broadly speaking, one creates a circular
8 DNA molecule and initiates polymerization of a
9 nucleic acid strand that goes around and around
10 until it stops.

11 Q When was rolling circle amplification
12 first performed?

13 A I don't know.

14 Q Would a person of ordinary skill in the
15 art have known about rolling circle amplification?

16 MS. KHANDURI: Objection. Form.

17 A To the best of my knowledge, rolling
18 circle amplification was invented prior to the
19 filing date of this IPR -- sorry, of the filing
20 date of the patent.

21 Q Is rolling circle amplification a form of
22 DNA synthesis?

1 A A POSA may or may not say yes to that.
2 It uses DNA synthesis, for sure.

3 Q And what would you say?

4 A It would depend on the context of the
5 language.

6 Q In the context of the '142 patent, when
7 you perform rolling circle amplification, are you
8 performing DNA synthesis?

9 A I'm not sure.

10 Q How does rolling circle amplification
11 differ from PCR?

12 MS. KHANDURI: Objection. Relevance.

13 A Well, again, I'm going to use just the
14 classic definition of PCR rather than the many
15 hundreds or thousands of derivatives of PCR.

16 But rolling circle amplification, some
17 versions of it only use one strand. I believe
18 there are others that go in both directions and
19 create rolling circles of circles. But the
20 simplest version of rolling circle amplification,
21 to my knowledge, extends in one direction and does
22 not have a stop as you would traditionally have in

1 PCR.

2 Q Does rolling circle amplification involve
3 primers as understood in the original
4 understanding you gave earlier?

5 MS. KHANDURI: Objection. Form.

6 A I don't think it has to. I think if one
7 is using an RNA polymerase, one could do rolling
8 circle amplification without. So it would just
9 depend on the exact configuration of the assay.

10 Q So just to confirm, a rolling circle
11 amplification can involve no primers.

12 Is that right?

13 A If one was using an RNA polymerase, one
14 could perform rolling circle without -- without a
15 primer, I believe. But again, it would depend on
16 the use case and how it's defined in the -- in the
17 assay as developed.

18 Q Does rolling circle amplification
19 involving two primers?

20 MS. KHANDURI: Objection. Relevance.

21 A I'm sure someone has done a process of
22 rolling circle amplification with more than one

1 primer.

2 Q So to confirm, rolling circle
3 amplification can be performed with zero primers
4 up to any number of primers.

5 Is that correct?

6 MS. KHANDURI: Objection. Form.
7 Relevance.

8 A In the broadest scheme, yes, I think it
9 could.

10 Q And how about with just one primer?

11 MS. KHANDURI: Objection. Form.
12 Relevance.

13 A That would be the simplest and most
14 obvious design.

15 Q Is that also the most common design?

16 MS. KHANDURI: Objection. Form.
17 Relevance.

18 A I have not done a deep assessment of all
19 the ways people are most commonly using rolling
20 circle amplification.

21 Q To your understanding, is using one
22 primer with rolling circle application the most

1 common configuration?

2 MS. KHANDURI: Objection. Form.

3 Relevance.

4 A I don't know.

5 Q Dr. Spellman, have you heard of
6 solid-phase amplification?

7 A Yes.

8 Q How long has solid-phase amplification
9 been performed?

10 A I couldn't tell you exactly.

11 Q Was solid-phase amplification performed
12 before 2015?

13 A Yes.

14 Q Would a person of ordinary skill in the
15 art have known about solid-phase amplification?

16 A It was published prior to 2015, so I
17 would think so.

18 Q What is your understanding of solid-phase
19 amplification?

20 A Very broadly speaking, solid-phase
21 amplification can include methods in which there
22 is, instead of being in solution, the reaction

1 occurs with a covalent attachment to a solid
2 substrate.

3 Q Is this the understanding you applied in
4 your declaration in this case?

5 A I think you will find in my declaration
6 there is at least one situation where I use
7 NanoString's interpretation infringement position
8 to guide my interpretation of solid-phase
9 amplification.

10 Q To your understanding, is there any
11 difference of the term "solid-phase amplification"
12 between what a person of ordinary skill in the art
13 will understand and what you have applied in this
14 case?

15 MS. KHANDURI: Objection. Form.

16 A Again, I think rolling -- sorry,
17 "solid-phase amplification" is a very broad term,
18 and it can mean lots of things.

19 Q Dr. Spellman, can you be any more
20 specific?

21 A No.

22 Q Let me repeat the question. What is the

1 difference between your understanding of
2 solid-phase amplification and what NanoString's
3 contentions for solid-phase amplification are?

4 MS. KHANDURI: Objection. Form.

5 A I have evaluated NanoString's
6 infringement positions and applied that logic to
7 the specification and the claims to evaluate
8 whether or not prior art meets the limit --
9 existed prior to the filing date of the '142
10 patent. And I conclude that based on that, that
11 the patent is not valid.

12 So I've only evaluated in the context
13 exactly of the -- of the specification and the
14 infringement contentions.

15 Q Dr. Spellman, that's nonresponsive and
16 not what I was asking.

17 Can you, sitting here now, tell me
18 specifically if there is any difference in the
19 meaning of the term "solid-phase amplification"
20 between your general understanding of this term
21 and what you contend is NanoString's
22 interpretation of the term that you applied in

1 your declaration?

2 MS. KHANDURI: Objection. Form.

3 A As I've said before, Counselor, my
4 declaration is my testimony. I've evaluated the
5 claims in the context of the specification and the
6 infringement positions from NanoString. That is
7 all I have done.

8 Q Dr. Spellman, that's not what I'm asking.
9 That's still nonresponsive.

10 I'm asking you now, can you specifically
11 tell me the definition of solid-phase
12 amplification you applied in your analysis in your
13 declaration that is different from your
14 understanding of the term "solid-phase
15 amplification"?

16 MS. KHANDURI: Objection. Form.

17 A I don't have a specific definition of
18 solid-phase amplification.

19 I know -- I know things that are, and I
20 know things that are not. And then there are
21 boundary conditions. And it would depend on the
22 interpretation, and in this case the specification

1 and the infringement positions.

2 Q Dr. Spellman, you told me earlier that a
3 person of ordinary skill in the art would
4 understand solid-phase amplification to be
5 something involving an attachment to a solid
6 surface.

7 Now, is this understanding any different
8 from what you applied in your declaration?

9 A The requirement --

10 MS. KHANDURI: Objection. Form.

11 A The requirement for a solid substrate I
12 did not obviate.

13 Q Dr. Spellman, what do you mean by "not
14 obviate"?

15 A I used the requirement for a solid
16 substrate in my assessment.

17 Q Are there any other differences?

18 A As I've discussed in my declaration,
19 there are specific utilization of the infringement
20 position that is interpreted in the context of the
21 specification.

22 Q And how was that specific utilization

1 different from the understanding that a person of
2 ordinary skill in the art would have of
3 solid-phase amplification?

4 A So my discussion of this starts on Page
5 83 of my declaration and Claim 5 regarding
6 solid-phase amplification reactions. And you'll
7 note in the top of Page 84 I take the NanoString
8 infringement position and its use of its
9 interpretation of what constitutes solid-phase
10 amplification.

11 It's in my declaration.

12 Q So what constitutes solid-phase
13 amplification, as you've applied in your
14 declaration?

15 A You just would like me to read my Claim 5
16 discussion starting on Page 83?

17 Q I would like you to answer my question.

18 A My discussion starting on Page 83 of
19 Claim 5.

20 Q So in your declaration, which paragraph
21 sets out the definition of solid-phase
22 amplification that you used?

1 A You'll see that on the top of Page 84
2 there is a figure from the -- from the -- from the
3 process Visium Fresh Frozen that -- in which
4 NanoString identifies its contention that this is
5 solid-phase amplification, the second strand
6 synthesis step identified in that figure, as a
7 minimum.

8 Q So is there any difference between your
9 definition of solid-phase amplification that you
10 draw from that figure you just pointed me to that
11 is different from the general understanding of the
12 term "solid-phase amplification"?

13 MS. KHANDURI: Objection. Form.

14 A The literature is very broad, and I am
15 certain that under some pieces of literature this
16 would not meet the definition, and in other pieces
17 of the literature it would. So I'm not sure how
18 to answer the question.

19 Q To your understanding, is the term
20 "solid-phase amplification" defined in the patent?

21 MS. KHANDURI: Objection. Form.

22 A I'd have to review the '142 specification

1 in detail to be sure, to identify that.

2 MR. CHEUNG: Dominic, can you bring up
3 Exhibit 1043, which is the '142 patent. And let's
4 look at the claims on the last page.

5 MS. KHANDURI: Can we also get a copy of
6 the exhibit in the chat so Dr. Spellman can
7 download it.

8 Q Dr. Spellman, I want to direct you to
9 Claim 7.

10 Do you see that Claim 7 requires
11 amplifying a library using the DNA products as
12 templates?

13 A Yes.

14 Q And now I will direct you to Claim 5.

15 Do you see that Claim 5 requires
16 performing a solid-phase amplification reaction
17 during Steps C and D of Claim 1?

18 A Yes.

19 Q Do you see that Claim 7 depends on Claim
20 1?

21 A Yes.

22 Q Do you see that Claim 5 indirectly

1 depends on Claim 1?

2 A Yes.

3 Q Now I would like to direct you to Claim
4 1, Steps C and D.

5 Do you see that these steps require
6 synthesizing DNA products?

7 A Yes.

8 Q Do you agree that Claim 1 is not limited
9 to amplification reactions to synthesized DNA
10 products?

11 MS. KHANDURI: Objection. Form.

12 A You're asking whether or not the reaction
13 in C and D, it does not have to be an
14 amplification reaction. Correct?

15 Q Correct, that was the question. Yes.

16 A That's correct.

17 Q Looking back again at Claim 1, Step C and
18 D.

19 Do you see that these steps require
20 synthesizing pluralities of DNA products?

21 A Yes.

22 Q Now can you turn to Paragraph 107 of your

1 declaration.

2 A Yes.

3 Q In Paragraph 107, do you see that you
4 italicized cDNA synthesis, and then again cDNA
5 synthesis, and then two rows down, synthesized
6 cDNA?

7 A Yes.

8 Q And then near the end of that paragraph
9 do you see you included an annotated figure of 1A?

10 A Yes.

11 MS. KHANDURI: Objection. Form.

12 Q And do you see that you state that Figure
13 1A depicts cDNA synthesis as red bars?

14 A Yes.

15 Q Do you agree that you identified the red
16 bars as the claimed DNA products?

17 A The DNA products that meet the limitation
18 of the claim are visualized in Stahl in Figure 1A.
19 But the method that Stahl develops is stepwise.
20 And the method that meets the limitations of
21 claims actually depends on Figure 2A as a -- to
22 understand the spacial detection method of Stahl.

1 Q Right. So my question is a little
2 different; it's which molecule is the synthesized
3 DNA product in this claim step?

4 MS. KHANDURI: Objection. Form.

5 A Products that meet the limitations of
6 Claim 1 include both the first and second strand
7 synthesis.

8 Q Can you show me where you identified the
9 second strand as meeting the claimed DNA products?

10 A If you go to my discussion of Claim 5 on
11 Page 83, you'll see that I reference the second
12 strand as meeting the claimed -- as meeting the
13 claim limitation. And my declaration is in its
14 entirety. And claim -- and it should be read that
15 way.

16 Q Did you identify the second strand in
17 Paragraphs 107 to 108?

18 A As I've discussed, Claim -- my discussion
19 of Claim 5 also identifies the second strand
20 synthesis limitations of Claim 1 synthesis step.

21 Q Dr. Spellman, can you identify the
22 paragraph number where you identify the second

1 strand as meeting the claimed DNA products?

2 A Paragraph -- I believe Paragraph 169
3 meets it, that the entire discussion of Claim 5
4 identifies second strand synthesis as including
5 all of the elements of first strand synthesis.

6 Q Dr. Spellman, what is the language in
7 Paragraph 169 that points to the second strand
8 cDNA as the claimed DNA products?

9 A I believe the first sentence covers it.

10 Q Do you rely on anything else in Stahl for
11 disclosing the claimed DNA products?

12 A I will highlight that my declaration is
13 my testimony, and I stand by it fully. I also
14 believe that the infringement positions of
15 NanoString identify second strand synthesis as a
16 synthesis reaction.

17 Q Is there anywhere else in your
18 declaration other than Paragraph 169 where you
19 point to the second strand synthesis as meeting
20 the claimed DNA products?

21 A My entire discussion of Claim 5 is
22 relevant to the topic.

1 Q Is there any other specific paragraph
2 where you can point to to show this?

3 A I just pointed to an entire section. I'm
4 not sure what you need me to do. It's all
5 relevant.

6 Q Can you point to a specific paragraph
7 other than Paragraph 169 where you state that the
8 second strand cDNA is the claimed DNA products?

9 MS. KHANDURI: Objection. Form.

10 A I believe all of this section on Claim 5
11 is relevant, as well as much of the remaining
12 document, Paragraphs 166, 167, the figure at the
13 top of Page 84, 168, 170, 171 I believe.

14 Q Out of this entire section, what is the
15 clearest disclosure that the second strand cDNA is
16 the claimed DNA product?

17 MS. KHANDURI: Objection. Form.

18 A I actually think the clearest disclosure
19 is in 167, in that the Visium Fresh Frozen product
20 is identified as infringing, and specifically the
21 second strand synthesis, which is a synthesis
22 reaction that uses a molecule copied from the

1 template as a basis, creates all of the elements
2 that are necessary for Claim 1. And it's an
3 infringement position of NanoString that does
4 that.

5 Q Can you go to Paragraph 209 of your
6 declaration.

7 Do you see that you included an annotated
8 Figure 25A in Paragraph 209?

9 A Yes.

10 Q Do you see the annotation you added of,
11 quote, "synthesizing a plurality of DNA products,
12 first strand cDNA," with an arrow pointing at the
13 dotted line in the figure?

14 A Yes.

15 Q Do you agree for So '456 that you
16 identified the first strand cDNA as the claimed
17 DNA products?

18 MS. KHANDURI: Objection. Form.

19 A I identified that the first strand cDNA
20 meets the limitations, yes.

21 Q Do you rely on anything else in So '456
22 for disclosing the claimed DNA products?

1 A The entire declaration is my testimony.
2 So, yes, I rely on my entire declaration.

3 Q Sitting here today, are you able to point
4 me to any specific paragraph where you clearly
5 identify a specific portion of So '456 for meeting
6 the claimed DNA products?

7 A Page 106, Paragraph 217. So '456 method
8 synthesizes the second strand cDNAs using the
9 first strand cDNAs as templates. And so the first
10 strand cDNAs used the collected mRNAs as templates
11 and, thereby, the second strand cDNA is
12 template-derived from the captured mRNA.

13 Later on in the same paragraph I discuss
14 releasing the second strand cDNAs comprising the
15 sequence complementary to the first cDNA including
16 all the required elements of the first capture
17 probe.

18 And then in Claim -- the whole discussion
19 of Claim 5 would be relevant for So '456 as well.
20 Particularly Paragraph 231. The entire Claim 5
21 discussion starting at Page 110, particularly 231,
22 232, 233, 234, 235, and the rest of the document.

1 Q Which paragraph has the clearest opinion
2 of which strand is the claimed DNA product?

3 MS. KHANDURI: Objection. Form.

4 A All of Claim 5, but specifically 231 and
5 232 and onward.

6 Q Please go to Paragraph 142 of your
7 declaration. Let me know when you're there.

8 A Yes, I'm at Paragraph 142.

9 Q Do you see the second sentence in that
10 paragraph where you state, "Specifically, Stahl
11 2016's method performs an initial in vitro
12 transcription/amplification to produce amplified
13 RNA molecules followed by adding DNA adapters to
14 the end of the amplified RNA, reverse transcribing
15 the amplified RNA into cDNA, and then performing
16 PCR to amplify the cDNA to add Illumina paired-end
17 sequencing flow-cell binding sites and index
18 sequences before sequencing"?

19 A Yes.

20 Q Do you see in that paragraph where you
21 italicized three phrases: "Amplified a cDNA,"
22 "amplified by qPCR," and "were amplified"?

1 A Yes.

2 Q Is the cDNA that is reverse transcribed
3 from amplified RNA, what is being amplified?

4 MS. KHANDURI: Objection. Form.

5 A Sorry, I don't understand the question,
6 sir.

7 Q In that paragraph where you have
8 highlighted amplifying cDNA, is that cDNA the
9 product of reverse transcribing the amplified RNA?

10 MS. KHANDURI: Objection. Form.

11 A The Stahl method is extremely
12 complicated, it has lots and lots of steps.

13 Your specific question is whether or not
14 the amplified material that I've identified here
15 amplifying the cDNA, it is amplified in Stahl's
16 publication method from in vitro transcribed RNA.

17 Is that your question?

18 Q Yes, I'm just asking, in the italicized
19 "amplified cDNA," is that cDNA what is described
20 in the phrase directly before, "reverse
21 transcribing the amplified RNA into cDNA"?

22 A I think it would probably be easier to

1 look at the drawing of this figure, if you really
2 wanted to point out specific steps.

3 But the text I think is clear, and I
4 think it's accurate.

5 Q The cDNA that is reverse transcribed from
6 amplified RNA, is that the template in the
7 amplification reaction?

8 A There are many amplification reactions in
9 Stahl, so I'm not sure how to answer that.

10 Q I'm referring to the specific
11 amplification that you have pointed to in the then
12 performing PCR to amplify the cDNA to add Illumina
13 paired-end sequencing flow-cell binding sites and
14 index sequences.

15 MS. KHANDURI: Objection. Form.

16 A I'll not sure how to answer your
17 question, sir. For example, in the same paragraph
18 I say, To produce amplified RNA molecules.
19 Amplification is all over Stahl.

20 Q In the reaction in Stahl where cDNA
21 reverse transcribed from amplified RNA is
22 amplified to add Illumina paired-end sequencing

1 flow-cell binding sites and index sequences, what
2 is the template?

3 A I don't understand the question.

4 Q You agree that in an amplification
5 reaction, there is a template?

6 A Generally, yes.

7 Q In the amplification reaction, where cDNA
8 is being amplified to add Illumina paired-end
9 sequencing flow-cell binding sites and index
10 sequences, is there a template?

11 A In the specific discussion of Stahl 2016
12 that's discussed there, yes, that -- one of the
13 last amplification reactions, not the last, is --
14 is from amplified RNA, if that's your question.

15 Q So to clarify, is the template in the
16 amplification reaction to add Illumina paired-end
17 sequencing flow-cell binding sites and index
18 sequences, the cDNA that is reverse transcribed
19 from amplified RNA?

20 MS. KHANDURI: Objection. Form.

21 A I think so. I mean, the text is correct,
22 so I think you're just reiterating the text, but

1 you're doing it in a way that's less clear and
2 without a drawing, so I don't know. Qualified
3 yes.

4 Q Please go to Paragraph 182 of your
5 declaration.

6 A Yes, I am at 182.

7 Q Do you see in that paragraph where you
8 have listed out four steps in Stahl's work flow?

9 A Yes.

10 Q Do you see at the first step is
11 synthesizing a second-strand cDNA. The second
12 step is synthesizing amplified RNA. The third
13 step is reverse transcribing the amplified RNA to
14 resynthesize the cDNA. And the fourth step is
15 generating a sequencing library by amplifying the
16 cDNAs.

17 Do you see that?

18 A Yes.

19 Q Let's look at Stahl.

20 MR. CHEUNG: Dominic, can you bring up
21 Exhibit 1016. And drop a copy in the Zoom chat.

22 (A discussion was held off the record.)

1 (Exhibit 1016, previously marked, not
2 attached.)

3 Q And when that's ready we can turn to Page
4 12 of the PDF.

5 MS. KHANDURI: Can we get a copy in the
6 chat?

7 MR. CHEUNG: Could we take a five-minute
8 break while this is being sorted out.

9 MS. KHANDURI: Sure.

10 MR. CHEUNG: Let's go off the record.

11 (A recess was taken.)

12 BY MR. CHEUNG:

13 Q Dr. Spellman, do you have the Stahl 2016
14 reference?

15 A I see it in the chat. I'm downloading it
16 now.

17 Q Okay.

18 A Yep, I have it.

19 Q Okay. If you could turn to Page 12 of
20 the PDF.

21 A Yes.

22 Q Which is also Page 6 of the supplemental

1 materials.

2 A I am on Page 6 of the supplement, Page 12
3 of the document.

4 Q Okay. Do you see the heading that says,
5 "cDNA library preparation for sequencing"?

6 A I do.

7 Q Let's go through the work flow.

8 Let's look at the first sentence.

9 Do you agree that this is a cleavage
10 step?

11 MS. KHANDURI: Objection. Form.

12 A I mean, it serves to release the -- the
13 cDNA that's been created on the array from -- or
14 on the substrate from the solid substrate. I'm
15 not sure I -- the description of a cleavage step
16 versus a this or a that. One needs to evaluate
17 what's happening and whether or not it meets some
18 specific criterias or not.

19 So this does release the molecule. You
20 could call it a cleavage step, that's fine, but
21 it's not -- you know, it's -- it's not like
22 there's a standard cleavage step.

1 Q With your understanding, what is the
2 mechanism that the cDNA is released from the array
3 in the step outlined here in the first sentence?

4 A The USER enzyme modifies the DNA sequence
5 on the surface to -- the nucleic acid sequence on
6 the surface to allow it to be subject to enzymatic
7 cleavage.

8 Q Do you agree that the USER enzyme is the
9 enzyme that performs a cleavage so that the first
10 cDNA strand is released?

11 A I believe that --

12 MS. KHANDURI: Objection form.

13 A I believe that's correct.

14 Q Let's move on to the second sentence,
15 which starts with, "5 microliter of second strand
16 mix containing," so forth.

17 Do you agree that a second strand cDNA is
18 synthesized in this step?

19 A Yes.

20 Q So after this step is performed, do you
21 agree that there is in solution double-stranded
22 cDNA cDNA molecule?

1 MS. KHANDURI: Objection. Form.

2 A Yes. It's not necessarily fully
3 double-stranded, but yes.

4 Q And on to the next sentence, which starts
5 with, "25 microliter of deionized water."

6 Do you see that sentence?

7 A Yes.

8 Q What is occurring in this step?

9 A I believe it's a cleanup step.

10 Q And on to the next sentence, which starts
11 with, "5.6 microliter of the samples were mixed
12 with 10.4 microliter in vitro transcription mix."

13 What is your understanding of what this
14 sentence is describing?

15 A It's an amplification step.

16 Q What is being amplified?

17 A The double-stranded cDNA above is being
18 amplified.

19 Q And what is the product?

20 A The product is a -- is a large set of RNA
21 molecules.

22 Q Are these amplified RNA single-stranded?

1 A Yes.

2 Q And on to the next paragraph.

3 Do you agree that the first sentence is
4 another cleanup step?

5 A Yes.

6 Q Let's look at the next sentence, starting
7 with, "The amount and average fragment length of
8 amplified RNA was determined by using the RNA 6000
9 PECO Kit with a 2100 bioanalyzer (Agilent)
10 according to the manufacturer's protocol."

11 Do you see that sentence?

12 A I do.

13 Q What is your opinion on the purpose of
14 this step involving the bioanalyzer?

15 A They're just assessing the size of the
16 RNA molecules that were created.

17 Q Let's keep going.

18 So samples were heated at 70 degrees
19 Celsius for 2 minutes, then placed on ice before
20 4.5 microliter ligation mix was added to a final
21 content of 1X T4 RNA Ligase Reaction Buffer, 20
22 unit per microliter T4 RNA Ligase2, truncated, 4

1 unit per microliter RNase inhibitor, Murine, and
2 0.5 micromolar ligation adapters. Samples were
3 incubated for 25 degrees Celsius for 1 hour.

4 Do you see that?

5 A Yes.

6 Q Do you agree that ligation adapters are
7 being ligated to the amplified RNA in the step I
8 just read to you?

9 A Yes.

10 Q Based on your understanding, are the
11 ligation adapters ligated onto only one end of the
12 amplified RNA?

13 A That is correct, yeah.

14 Q And following that, the next sentence
15 describes, "The samples were purified using
16 Agencourt RNAClean XP beads," and so on.

17 Do you agree that this is another cleanup
18 step?

19 A Yes.

20 Q Now following that, the next sentence,
21 which states, Samples were heated at 65 degrees
22 Celsius for 5 minutes and then placed on ice. 8

1 microliter reverse transcription mix was added to
2 a final content of 1X First Strand Buffer, 0.05
3 molar DTT, 500 micromolar of each dNTP, 1
4 micromolar -- millimolar, excuse me, RT-primer, 10
5 unit per microliter Superscript III and 2 unit per
6 microliter of RNase out.

7 Do you see that?

8 A Yes.

9 Q In your opinion, what is occurring in
10 this step?

11 A cDNA is being generated.

12 Q Is the product after this step an
13 amplified RNA cDNA double-strand?

14 MS. KHANDURI: Objection. Form.

15 A I believe so.

16 Q Let's skip the next sentence and to the
17 one after it, which starts with, "After
18 determining the amount of cycles needed based on
19 the qPCR, the samples were amplified in a total
20 reaction volume of 25 microliter."

21 Do you see that?

22 A Yes.

1 Q Do you agree that the cDNA is being
2 amplified in this step?

3 A Yes.

4 Q And if you read through the rest of this
5 section, do you agree that the amplified cDNA is
6 then sequenced on an Illumina NextSeq platform?

7 MS. KHANDURI: Objection. Form.

8 A Yes.

9 Q Do you have an explanation for why Stahl
10 sequenced the cDNA product as reverse transcribed
11 from the amplified RNA and not the first reverse
12 transcribed cDNA product?

13 MS. KHANDURI: Objection. Form.

14 A Mechanistically Stahl is passing
15 information from its first strand cDNA, through a
16 series of intermediaries, and sequencing the first
17 strand cDNA.

18 And I think I cover this in my
19 declaration fairly completely. That the purpose
20 of these intermediary steps fitting with the
21 comprise is to manipulate molecules you've
22 collected and manufactured in precise ways that

1 help in this case in the sequencing reaction, or
2 the sequencing process.

3 So the obvious interpretation is that
4 they're doing this to make sequencing easier.

5 Q Can you elaborate on how going through
6 this process may make sequencing easier?

7 MS. KHANDURI: Objection. Form.

8 A Circa -- Stahl actually begins its work
9 prior to the publication date. And when Illumina
10 sequencers first were released, you were often
11 bound by how much material you could effectively
12 amplify. And there were often concerns about the
13 ability of PCR to nonlinear amplify products. So
14 it is common in the art to switch between
15 different methods of amplification, as we've
16 talked about. There are lots of different methods
17 of amplification, and they're often considered
18 equivalent in many concepts.

19 So as I discuss in my declaration, the
20 process of generating in this case the sequencing
21 library for sequencing can have many intermediary
22 steps that are useful.

1 Q Do you have an explanation for why Stahl
2 chose to generate amplified RNA?

3 MS. KHANDURI: Objection. Form. Scope.

4 A Amplified --

5 MS. KHANDURI: Relevance.

6 A Amplified RNA was common as a method
7 of -- of amplification. In vitro transcription is
8 fast and easy. And you -- and linear. So there
9 are reasons to utilize it or some other
10 amplification technology. It is an amplification
11 technology and has certain benefits and
12 limitations. I think I discussed this in my
13 declaration fairly completely.

14 Q Would a person of ordinary skill in the
15 art understand that the first strand and second
16 strand cDNA product can be directly sequenced
17 using an Illumina next generation sequencing
18 platform?

19 MS. KHANDURI: Objection. Form.

20 A Not exactly.

21 I mean, the process of Illumina
22 sequencing circa when Stahl starts developing its

1 work, which is at least 2012 based on the Frisen
2 patent date, but even in 2016, it's a constantly
3 experiment system, and there are dozens if not
4 hundreds of protocols being developed that meet
5 various requirements of Illumina sequencing.

6 Illumina sequencing always requires
7 amplification. It never is capable of sequencing
8 individual molecules directly. So I'm not sure
9 how to answer the question.

10 Q Do you agree that in Stahl the second
11 cDNA product that is reverse transcribed from the
12 amplified RNA is being amplified and sequenced?

13 A The double-stranded -- the cDNA
14 synthesized from the aRNA is being sequenced, yes.

15 Q Okay. Now, what would prevent that first
16 strand cDNA or the second strand cDNA from being
17 sequenced with an Illumina platform?

18 MS. KHANDURI: Objection. Form.

19 A I already answered that. The first
20 individual molecules can never be directly
21 sequenced on Illumina because the very first --
22 one of the very first steps in Illumina is on

1 flow-cell amplification.

2 So you never have the original molecules
3 that are being sequenced, particularly on the
4 second strand, where the second strand synthesis
5 destroys the first strand. So you -- the
6 second -- the second read has no original template
7 molecules left. So all methods that are like
8 Illumina require many, many, many copies of the
9 original molecule being made in order to sequence
10 it. It's just not possible.

11 Q So is it your opinion that looking at
12 Stahl's entire work flow which we just went
13 through together, there is no way to skip the
14 amplified RNA step?

15 A I never testified to that.

16 Q Is the cDNA product, prior to generating
17 amplified RNA in Stahl, can that cDNA product be
18 sequenced on an Illumina platform?

19 MS. KHANDURI: Objection. Form.

20 A One could take the first or second strand
21 molecules. And instead of piping them into the in
22 vitro transcription reaction, put them into some

1 other process that would yield material that would
2 be appropriate for Illumina sequencing.

3 I can think of modifications to the
4 protocol as written in Stahl. Stahl is a specific
5 implementation that achieves the goal of spacial
6 detection using collected templates and a whole
7 series of other things that meet the limitations
8 of the claims.

9 Q What is the difference between -- between
10 the first cDNA product prior to the amplified RNA
11 amplification and the second cDNA product at the
12 end of Stahl's work flow?

13 MS. KHANDURI: Objection. Form.

14 A From an information content, nothing.
15 From the point of view of if you look at this
16 language of Claim 1 -- if you look at the language
17 of Claim 1 in Step E, identifying the first
18 plurality of DNA products and the second plurality
19 of DNA products by sequencing, the relevant bit is
20 to get the sequence of the mRNA that identifies
21 the mRNA and the sequence of the region of
22 interest and the UMI, as well as other things that

1 are specified in my declaration. And the
2 information flow is maintained.

3 There are extra bits added and
4 potentially subtracted from the molecules. They
5 are not identical sequences out the other end.
6 But all of the relevant pieces remain.

7 Q Do you have an explanation for why Stahl
8 chose to implement the amplified RNA step rather
9 than directly performing PCR on the first strand,
10 second strand cDNA product?

11 MS. KHANDURI: Objection. Scope.
12 Relevance. Form.

13 A As I believe I've testified, the Illumina
14 sequencer requires -- well, cannot sequence an
15 individual molecule, always requires
16 amplification. And it is customary, when you have
17 a limited number of molecules to engage in rounds
18 of amplification between the creation of your
19 original molecules and the -- and the flow cell
20 itself, to create extra copies. And they've
21 chosen to use a relatively standard amplification
22 method of in vitro transcription, which has nice

1 properties, but it is an amplification method just
2 like other amplification methods we've discussed.

3 Q Do you agree that the Illumina sequencing
4 method, there is an amplification step on the
5 flow-cell, on the molecules you're trying to
6 sequence?

7 A Yes.

8 Q So is there anything that would prevent
9 applying that first strand second strand cDNA
10 product directly onto the flow-cell so that it can
11 be amplified and sequenced?

12 MS. KHANDURI: Objection. Form.

13 A Illumina sequencing protocols at this
14 time, and the vast majority to this day, use
15 amplification between the collection of the
16 molecules you want and their placement and then
17 subsequent amplification on the flow-cell. It is
18 a standard step in Illumina sequencing to do that.

19 So is it possible to skip it? Some
20 people do it. It requires very specific
21 conditions, and it is uncommon today and was
22 extremely uncommon circa 2012 to 2015.

1 Q Is performing transcription cDNA to
2 generate amplified RNA and then reverse
3 transcribing back to cDNA, a popular method that
4 person -- person of ordinary skill in the art
5 would have performed prior to Illumina sequencing?

6 A For Illumina commonly, I will tell you
7 that the Affymetrix array system for measuring
8 gene expression used amplified RNA in vitro
9 transcription as the entire basis of its mRNA
10 detection platform.

11 So in this field of gene expression
12 analysis, in vitro transcription amplified RNA was
13 an absolutely standard method for measuring mRNAs
14 in the field. The Affymetrix platform controlled
15 huge swaths of the market circa 2000 until around
16 the time of these papers.

17 So, yeah, I think that in vitro
18 transcription is a totally standard method.

19 Q But was it a standard method as it
20 pertains to next-generation sequencing?

21 MS. KHANDURI: Objection. Form.

22 A I'd have to read thousands of papers, if

1 not tens of thousands of papers, to know. And it
2 would depend entirely on the definition of
3 "standard."

4 But in vitro transcription is a
5 well-known and extremely standard method for
6 amplifying molecules in a linear manner.

7 Q What are advantages of performing in
8 vitro transcription to amplify your template, as
9 opposed to performing PCR?

10 A In vitro transcription suffers far less
11 from PCR biases and depletion. It also minimizes
12 duplex and cross-priming reactions, which
13 potentially could be a problem in Stahl,
14 technically.

15 So there are a variety of reasons. But
16 in many case it is an amplification reaction, and
17 it -- and it acts in that capacity here.

18 Q But do you have any explanation for why
19 Stahl specifically chose in vitro transcription to
20 generate the amplified RNA?

21 MS. KHANDURI: Objection. Form. Scope.
22 Relevance.

1 A They wanted to amplify material, and they
2 knew how to do this well. That would be my
3 simplest explanation.

4 Q In your opinion, would performing PCR
5 work just as well?

6 MS. KHANDURI: Objection. Form.

7 A I think so. I mean, I think there are
8 ways to make the PCR work just as well.

9 Q Are you familiar with stranded RNA
10 sequencing, also known as strand-specific RNA
11 sequencing?

12 A Broadly. It's been many years since I've
13 done it in a lab; but yes.

14 Q What is stranded RNA sequencing, to your
15 understanding?

16 A Most RNA sequencing protocols make
17 double-stranded DNA, which prevents you from
18 knowing when you sequence it whether or not the
19 RNA you've collected came from -- which direction
20 it was transcribed. And so you only know that
21 there is a molecule of RNA that came from some
22 region of the genome, but you don't know which

1 side or direction it was transcribed in.

2 Strand-specific maintains that
3 information so the molecules keep track of which
4 way they were transcribed.

5 Q Do you know when stranded RNA sequencing
6 was first performed?

7 A Exactly, no.

8 Q Was it prior to 2000?

9 A I don't know. It could have been.

10 Q Would you know if it was prior to 2010?

11 A Oh, yeah, I'm sure it was. It -- sorry,
12 my previous answer is not on Illumina sequencers,
13 which didn't exist prior to 2000. But there are
14 other ways to do things that are equivalent to RNA
15 sequencing that maintains strand information. So
16 I'm nearly certain that work from Ricken and many
17 other places maintained ordered arrays of ordered
18 cDNA directions so that you could back-infer.

19 Q Do you have an opinion on whether Stahl
20 is performing a form of stranded RNA sequencing?

21 MS. KHANDURI: Objection. Form. Scope.
22 Relevance.

1 A I'd have to think about it. I'm not
2 prepared to render an opinion on that at the
3 moment.

4 Q Looking at the work flow we just went
5 over together, are you able to render an opinion
6 on whether that is a form of stranded RNA
7 sequencing?

8 MS. KHANDURI: Objection. Form. Scope.
9 Relevance.

10 A Not a formal opinion, no.

11 Q Let's turn to Paragraph 171 of your
12 declaration.

13 MS. KHANDURI: Counsel, can we -- can we
14 take a break after this question?

15 MR. CHEUNG: Let's take a break now,
16 then.

17 MS. KHANDURI: Okay.

18 MR. CHEUNG: Off the record.

19 (A recess was taken.)

20 BY MR. CHEUNG:

21 Q Dr. Spellman, please turn to Paragraph
22 171 of your declaration.

1 A Yes, I'm there.

2 Q Do you see in the first sentence you
3 state that, "A POSA would have known that the
4 second-strand cDNA synthesis and library
5 amplification can be performed on Stahl 2016's
6 array, i.e., microscope slide"?

7 Do you see that?

8 A Yes.

9 Q So do you agree that in Stahl 2016, the
10 second-strand cDNA synthesis and library
11 amplification steps are not performed on the
12 array?

13 A In the Stahl 2016 paper, the second
14 strand synthesis happens in solution. I
15 believe --

16 Q So -- continue.

17 A Yes.

18 Q So is it your opinion that Stahl can be
19 modified so that the second-strand cDNA is
20 synthesized while immobilized on the array?

21 MS. KHANDURI: Objection. Form.

22 A Can you repeat the question, please?

1 Q Is it your opinion that Stahl can be
2 modified so that the second-strand cDNA is
3 synthesized while immobilized on the array?

4 MS. KHANDURI: Objection. Form.

5 A In the same Paragraph 171 I discuss that
6 the Stahl authors previous to the publication of
7 Stahl suggested that their spacial detection
8 method can include second-strand cDNA synthesis
9 and library amplification on the array.

10 Q So you agree that the method as published
11 in the Stahl 2016 paper can be modified so that
12 the second-strand cDNA synthesis and library
13 amplification can occur on the array.

14 Is that correct?

15 MS. KHANDURI: Objection. Form.

16 A The method can be performed in a way in
17 which second-strand cDNA synthesis and library
18 amplification are done on the barcoded array.

19 Q Can you explain in what way the method
20 published in Stahl can be modified so that the
21 second-strand cDNA is synthesized on the array?

22 MS. KHANDURI: Objection. Form.

1 A Very broadly speaking, the second-strand
2 synthesis brings in a primer complement --
3 typically something like random hexamers, but
4 there are a variety of ways it could have been
5 done, and uses DNA polymerase to make
6 second-strand DNA in much the same way that it's
7 done in solution.

8 Q So if the second-strand cDNA is
9 synthesized on the array, then the step in Stahl
10 where the release mix with a user enzyme is added,
11 that step needs to be skipped.

12 Is that right?

13 A No, that's --

14 MS. KHANDURI: Objection. Objection.
15 Form.

16 A It doesn't need to be skipped.

17 Oh, oh, sorry. To do it in -- on the
18 array itself, yes, you would -- you would
19 either -- you would move the order of that
20 potentially, or skip it.

21 Q All right. So you can modify Stahl by
22 performing the second-strand cDNA before the

1 release mix is added, and that would achieve
2 having the second-strand cDNA synthesis on the
3 array.

4 Is that right?

5 MS. KHANDURI: Objection to form.

6 A Yes, you would have to do the synthesis
7 before the release.

8 Q Is it your opinion that solid-phase
9 amplification is better than in-solution
10 amplification?

11 MS. KHANDURI: Objection. Form.

12 A I don't think I've rendered a specific
13 opinion on one or the other.

14 Q In your opinion, why would a person of
15 ordinary skill in the art modify Stahl so that the
16 second-strand cDNA is synthesized on the array?

17 MS. KHANDURI: Objection. Form.

18 A It could be as simple as wanting to skip
19 the user enzyme step, for example. There are a
20 large number of reasons you might want to do that.

21 Q Is there any reason that would improve
22 the end product if you modify it?

1 A Well, if you go to my declaration,
2 there's an extensive discussion of solid-phase
3 amplification and its potential benefits starting
4 at 172. I mean, I can go through them all and why
5 they could have benefit.

6 Q So in your opinion, a person of ordinary
7 skill in the art would want to modify Stahl
8 because of the advantages you cite in Paragraph
9 172.

10 Is that right?

11 A I would say they could be motivated to
12 add solid-phase amplification because of the
13 advantages listed in 172.

14 Q Is your opinion that a person of ordinary
15 skill in the art could be or would be motivated to
16 modify Stahl?

17 MS. KHANDURI: Objection. Form.

18 A Well, I say right there in 172 it's my
19 opinion that a POSA would have been motivated to
20 modify Stahl.

21 Q What are the advantages of solid-phase
22 amplification over in-solution amplification?

1 MS. KHANDURI: Objection. Form.
2 Foundation.

3 A Would you like me to read out the section
4 starting at 172? I mean, it's all listed there.

5 Q Let's look at Paragraph 172.

6 So is it your opinion that solid-phase
7 amplification improves sensitivity, selectivity,
8 and scalability compared to in-solution
9 amplification?

10 A Which -- I see the first part of my -- in
11 my opinion -- my declaration. The scalability --
12 yes. Additional sensitivity, specificity, and
13 scalability, yes.

14 Q Then let's look at Paragraph 173 right
15 below that.

16 Is it your opinion that solid-phase
17 amplification minimizes undesirable primer
18 interactions such as primer dimers?

19 A Yes, that's correct.

20 Q Does solid-phase amplification provide
21 this benefit if only the forward primer is
22 immobilized on a solid array?

1 MS. KHANDURI: Objection. Form.

2 A I'd have to think about that more and
3 read. I'm not sure.

4 Q Moving back to Paragraph 172. The very
5 first sentence where you state that a POSA would
6 have been motivated to modify Stahl?

7 A Yes.

8 Q When you refer to modifying the library
9 amplification to be performed on the array, what
10 are you referring to?

11 A Well, in Paragraph 171, Frisen themselves
12 refer to library amplification on the array. So
13 I'm minimally referring to that. But the process
14 of making material that you're -- that you're
15 going to put into a sequencer machine.

16 Q So is it your opinion that the work flow
17 in Stahl that we went over together about the
18 cDNA, the amplified RNA, back to the cDNA, all of
19 those steps can be performed on the array as a
20 solid-phase amplification.

21 Is that what you're saying?

22 MS. KHANDURI: Objection to form.

1 A I don't know that it has to be in exactly
2 the structure that's in the Stahl 2016 reference.
3 But methods that achieve the same processes are.

4 Q Right. But your opinion is that Stahl
5 can be modified. So starting from Stahl, can you
6 explain how you can modify Stahl so that the
7 library amplification steps occur on the array?

8 A You would have to have a second primer to
9 do that. You would have to bind the cDNA. I'd
10 have to draw it out.

11 Q Are you referring to, essentially, a form
12 of clonal amplification?

13 A Yes, that would be the most logical
14 thing. Since you're doing Illumina sequencing,
15 which does clonal amplification, and that's the
16 basis, you're basically going closer from what
17 you've done in vitro, what you've done in the very
18 first cDNA and second cDNA steps closer to clonal
19 amplification.

20 Q Let's move to Paragraph 174.

21 A Yes.

22 Q Do you see in the first sentence you

1 state that, "Further solid-phase amplification was
2 desirable for high throughput methods because it
3 allows the parallelization of the DNA
4 amplification process without any direct human
5 intervention."

6 Do you see that?

7 A I do.

8 Q Can you explain what you mean by
9 "parallelization of the DNA application process
10 without any direct human intervention"?

11 A Well, I'm quoting from Exhibit 1050
12 there. So can we bring up Exhibit 1050?

13 MR. CHEUNG: Okay. Can we bring up
14 Exhibit 1050.

15 MS. KHANDURI: And can we also drop it in
16 the chat for Dr. Spellman.

17 (Exhibit 1050, previously marked, not
18 attached.)

19 Q Mr. Spellman, are you at Page 2079, the
20 page you cited?

21 A I'm looking for the quote there.

22 Yes.

1 Q Are you now able to explain what you mean
2 by "parallelization of the DNA amplification
3 process without any direct human intervention"?

4 A This is similar to the way Illumina
5 works. The idea is you want to spacially restrict
6 individual copies of molecules. And in solution
7 these will mix together, but in solid phase
8 they'll maintain their spacial restrictiveness,
9 for lack of a better word. And as a consequence,
10 you don't have to manually intervene to keep the
11 molecules separate from one another as a potential
12 benefit. It is, in fact, the basis for Illumina
13 sequencing.

14 Q So you're referring to separating the
15 amplification product from different reactions
16 occurring at the same time.

17 Is that right?

18 MS. KHANDURI: Objection. Form.

19 A I mean, I probably wouldn't use that
20 language, but that's fairly close.

21 Q I'm just trying to understand what the
22 "without any direct human intervention" means.

1 Like, how is that different between solid-phase
2 amplification and in-solution amplification?

3 A Yes. In solid phase the molecules are
4 tied to their localization. And that has
5 potential advantages in many aspects. And it is
6 the core of Illumina sequencing, for example,
7 since -- so it seems directly relevant.

8 Q I see. So correct me if I'm wrong also,
9 we're talking about the amplification products
10 which are themselves immobilized on a solid
11 surface.

12 Is that right?

13 A Correct.

14 Q So do you have an opinion on whether
15 solid-phase amplification is superior to
16 in-solution amplification?

17 MS. KHANDURI: Objection. Scope. Form.

18 A It would depend entirely on the method
19 and what one was trying to achieve.

20 Clearly there are times when
21 solution-based amplification is a terrific choice.
22 In some methods solid-phase amplification is a

1 requirement. It would just depend on how you're
2 putting your protocol together.

3 Q Do you have an explanation for why the
4 authors of Stahl did not choose to perform
5 solid-phase amplification?

6 MS. KHANDURI: Objection. Relevance.
7 Scope.

8 A I'm not sure -- I'm not sure they didn't
9 choose to. They published a method that doesn't.
10 I'm not sure that it's -- they found something
11 that worked.

12 Q Do you agree that the authors of Stahl
13 knew about solid-phase amplification?

14 MS. KHANDURI: Objection. Form.
15 Foundation.

16 A Yes.

17 Q And you agree that the authors of Stahl
18 knew that synthesis of the second-strand cDNA can
19 occur on the array?

20 A They knew --

21 MS. KHANDURI: Objection. Objection.
22 Relevance. Form.

1 A I cite that directly in 171, Paragraph
2 171.

3 Q All right. So you agree that the authors
4 of Stahl, who knew about solid-phase amplification
5 and knew that the synthesis of the second-strand
6 cDNA can occur on the array, published a paper
7 where they did not utilize either of these
8 techniques?

9 MS. KHANDURI: Objection. Form.

10 A That is correct.

11 Q Let's turn to Paragraph 187 of your
12 declaration.

13 A Yes, I am at 187.

14 Q Do you see in the second sentence where
15 you state, "First, in my opinion, a POSA would
16 have appreciated that Frisen discloses array-based
17 spacial detection methods using solid-phase
18 second-strand cDNA synthesis and solid-phase
19 library amplification steps."

20 Do you see that sentence?

21 A Yes.

22 Q What is "solid-phase library

1 amplification"?

2 A Solid-phase library amplification would
3 be taking molecules that are directly ready for
4 sequencing and amplifying them on a solid
5 substrate, broadly speaking. Although there may
6 be other interpretations consistent with the
7 infringement positions of Bruker.

8 Q Let's turn to Paragraph 204 of your
9 declaration.

10 A Yes, Paragraph 204.

11 Q Do you see that you included an annotated
12 Figure 1A at the end of that paragraph?

13 A Yes.

14 Q What does Figure 1A show?

15 A I state that it -- in my declaration that
16 it shows capture probes immobilized at each of the
17 capture sites on the array.

18 Q Let's look at the description of Figure
19 1A in So '456.

20 MR. CHEUNG: Can we bring up Exhibit
21 1005.

22 MS. KHANDURI: And do you mind dropping

1 it in the chat also.

2 (Exhibit 1005, previously marked, not
3 attached.)

4 Q Dr. Spellman, when you have it, if you
5 could turn to Paragraph 141.

6 A Yes, I am at Paragraph 141.

7 Q Do you see that it says Figure's 1A
8 illustrates a plan view of an exemplary embodiment
9 of a capture array 100 for capture of nucleic acid
10 in a tissue sample."

11 Do you see that?

12 A Yeah.

13 Q And following that, the next sentence, do
14 you see where it says, "Capture array 100
15 comprises an arrangement, (e.g., rows and
16 columns), of capture sites 105 on a solid support
17 110."

18 Did I read that correctly?

19 A Yes.

20 Q So do you agree that Figure 1A shows
21 capture sites that are arranged in rows and
22 columns?

1 A I think the image there is an exemplar.
2 And it says, For example, rows and columns. But,
3 yes, what's shown appears to be rows and columns.

4 Q So a capture site on Figure 1A can be
5 located on a specific row and column.

6 Is that right?

7 A As an exemplar. I don't think they limit
8 themselves to that. But, yes.

9 Q So in the context of So '456, would you
10 agree that a spacial barcode provides the row and
11 column of the capture site?

12 A I would say the spacial barcode is linked
13 to the capture site.

14 Q And the capture site can be expressed in
15 a row and column on the array.

16 Is that right?

17 A It can be. Does not have to be.

18 Q If the array is configured like how it is
19 shown in Figure 1A, then would the spacial barcode
20 correspond to a capture site on a particular row
21 and column?

22 MS. KHANDURI: Objection. Form.

1 A Presumably, although there are other
2 possibilities.

3 Q Can you provide an example of one of
4 these possibilities?

5 A Let me read the description more closely.
6 The -- I believe I'd need to go to Figure
7 25A to intersect how the spacial bar codes are
8 positioned.

9 Q Dr. Spellman, I'm asking you about what
10 that spacial barcode correlates to. Like whether
11 it is a row and a column?

12 A I don't think that So is constrained
13 in -- in the way that you're sort of representing
14 it as rows and columns.

15 Q But I'm asking, in Figure 1A would a
16 spacial barcode correlate to a row and column on
17 that array?

18 A And I'm telling you that the discussion I
19 believe -- well, I can read this. Let me read the
20 section on Figure 1A in a little more depth here.

21 So further down they describe under
22 Figure 1A the cleavable region 120 can be used to

1 release captured nucleic acid from capture array
2 100 such the spacial address region 130 is
3 included and the nucleic acid is tagged.

4 So -- and then they go on to describe
5 that each capture probe 115 at a capture site 105
6 comprises a unique spacial address region 130.

7 So in that context, each capture site,
8 which is nonlimiting to the row and column
9 implementation, has a unique spacial address.

10 Q So you agree that a spacial address
11 corresponds to a row and column on the array.

12 Is that right?

13 A I will reiterate that it does not -- it
14 says, an arrangement, for example rows and
15 columns. But it doesn't say that it has to be
16 rows and columns.

17 Q If the array is exactly as illustrated in
18 Figure 1A, in rows and columns, then would the
19 spacial barcode correspond to a row and column?

20 MS. KHANDURI: Objection. Form.

21 A Very clearly from this specification,
22 spacial address region 130 corresponds to the

1 position of a capture probe 115. So each
2 elements, each of the gray circles in Figure 1A,
3 is a capture probe. And each of those has its own
4 sequence 130, which is the spacial address.

5 Q And do you agree that each capture site
6 115 is in its own row and column as depicted in
7 Figure 1A?

8 A The exact description in Figure 1A is a
9 row and column ordering, yes.

10 Q Let's look at Claim 1A and 1B.

11 MR. CHEUNG: So if you can bring up the
12 '142 patent, which is Exhibit 1043. And go to the
13 last page.

14 Q Dr. Spellman, do you have it in front of
15 you?

16 A 1043, last page, claims. Claim 1. Yes.

17 Q Do you see that Claim 1A and 1B both
18 require collecting oligonucleotides under
19 conditions that release the plurality of
20 oligonucleotides from the first or second location
21 of the tissue sample?

22 A Yes.

1 Q To a person of ordinary skill in the art,
2 what would be some conditions that allow
3 oligonucleotide to be released from a tissue
4 sample?

5 A I discuss this in my declaration, so I
6 refer to my declaration.

7 But broadly speaking, it would depend
8 upon the state of the tissue sample. It could be
9 as simple as lysing cells. It could be as simple
10 as thawing of frozen section of cells. It could
11 be far more complicated.

12 But broadly speaking, it is a step that,
13 prior to doing that step, the RNAs cannot move
14 around very much, and after that they are allowed
15 to be collected and released to be collected.

16 Q So do you agree that a tissue sample
17 would require some treatment so that the
18 oligonucleotides can be released?

19 A Treatment is very broad, and I have a
20 very broad definition of treatment. And it can --
21 as I said, it can be as simple as time. It can be
22 as complicated as you want it to be.

1 Q So do you agree that there must be some
2 action taken so that a tissue sample will be under
3 a condition that oligonucleotides are released?

4 A The, quote, action taken as you've
5 described it, I describe extensively in my
6 declaration. And very broadly speaking that
7 axonal has to mean that prior to the tissue, the
8 oligonucleotides of the claim are not able to
9 move; and after this process, the oligonucleotides
10 of the claim do move and are collected.

11 It is a -- it is a nearly endless set of
12 possibilities.

13 Q Do you agree that given a tissue sample,
14 some action must be performed on the tissue sample
15 before oligonucleotides can be released from the
16 tissue sample?

17 A Again, I will reiterate that my
18 declaration describes a wide number of conditions
19 that would meet this, and that the conditions
20 themselves could be as simple as taking a frozen
21 section and letting it thaw; i.e., like not -- you
22 know, passively taking it out of the freezer and

1 while it's being placed on there it thaws.

2 The condition does not require an action
3 in the way I believe you're implying. It could be
4 inaction.

5 Q So is it your opinion that thawing tissue
6 sample would release mRNA on the tissue?

7 MS. KHANDURI: Objection. Form.

8 A Depending what had happened previously,
9 absolutely.

10 Q How about a fresh tissue sample?

11 A A fresh tissue sample would very likely
12 need to have the cells lysed at a minimum.

13 Q Are you familiar with permeabilization?

14 A Broadly.

15 Q Can a tissue sample be treated so that is
16 it is permeabilized to allow oligonucleotides in
17 the tissue to be released?

18 A Yes.

19 Q Let's go to Paragraph 105 of your
20 declaration.

21 A Yes, I am at 105.

22 Q Do you see you state that Stahl 2016

1 discloses collecting mRNA under conditions that
2 release the mRNAs from their locations in the
3 tissue.

4 Do you see that?

5 A I do.

6 Q Do you see the next sentence where you
7 explain that this is because Stahl 2016 discloses
8 a process of tissue permeabilization?

9 Do you see that?

10 A Yes.

11 Q Is it your understanding that treating a
12 tissue sample with 0.01 percent pepsin dissolved
13 in 0.1 molar HCl will permeabilize a tissue
14 sample?

15 A That is consistent with my understanding,
16 yes.

17 Q And just to clarify, is it your
18 understanding that mRNA from a tissue sample will
19 be released if the tissue is permeabilized?

20 A Unless something else has been done to
21 prevent it, I think that's consistent with my
22 understanding.

1 Q Let's go to Paragraph 207 of your
2 declaration.

3 A Yes.

4 Q You opine here that "So '456 discloses
5 collecting the oligonucleotides and mRNAs under
6 conditions that release the oligonucleotides from
7 their locations in the tissue sample."

8 Is that right?

9 A Yes.

10 Q What are the conditions in So '456 that
11 allows mRNA to be released from the tissue sample?

12 A I think if you look at my discussion of
13 207, under -- in Paragraph 207 and 208, and as
14 well as the rest of the declaration, the
15 conditions here are -- it could be as simple as
16 transferring the frozen section onto the array and
17 letting it thaw, depending on how it was frozen.

18 You know, the So '456 explicitly
19 identifies the target nucleic acid mRNA diffuses
20 from the tissue onto the array. Those -- so if --
21 if the diffusion was happening prior to the
22 placement on the array, it would have lost its

1 spacial localization and would have diffused
2 throughout the tissue already. So the act of
3 placing it on the array in the context here of
4 like unfreezing the tissue, is allowing the
5 tissue -- you know, so going from a solid state to
6 a -- to a semi-solid, you know, tissue state could
7 do this.

8 And, you know, quite plausibly if the
9 tissue were frozen, ice crystals form in tissues,
10 puncture holes in it, creating the kind of
11 permeabilization you see in Stahl.

12 So I think it's entirely plausible
13 that -- that it is -- it is as simple as thawing.

14 Q Is it your opinion that So '456 discloses
15 thawing?

16 A It discloses preparing a tissue for
17 analysis, which is a very broad set of processes
18 well understood to a POSA.

19 Q Is there permeabilization disclosed in So
20 '456?

21 A The entire So '456 is available for a
22 POSA to evaluate. It's clear to a POSA that they

1 need to transfer the tissue and prepare it for
2 analysis so that the material can be captured onto
3 the array. I believe they disclose the diffusion
4 explicitly, that you want the RNA to diffuse from
5 the array.

6 MS. KHANDURI: Counsel, can we take a
7 lunch break soon?

8 MR. CHEUNG: Let me finish with my round
9 of questions first.

10 MS. KHANDURI: Sounds good.

11 Q Dr. Spellman, what are the conditions
12 that would allow the diffusion of the mRNA that
13 you just mentioned?

14 A Can we bring up So '456, please.

15 MR. CHEUNG: Sure. Let's look at Exhibit
16 1005. Let's look at the paragraphs in So '456
17 that you cited in your Paragraph 207.

18 A Yes.

19 Q So you first cite Paragraph 152 in So
20 '456. Let me know when you're there.

21 A Yeah, I'm at 152.

22 Q And Paragraph 152, what are the

1 conditions here that would release the mRNA?

2 A If the tissue was frozen and had been
3 frozen so that ice crystals formed, minimally the
4 thawing process would release RNA.

5 If the tissue were fresh tissue and it
6 was allowed to sit for some time, cells would
7 likely die and release RNA.

8 So I think there's a broad set of
9 conditions explicitly identified in 152 that
10 create conditions that are compatible with
11 releasing of the RNA.

12 Further, I also cite to 154, where you
13 transfer the section that the -- the sample
14 tissue -- sorry, the tissue section is transferred
15 onto an array, and the target nucleic -- and
16 the -- and you're collecting the mRNA, so it's
17 describing collecting the mRNA from the tissue.

18 It's explicitly describing embodiments in
19 which the nucleic acid is captured by
20 single-stranded ligation.

21 Then we go to Paragraph 155. The
22 tissue -- the target -- the tissues directly

1 placed on the surface comprising the probes
2 with -- with a modified layer in between, such
3 that the nucleic acids can filter through the
4 modified layer. This can be a gel or anything
5 that facilitates. And so, actually, the use of
6 that layer can help facilitate the transfer of the
7 collected mRNAs.

8 So that's an explicit discussion of
9 processes. And they specifically say in each case
10 the technique is selected to substantially
11 maintain information encoding the spacial
12 orientation in the targets sample.

13 And so the goal is to release the mRNA in
14 this case in a way that does not allow it to
15 diffuse very far.

16 If we go to Paragraphs 308, our tissue
17 sample is contacted with the capture array, and
18 the gene-specific mRNA capture molecules grab the
19 mRNAs.

20 And then again in Paragraph 315, I again
21 talk about capturing the tissue sample being used
22 to capture the mRNA molecules, the tissue sample

1 containing the mRNAs is -- comprising the mRNAs is
2 derived from the tissues. Those are contacted.
3 And so something has happened in that step
4 explicitly; for example, the tissue sample
5 containing mRNA molecule 2510 or a substrate
6 comprising mRNA molecule 2510 derived from the
7 tissue sample is contacted with probes 2310.

8 So in that case they're talking about
9 disrupting the tissue sample in some way such that
10 the mRNAs are free, that they can then hybridize
11 with the array.

12 Q In the paragraph of So '456 that you just
13 discussed, are there any language that explicitly
14 states a condition that releases the mRNA?

15 A I've described very explicitly how I
16 think a frozen tissue section would, when placed
17 on a room-temperature array, release molecules. I
18 think that's quite obvious.

19 I think that the conditions of those
20 paragraphs again, and the rest of the
21 specification, are consistent with the idea that
22 the POSA chooses a method appropriate for doing

1 this. But it must happen, because you have to get
2 the mRNA onto the surface of the array.

3 Q If we look at Paragraph 152 of the So
4 '456, and limiting your response to only about
5 Paragraph 152, is it your opinion that where it
6 states "fresh tissue," "frozen tissue," et cetera,
7 that is the disclosure of conditions that release
8 mRNA from the tissue sample?

9 A Counsel, that's not what I said.

10 Q Can you point me to anything in this
11 paragraph that talks about releasing mRNA from the
12 tissue sample?

13 A First sentence. "A tissue is prepared
14 for analysis." That means that you're preparing
15 it for the release. And it's clear from all the
16 other sections that I cited that that release must
17 happen. So it's consumed within that "prepared
18 for analysis."

19 I explicitly identify a condition in
20 which essentially no action has to be taken, where
21 frozen tissue is simply thawed that would allow
22 the release of mRNAs.

1 Q So is it your opinion that a person of
2 ordinary skill in the art would be -- would be
3 able to select a condition and perform it to
4 release mRNA from a tissue sample?

5 MS. KHANDURI: Objection. Form.

6 A I think that is consistent with So.

7 Q So to clarify, when a person of ordinary
8 skill in the art performs the method described in
9 So '456, mRNA would be released from the tissue
10 sample?

11 A It would be required so that it can be
12 captured on the array.

13 Q Okay. So to be clear, your opinion is,
14 for the claim element we're talking about, under
15 conditions that release the plurality of
16 oligonucleotides from the first and second
17 location of the tissue sample, this necessarily
18 must be present in So '456?

19 A It says that it happens. It literally
20 says it. It says the array elements collect the
21 mRNA.

22 Q And the person of ordinary skill in the

1 art will be able to determine a method to allow
2 the mRNA to be released and captured by the
3 capture array.

4 Is that right?

5 MS. KHANDURI: Objection. Form.

6 A Yes. Literally the simplest version is,
7 they just take a frozen section that wasn't
8 prepared very well and they let it thaw.

9 Q By thawing a tissue sample in the way you
10 described, would that still retain the relevant
11 spacial positioning of the mRNA in the tissue
12 sample?

13 A Yes, I believe it would. It's in a
14 frozen state. It's immobile. There's holes
15 punctured in the cell wall, cell membranes, from
16 crystals permeabilizing them. And then you place
17 them on the surface and they will diffuse -- and
18 stuff will diffuse out. I think that's quite
19 consistent.

20 But it's not all that it's limited to,
21 it's just the most blindingly obvious one.

22 Q And in the other method you described,

1 you take a fresh tissue sample and just let it sit
2 for a long period of time, would the mRNA that is
3 released from that tissue sample also maintain its
4 original location within the tissue sample?

5 MS. KHANDURI: Objection. Form.

6 A As I've said, So discloses that you
7 collect on the array, and that you prepare the
8 tissue for analysis. A component of that must be
9 that the nucleic acid that you're collecting, in
10 this case mRNA, diffuses in a way that collects
11 onto the elements, retaining spacial information.

12 MR. CHEUNG: Can we take a quick
13 five-minute break? We are near the end.

14 MS. KHANDURI: Sorry, I would suggest we
15 take lunch break now. Because it's been --

16 MR. CHEUNG: I think I'm near the end.
17 So I think I just need to review my notes for a
18 few minutes, but I think I'm done. So I think a
19 few minutes would be good.

20 MS. KHANDURI: Okay. Sounds good.

21 (A recess was taken.)

22 BY MR. CHEUNG:

1 Q Dr. Spellman, did you speak to anyone
2 during any of the breaks we've had today?

3 A No. Well, I spoke to my wife. She was
4 on the other side of the house.

5 Q Understandable.

6 MR. CHEUNG: That's all I have. I'll
7 pass the witness.

8 MS. KHANDURI: Thank you. Let's have 15,
9 20 minutes break, and then we'll come back.

10 Sounds good?

11 THE WITNESS: Fine by me.

12 MR. CHEUNG: Sure. We'll come back at
13 12:40 Pacific. Is that right?

14 MS. KHANDURI: It's 12:40, yes.

15 (A recess was taken.)

16 MS. KHANDURI: We do not have any
17 questions for Dr. Spellman.

18 Thank you, Dr. Spellman, for your time.

19 (Off the record at 3:42 p.m. EST.)
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ACKNOWLEDGMENT OF DEPONENT

I, PAUL T. SPELLMAN, Ph.D., do hereby
acknowledge that I have read and examined the
foregoing testimony, and the same is a true,
correct and complete transcription of the
testimony given by me, and any corrections appear
on the attached Errata sheet signed by me.

(DATE)

(SIGNATURE)

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C E R T I F I C A T E

I, Debra Ann Whitehead, E-Notary Public in and for
the Commonwealth of Virginia, do hereby certify:

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

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

I further certify that the deposition of
PAUL T. SPELLMAN, Ph.D., occurred virtually, on
Thursday, November 7, 2024, from 11 a.m. to 3:42
p.m. EST.

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 hereunto set my
9 hand this 9th day of November, 2024.

10
11 My commission expires:

12 October 31, 2027

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