

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2
3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4
5 10X GENOMICS, INC.,

6 Petitioner,

7 vs.

8 BRUKER SPATIAL BIOLOGY, INC.,

9 Patent Owner.

10
11 Case: IPR-2023-01300

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

13
14 DEPOSITION OF DAVID SHERMAN, Ph.D.

15 3223 South State Street, Ann Arbor, Michigan

16 Thursday, January 30, 2025

17 9:04 a.m.

18
19
20 Job No.: 2025-970576

21 Pages: 1 - 90

22 Stenographically Reported By:

23 Alison C. Webster, RPR, CRR, RMR, RDR, CSR-6266 (Michigan);

24 License No. 14559 (California); License No. 084.004953

25 (Illinois); CSR-12432 (Texas)

A P P E A R A N C E S

APPEARING ON BEHALF OF PETITIONER

DAVID H. HOLMAN, ESQUIRE

PRATIBHA KHANDURI, PH.D., ESQUIRE

Sterne, Kessler, Goldstein & Fox PLLC

1101 K Street NW

10th Floor

Washington, D.C. 20005

202.772.8989

pkhanduri@sternekessler.com

dholman@sternekessler.com

APPEARING ON BEHALF OF PATENT OWNER

CONCORD CHEUNG, ESQUIRE

DEREK C. WALTER, ESQUIRE

Weil, Gotshal & Manges LLP

201 Redwood Shores Parkway

Redwood Shores, California 94065

650.802.3934

concord.cheung@weil.com

derek.walter@weil.com

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

T A B L E O F C O N T E N T S

Witness	Page
DAVID SHERMAN, Ph.D.	
EXAMINATION	
BY MS. KHANDURI:	4
EXAMINATION	
BY MR. CHEUNG:	87

E X H I B I T I N D E X

Exhibit	Page
(Exhibits retained by counsel.)	
PREVIOUSLY MARKED EXHIBIT 2008	10
PREVIOUSLY MARKED EXHIBIT 1043	29
PREVIOUSLY MARKED EXHIBIT 1016	67

DEPOSITION OF DAVID SHERMAN, Ph.D.

Thursday, January 30, 2025

STENOGRAPHER: Dr. Sherman, would you
please raise your right hand.

Do you swear or affirm the testimony you
are about to give in this matter will be the truth,
the whole truth, and nothing but the truth?

DR. SHERMAN: Yes.

STENOGRAPHER: Thank you.

You may proceed.

MS. KHANDURI: Good morning, Dr. Sherman.

THE WITNESS: Good morning.

MS. KHANDURI: My name is Pratibha
Khanduri, and it's nice to see you again today.

As you know, I'm with the law firm
Sterne Kessler Goldstein & Fox, and I represent
10x Genomics, and with me I have David Holman, my
colleague at Sterne Kessler.

DAVID SHERMAN, Ph.D.,
was thereupon called as a witness herein, and after
having first been duly sworn to testify to the truth,
the whole truth and nothing but the truth, was
examined and testified as follows:

EXAMINATION

1 BY MS. KHANDURI:

2 Q. Could you please state your name and place of
3 residence for the record.

4 A. My name is David Howard Sherman, and I reside here in
5 Ann Arbor, Michigan.

6 Q. Thanks. You are also Bruker's expert in another 10x
7 proceeding, 10x versus Bruker proceeding that you were
8 deposed on earlier, right, last year?

9 A. Right, that's correct.

10 Q. And we met at that time at your deposition back in
11 October of last year.

12 A. Correct.

13 Q. Okay. Have you been deposed since that last
14 deposition when we met in October?

15 A. No.

16 Q. Have you testified in any trial since last October?

17 A. No.

18 Q. So you've been sworn in today and you've gone through
19 this exercise before at least once with us, but still
20 the rules require us to state some guidelines,
21 principles for depositions, so I'm just going to state
22 those. Okay?

23 A. Okay.

24 Q. So you understand that you are testifying under
25 oath --

1 A. Yes.

2 Q. -- and under penalty of perjury in the United States.

3 Right?

4 A. Right. Yes.

5 Q. Okay. And you understand that that means that you

6 have to testify truthfully and accurately to the

7 questions I ask you.

8 A. Yes.

9 Q. Do you understand that?

10 A. I do.

11 Q. Okay. We have a court reporter with us today, and as

12 you know, she will be transcribing our conversations.

13 Once the transcript is entered into record, it will

14 become public. Do you understand that?

15 A. I do.

16 Q. And because we have the court reporter transcribing

17 today, you know, like before as we went through last

18 time, you know, I would request to wait for me to

19 complete my question before you answering, and I'll do

20 the same, I'll wait for you to complete your answer so

21 that we don't overlap or interrupt each other. Thank

22 you.

23 And you also understand that if you have a

24 question, you must ask me for clarification or

25 explanation and not your counsel.

1 A. I will. Thank you.

2 Q. Okay. And then you are not permitted to speak with
3 your counsel until this deposition is over, including
4 during breaks. Do you understand that?

5 A. I do. Thank you.

6 Q. We'll take reasonable -- we'll take breaks during --
7 at reasonable intervals, but if you need a break, just
8 ask me, we'll take a break at that time. The only
9 caveat to that is, if a question is pending, I would
10 request you to just answer the question before we take
11 a break. Okay?

12 A. Yes.

13 Q. Thank you. And one last thing. As you know, your
14 counsel may object to my questions. If they do, you
15 must still answer my questions unless your counsel
16 advise you not to. You understand that?

17 A. I do understand. Thank you.

18 Q. Okay. I see you don't have any documents with you,
19 Dr. Sherman; is that right?

20 A. That's correct.

21 Q. Okay. And you understand why you're being deposed
22 today?

23 A. I do.

24 Q. And what's your understanding?

25 A. There is an IPR matter involving the '142 patent, and

1 so I'm being deposed regarding the content of my
2 declaration relating to that '142 IPR.

3 Q. Okay. And you understand that this IPR that we are
4 involved in today was filed by NanoString, right,
5 earlier?

6 A. The IPR...

7 Q. I'm sorry, strike that.

8 The IPR we are involved in today was filed
9 by 10x against NanoString. You understand that,
10 right?

11 A. That's my understanding.

12 Q. And then after the IPR was filed, Bruker acquired
13 NanoString. You understand that?

14 A. I do.

15 Q. And I may use Bruker and NanoString interchangeably.
16 Would that be okay with you?

17 A. That's fine.

18 Q. Okay. Thank you. When did you learn about this IPR
19 proceeding for which we are being -- you are being
20 deposed today?

21 A. There was some discussion of it early in the fall or
22 late summer in terms of the two patents, the '689,
23 which I was in -- I was engaged in first and deposed
24 in October, as you recall, and so as that was
25 proceeding there was some discussion about playing a

1 similar role for the '142.

2 Q. So you were contacted for the '689 IPR and the '142
3 IPR at the same time?

4 A. No.

5 Q. At separate times?

6 A. Yes.

7 Q. You were contacted for the '142 IPR after you were
8 contacted for the '689 IPR.

9 A. Correct.

10 Q. Who contacted you for the 68 -- strike that.

11 Who contacted you for the '142 IPR?

12 A. I believe it was a discussion with counsel who's here
13 today.

14 Q. Aside for -- aside from serving as an expert witness
15 in the IPRs between 10x and Bruker, do you have any
16 other professional relationships with Bruker?

17 A. No.

18 Q. Or what about NanoString?

19 A. No, no relationships.

20 Q. And you are being compensated for your testimony in
21 this case. Right?

22 A. I am.

23 Q. What's your billing rate, if you recall?

24 A. I believe it's \$700 an hour.

25 Q. And do you recall total amount of -- the total amount

10

1 that you have invoiced for this IPR?

2 A. I really -- I haven't calculated that.

3 Q. Okay.

4 A. I would have to go through my records.

5 Q. Are you able to give a ballpark estimate?

6 A. Oh, wow. About 20,000.

7 Q. Okay.

8 A. That's a ballpark.

9 Q. Sure.

10 A. So...

11 Q. Okay. I'm going to hand you, Dr. Sherman, your
12 declaration in this case --

13 A. Okay.

14 Q. -- which has been marked Exhibit 2008.

15 ENTERED INTO THE RECORD:

16 PREVIOUSLY MARKED EXHIBIT 2008

17 9:11 a.m.

18 BY MS. KHANDURI:

19 Q. Do you recognize this document, Dr. Sherman?

20 A. I do.

21 Q. And this is your declaration that's submitted in this
22 IPR?

23 A. Yes.

24 Q. And at the end, on the last page, which is page 71,
25 could you confirm that it's your signature?

1 A. It is my signature.

2 Q. And you signed it on November 20th, 2024.

3 A. I did.

4 Q. Let's go to paragraph 14 of your declaration. In
5 paragraph 14, you list materials that you considered
6 in preparing your declaration; is that right?

7 A. That's correct.

8 Q. Did you read all of the materials that are listed in
9 this paragraph 14 before you prepared your opinions
10 for this declaration?

11 A. I did.

12 Q. Okay. So you reviewed the '142 patent, Exhibit 1043?

13 A. I did.

14 Q. And then you reviewed Dr. Spellman's declaration that
15 was submitted in this IPR, 1044?

16 A. Yes, I did.

17 Q. You also reviewed all the exhibits that are cited in
18 Dr. Spellman's declaration, 1044?

19 A. Yes, I did.

20 Q. You reviewed the board's decision, institution
21 decision in this matter. Correct?

22 A. Please ask that again.

23 Q. You also reviewed the board's institution decision in
24 this matter?

25 A. I did.

1 Q. Okay. And then, finally, all the materials that are
2 cited in your declaration, 2008?

3 A. Yes, I did review them.

4 Q. Did you rely on any documents that are not listed in
5 this paragraph 14 in preparing your declaration?

6 A. No.

7 Q. Approximately how many hours did you spend preparing
8 your declaration?

9 A. I cannot even begin to guess on that.

10 Q. Is it less than 50 hours?

11 A. I would just be speculating. It's not something I
12 calculated or think about, you know. I do the work
13 and proceed.

14 Q. Okay. Is it -- the number of hours that you spent on
15 this '142 IPR declaration, is that more than the
16 amount of time you spent for your '689 IPR declaration
17 that you submitted?

18 A. It was probably about the same.

19 Q. Okay. Did you meet with anyone to prepare for your --
20 to prepare your declaration?

21 A. To prepare the declaration... I -- I discussed with
22 counsel present here.

23 Q. Okay. And do you recall approximately how many hours
24 that you spent discussing before you prepared your
25 declaration?

1 A. Again, I would just be speculating.

2 Q. Okay. Did you meet with anyone who's not a lawyer
3 in -- while preparing your declaration?

4 A. No.

5 Q. And when did you last review your declaration?

6 A. This morning.

7 Q. Good. Is there anything you would like to change in
8 your declaration?

9 A. No.

10 Q. And you stand by your declaration?

11 A. I do.

12 Q. Similar questions, Dr. Sherman, for your depo prep.

13 A. Okay.

14 Q. What did you do to prepare for this deposition?

15 A. I reviewed my declaration and documents,
16 Dr. Spellman's declaration, the '142 patent, the
17 aligned exhibits, met with counsel for, you know,
18 some time.

19 Q. Okay. And, again, who did you meet with to prepare
20 for your deposition?

21 A. So primarily up until yesterday I met with the
22 gentleman sitting next to me; and then yesterday, the
23 two gentlemen next to me and I met.

24 Q. So you're saying you met with Concord Cheung and Derek
25 Walter?

1 A. Correct.

2 Q. How many meetings did you have to prepare for your
3 deposition?

4 A. We had one meeting.

5 Q. And how long was that meeting?

6 A. It was about three hours.

7 Q. Thank you. So you said you reviewed Dr. Spellman's
8 declaration while preparing for this deposition?

9 A. Correct.

10 Q. And did you review the '142 patent?

11 A. I did, yes.

12 Q. In your research, Dr. Sherman, have you used any
13 spatial genomics methods or products?

14 A. Yes.

15 Q. Which ones?

16 A. Both 10x and NanoString's. We have those instruments
17 at the University of Michigan.

18 Q. Okay. So let's talk about 10x's products that you
19 have used. Which products of 10x have you used?

20 A. So the Visium.

21 Q. Do you recall which type of Visium --

22 A. No.

23 Q. -- you used?

24 A. It's located at a core facility, so most of those
25 details are handled by a technician in terms of, you

1 know, which instrument and which specific method.

2 Q. Okay.

3 A. Yeah.

4 Q. Do you recall the type of tissue sample you used when
5 you were using Visium?

6 A. Right. They were human T cells.

7 Q. Was that a frozen sample?

8 A. They were both frozen and freshly prepared samples.

9 Q. Okay. And why were you using Visium in your research
10 with the T cells?

11 A. So I have a very active project to develop a new drug
12 as an HIV cure that we discovered over the past few
13 years with a colleague of mine in medical school
14 who's an HIV expert, and we've gotten together to
15 discover and develop a drug that would, if
16 successful, offer a cure as opposed to simply
17 controlling the disease.

18 And one of the questions, since we have
19 some very promising compounds, is how the -- where
20 those drugs are binding, what's the exact target, and
21 we're studying this now to validate the target and
22 show direct binding.

23 And one of the best ways to do that is
24 using spatial genomics, proteomics. So that's the
25 project.

1 Q. So were you locating the -- strike that.

2 Were you trying to determine the location
3 of the target molecules?

4 A. The location and identity.

5 Q. And were the target molecules nucleic acids?

6 A. Was the target molecule a nucleic acid?

7 Q. Uh-huh.

8 A. Well, I mean, we're -- we'd like to understand how
9 our drug molecules actually impact what we know to be
10 a potential target, so there's transcriptional
11 analysis, but we also know the -- we suspect the
12 actual protein identity of the target or at least a
13 subgroup of those targets.

14 So it's really, you know, both
15 transcriptional analysis and proteomic analysis.

16 Q. With Visium, what molecule were you looking at when
17 you were trying to determine the spatial location?

18 A. What molecule in the T cell?

19 Q. Yes.

20 A. So... yeah, this is a really -- really amazing
21 project. So we identified some molecules that impact
22 a protein called Nef, called HIV Nef, and Nef is the
23 molecule that allows HIV to hide itself from our
24 immune system. So we know the importance of HIV Nef,
25 and we've published on this, in fact, very recently.

17

1 And so what we're now looking at is whether
2 these drugs bind directly to HIV Nef or if it's part
3 of some sort of complex in which HIV Nef is included.
4 So that's why we're doing these experiments.

5 Q. So you were using Visium to spatially locate a
6 protein.

7 A. Right. But also transcripts to get a sense of how
8 the drug impacts expression of the messenger RNA and
9 subsequently, you know, the protein. So it's really
10 a drug validation effort, drug target validation
11 effort.

12 Q. And the drug that you were testing alters the levels
13 or spatial location of the mRNAs, for example.

14 A. So the idea is, because we know our drug will enable
15 complete restoration of the immune system to detect
16 an HIV infected T cell. So normally our immune
17 system won't detect HIV infected T cells. That's why
18 people get AIDS. And what we're working on is a drug
19 that reverses that ability of HIV to hide itself from
20 our immune system, and we found a drug that does
21 that.

22 What we're working on is understanding how
23 and what the role of Nef is and whether our drug binds
24 directly to it or part of a complex that includes Nef.
25 And it's a complicated story, but we're working it

1 out. And I can't disclose that here today, what the
2 results are, because it's proprietary.

3 Q. Did you use capture array when you were using Visium
4 in your research?

5 A. Yes.

6 Q. And the capture array had, of course, capture probes
7 on it.

8 A. That's right.

9 Q. And the capture probes were collecting nucleic acid
10 molecules from the --

11 A. Right.

12 Q. -- T cells.

13 A. That's right.

14 Q. And were the T cells a layer of T cells -- strike
15 that.

16 Was the sample a layer of T cells?

17 A. So, yes, we basically layer them on a sample plate.

18 Q. Okay. So you did not use a solid tissue sample.

19 A. Since they're cells and it's a -- we use both a cell
20 line, but also primary T cells. It's not a tissue in
21 that case.

22 Q. Okay. Dr. Sherman, you also mentioned that you have
23 used Bruker's products.

24 A. Right.

25 Q. Can you tell me which products you have used of

1 Bruker?

2 A. The GeoMx.

3 Q. And why did you use that product?

4 A. We wanted to compare the results of the two systems.

5 Q. Okay. So you used GeoMx for the same research,
6 basically.

7 A. That's right.

8 Q. When did you first use Visium's -- Visium product?

9 A. I would say, like, last spring or so.

10 Q. Before you got involved with 10x.

11 A. That's correct.

12 Q. How about GeoMx?

13 A. Same.

14 Q. You agree, Dr. Sherman, that the skill level of a POSA
15 relevant to the '142 patent is high. Correct?

16 A. Correct.

17 Q. And this high skill level includes skill for spatial
18 genomics approaches. Correct?

19 A. I'm just going to review my definition of a POSA,
20 which is -- starts on my paragraph 19.

21 Yeah. The answer is yes.

22 Q. And in paragraph 22 of your declaration you state, "A
23 POSA would have a strong understanding and/or
24 experience with the design and application of various
25 assays to manipulate polynucleotide sequences."

1 Did I read that correctly?

2 A. Yes, you did.

3 Q. What do you mean by that?

4 A. Well, so I write this sentence to manipulate
5 polynucleotide sequences and then I write below that,
6 specifically giving examples of techniques that I
7 note below.

8 Q. So the techniques that you have listed in paragraph 22
9 are just examples.

10 A. Those are examples.

11 Q. Okay. So does the first sentence in paragraph 22 also
12 apply to all spatial genomic techniques?

13 A. A POSA would understand those techniques.

14 Q. Okay. And they would have an understanding of design
15 and application of those techniques?

16 A. That's correct.

17 Q. And when you say "design and application of various
18 assays," what do you mean by that?

19 A. That the POSA would have enough background and
20 understanding to imagine some sort of experimental
21 approach, and understand how to design it, and to
22 proceed from that point.

23 Q. Does this design -- strike that.

24 Does this designing aspect that you
25 mentioned, Dr. Sherman, also include designing of

1 conditions for various spatial genomics approaches?

2 A. It really depends on the situation in terms of
3 conditions. You can design an experiment and imagine
4 the high-level view of conditions that you might need
5 but not necessarily have the expertise to execute all
6 of those conditions. It really depends.

7 Q. Does this designing aspect include designing capture
8 probes of various lengths?

9 A. Capture probes of various lengths would typically be
10 within the understanding of a POSA.

11 Q. And when you say "capture probes," could you elaborate
12 on what a POSA's understanding would be what a capture
13 probe is?

14 A. Can you give me like a -- some sort of scenario?
15 That's a pretty broad question.

16 Q. For spatial genomics approaches, what would a POSA's
17 understanding be about capture probe?

18 A. Nucleotide sequence that would be designed to bind to
19 a target.

20 Q. And typically a capture probe in spatial genomics
21 approaches would include a spatial barcode.

22 A. Some type of sequence that would enable the
23 experimentalist to have some information about where
24 that target is, some information.

25 Q. And when you say "some information about where that

1 target is," you mean the spatial location of the
2 target?

3 A. Some information. It depends.

4 Q. Dr. Sherman, the designing aspect that you mentioned
5 in paragraph 22 of your declaration, does that also
6 include selection of polymerases for synthesis
7 reactions?

8 A. Again, it depends on the situation because there are,
9 sort of, standard methods and then there are methods
10 that require specialized expertise to even understand
11 that you need some unique type of reagent or enzyme
12 or condition. So it really depends on the
13 circumstances.

14 Q. DNA polymerases were commonly used enzymes before
15 2020 -- excuse me, before 2018.

16 A. Well, you know, the word "polymerases" makes it seem
17 like they're all the same. I mean, they're not all
18 the same. So we kind of have to talk about what kind
19 of polymerase, what kind of circumstance, is it
20 engineered, is it from -- what kind of organism is it
21 from, can it tolerate extreme conditions.

22 So a polymerase can be -- can mean lots of
23 different things, and a POSA would have some
24 understanding of it, but given the particular
25 experimental requirement or demand, they may not have

1 that level of expertise to just proceed.

2 Q. So in response to my question, you said there are -- I
3 believe you said there are different kind of
4 polymerases.

5 A. Right.

6 Q. My question, however, was directed to DNA polymerases.

7 A. Okay.

8 Q. Is your answer different --

9 A. No.

10 Q. -- for DNA polymerases?

11 A. There are lots of different kinds of DNA polymerases
12 too.

13 Q. Okay. Okay. And then you mentioned the origin of
14 polymerases in your previous answer.

15 A. Right.

16 Q. So your opinion is that the polymerases from various
17 origins were not commonly known in the prior art
18 before 2018?

19 A. I mean, polymerases, that word, DNA polymerases was
20 known, and the, sort of, standard polymerases were
21 known for solution-based DNA synthesis. But for more
22 specialized purposes, it -- I would not assume that
23 that information would have been known to a POSA
24 without, you know, more intense investigation.

25 Q. What is the "specialized" purpose you are referring to

1 in your answer?

2 A. It really depends on the experiment. I mean, if you
3 can give me a certain example I'd be, you know, happy
4 to answer.

5 Q. Okay. Were DNA polymerases for solid-phase synthesis
6 known in the art before 2018?

7 A. There were some polymerases available for certain
8 types of solid-phase synthesis.

9 Q. DNA polymerases for which type of solid-phase
10 synthesis were known in the prior art?

11 A. You know, there were DNA polymerases known for
12 Illumina sequencing, for example. They may be -- and
13 particular types of sequencing, yeah, using DNA
14 molecules and -- but for other types of sequencing,
15 that may not have been immediately available or
16 obvious to a POSA.

17 Q. What do you mean by "immediately available"?

18 A. Well, you know, certain enzymes that are larger, like
19 RNA polymerases, if you're sequencing RNA and you
20 want to, you know, use it for solid-phase synthesis,
21 then, you know, the situation is different because
22 there's some limitations to that, to the ability to
23 do that solid-phase --

24 Q. But DNA --

25 A. -- which I discuss in my -- in my declaration here.

1 Q. But DNA-dependent DNA polymerases for solid-phase
2 synthesis were known in the art before 2018. Correct?

3 A. Certain types for certain circumstances. Whether
4 they work for everything, I don't think so. And how
5 well they work is a question. So to make a global
6 statement like that, that you can have a DNA
7 polymerase and use it for solid-phase synthesis, I
8 mean, that's just too big a landscape to say that
9 it's going to work for everything, so I don't agree
10 with that.

11 They were known, they were used in certain
12 circumstances, but whether they would be useful for
13 every potential application, I wouldn't agree with
14 that.

15 Q. Can you give me an example of DNA-dependent DNA
16 polymerase for solid-phase synthesis that was known in
17 the prior art?

18 A. That was known?

19 Q. Uh-huh.

20 A. You know, Illumina sequencing uses that type of
21 approach.

22 Q. Which DNA polymerase is used in Illumina sequencing?

23 A. I believe it's T4.

24 Q. So T4 DNA-dependent DNA polymerase is used in Illumina
25 sequencing.

1 A. I believe so.

2 Q. Okay. In paragraph 35 of your declaration you provide
3 a POSA's understanding of steps (c) and (d) of
4 Claim 1; is that right?

5 A. So we're looking at my paragraph 35 here?

6 Q. That's right.

7 A. Yes, I see that.

8 Q. And in paragraph 35, you state that -- strike that.

9 In paragraph -- in paragraph 35, your
10 opinion is that a POSA would understand that step (c)
11 of Claim 1 requires "a synthesis reaction that
12 generates DNA products."

13 Is that correct?

14 A. That's right.

15 Q. And then you also list two requirements for the
16 synthesis reaction. Correct? The first requirement
17 that you list is the collected oligonucleotides to be
18 used as a template, and the second requirement you
19 list is at location-identifying sequences to be
20 incorporated into the DNA products; is that correct?

21 A. That's right.

22 Q. And you have a similar opinion for step (d) of Claim 1
23 as well, which is that a POSA would understand
24 step (d) of Claim 1 to require "a synthesis reaction
25 that generates DNA products." Correct?

1 A. That's correct.

2 Q. And that step (d) requires that the synthesis reaction
3 meet two requirements: first, the collected
4 oligonucleotides to be used as templates; and, second,
5 the location-identifying sequences to be incorporated
6 into the DNA products.

7 A. That's correct.

8 Q. And the location-identifying sequences have also been
9 called spatial barcodes in this proceeding?

10 A. Yes, I believe so.

11 Q. So if I use the terms "spatial barcodes" and
12 "location-identifying sequences" interchangeably, you
13 would understand what I mean. Right?

14 A. Yes.

15 Q. So, Dr. Sherman, you agree that a POSA would
16 understand step (c) of Claim 1 to require a
17 single-synthesis reaction to use the collected
18 oligonucleotide as template and also to incorporate
19 the spatial barcode. Correct?

20 A. "A POSA would have understood this claim limitation
21 to require a synthesis reaction that generates DNA
22 products," and, "As part of the synthesis reaction
23 that results in DNA products, the remainder of
24 claim 1(c) and 1(d) require the collected
25 oligonucleotides to be used as templates and require

1 location-identifying sequences," spatial barcodes,
2 "to be incorporated into the DNA products."

3 Q. Okay. So going back to the sentence that you read,
4 Dr. Sherman --

5 A. Uh-huh.

6 Q. -- which is, "A POSA would have understood this claim
7 limitation to require a synthesis reaction that
8 generates DNA products," my question, Dr. Sherman, is,
9 in this sentence, you mean that a single-synthesis
10 reaction generates the DNA products. Correct?

11 A. A single-synthesis reaction generates the DNA
12 products.

13 Q. Is that right?

14 A. Yes. It's a single event, if that's what I
15 understood your question to mean. A single event
16 provides that synthesis of that product, yes.

17 Q. When you say an "event," what do you mean by that?

18 A. I mean that the -- there's a reaction and it
19 synthesizes the product in a single event. It's --
20 yeah, that's what I mean.

21 Q. So you just testified for step (c).

22 A. Uh-huh.

23 Q. Is your answer the same for step (d), Dr. Sherman?

24 A. Yes, it is.

25 Q. Okay. Dr. Sherman, steps (c) and (d) of Claim 1

29

1 require that the synthesis reaction use the collected
2 oligonucleotides as templates. Right?

3 A. That's right.

4 Q. Okay. So a POSA would understand that steps (c) and
5 (d) of Claim 1 exclude a synthesis reaction that does
6 not use an oligonucleotide template; is that correct?

7 A. Would I -- would you be able to give me the '142
8 patent, please?

9 Q. Sure.

10 A. Thanks.

11 ENTERED INTO THE RECORD:

12 PREVIOUSLY MARKED EXHIBIT 1043

13 9:46 a.m.

14 A. Thank you.

15 BY MS. KHANDURI:

16 Q. So let me ask my question again, Dr. Sherman, so that
17 you have it. My question is, steps (c) and (d) --

18 A. Right.

19 Q. -- of Claim 1 require that the synthesis reaction use
20 the collected oligonucleotides as templates. Correct?

21 A. That's right.

22 Q. Okay. And then a POSA would understand that step (c)
23 and (d) of Claim 1 exclude a synthesis reaction that
24 does not use an oligonucleotide -- strike that -- that
25 does not use a collected oligonucleotide template.

30

1 A. Well, I mean, that language isn't specifically used
2 here. It says something different, "by performing a
3 synthesis reaction" that uses a plurality of
4 oligonucleotides. I mean, there's no language about
5 exclusion in here, so... I don't know. I'm not gonna
6 read that in without seeing any language to that
7 effect.

8 Q. Dr. Sherman, you just testified that step (c) and (d)
9 of Claim 1 require the synthesis reaction to use the
10 collected oligonucleotides as a template --

11 A. Right.

12 Q. -- right?

13 A. Yes.

14 Q. You agree with that?

15 A. I do, yeah.

16 Q. Would you agree that the step (c) and (b) of Claim 1
17 require that the synthesis reaction use a -- an
18 oligonucleotide as a template?

19 A. I mean, that's what it says here, yeah.

20 Q. And in step (c) and (d) of Claim 1, what would a POSA
21 understand the term "template" to mean?

22 A. Basically, a template is the starting material of the
23 reaction. That's the critical starting material to
24 make a product.

25 Q. Do you have an understanding of phosphoramidite

1 synthesis?

2 A. I do.

3 Q. Does phosphoramidite synthesis use an oligonucleotide
4 as a template?

5 A. No, it does not.

6 Q. Let's stay with the '142 patent --

7 A. Okay.

8 Q. -- which is Exhibit 1043. And we were looking at
9 step (c) -- steps (c) and (d) of Claim 1. Right?

10 A. Okay.

11 Q. Dr. Sherman, does step (c) of Claim 1 require any
12 particular level of efficacy for synthesizing DNA
13 products?

14 MR. CHEUNG: Objection. Form.

15 A. So you asked about efficacy?

16 BY MS. KHANDURI:

17 Q. Strike that. I'll ask the --

18 A. Did I hear that correctly?

19 Q. You heard that correctly, but my question was wrong,
20 so let me ask you the question again.

21 You agree, Dr. Sherman, that step (c) of
22 Claim 1 does not require any particular level of
23 efficiency for the -- for synthesizing DNA products?

24 A. Well, insofar as it needs to work, that requires a
25 certain level of efficiency.

1 Q. So you are saying that all that step (c) of Claim 1
2 requires is that the synthesis -- strike that.

3 What you are saying is, all that step (c)
4 of Claim 1 requires is that there be some synthesizing
5 of DNA products. Correct?

6 A. But there's -- I mean, I don't see any level of
7 efficiency or quantification noted in these claims.
8 It has to work. And so to put some sort of specific
9 definitions in that respect, I mean, it's -- I don't
10 see it here, but it has to work.

11 Q. And your answer is the same for step (d) of Claim 1?

12 A. Yes.

13 Q. Do you have an understanding of plain and ordinary
14 meaning in the context of claim construction?

15 A. I do.

16 Q. And what's your understanding?

17 A. That a POSA would read the words and understand them
18 and what they mean.

19 Q. Okay. Let's go to paragraph 35 of your declaration.

20 And in paragraph 35, you say, "In my
21 opinion, a POSA would have understood the plain and
22 ordinary meaning of 'synthesizing a first plurality
23 [and second plurality] of DNA products by performing a
24 synthesis reaction.'"

25 Did I read that correctly?

1 A. Yes.

2 Q. And after that sentence you provide your opinion on
3 what that plain and ordinary meaning of the claim
4 limitation that I just read in quotes means. Right?

5 A. Right. The next sentence, "A POSA would have
6 understood this claim limitation to require a
7 synthesis reaction that generates DNA products."

8 Q. Uh-huh. So how did you determine plain and ordinary
9 meaning of the claim language for "'synthesizing a
10 first plurality [and second plurality] of DNA products
11 by performing a synthesis reaction'?"

12 A. So first of all, my, you know, experience as a person
13 of skill in the art enabled me to understand the
14 plain and ordinary meaning of that. And to confirm
15 that, I noted every time in the patent that the word
16 "synthesis" was used in '142. It's over 100 times.
17 It's used a lot. And I went through and that
18 confirmed what was my understanding of the plain and
19 ordinary meaning of a synthesis reaction.

20 Q. So you're saying that to determine plain and ordinary
21 meaning of the claim language quoted in paragraph 35
22 of your declaration you looked at the specification of
23 the '142 patent?

24 MR. CHEUNG: Objection. Form.

25 A. No. That -- that's not what I said. I used my own

1 understanding as a POSA to apply that claim language
2 and to understand it, and I went into the patent just
3 to make sure that, yeah, it all -- it's all
4 consistent over 100 times, so...

5 BY MS. KHANDURI:

6 Q. So your plain and ordinary meaning -- strike that.

7 The plain and ordinary meaning that you
8 provide in paragraph 35 is not based on the '142
9 patent specification?

10 A. No, it's based on my understanding of what that
11 means.

12 Q. Let's go to paragraph 29 of your declaration.

13 A. Okay.

14 Q. In paragraph 29, you are providing your opinions on "a
15 POSA's understanding of the claim language
16 "'identifying a first plurality [and second
17 plurality]' of a -- 'of DNA products by sequencing.'"

18 Is that right?

19 A. That's right.

20 Q. And you are providing a plain and ordinary meaning of
21 this claim language that I just read.

22 A. That's right.

23 Q. Did you apply the same kind of analysis to determine
24 plain and ordinary meaning for the claim language
25 quoted in paragraph 29 as you did for the claim

1 language quoted in paragraph 35?

2 A. Well, I used the same process. I -- as a person of
3 skill in the art, I thought about my own
4 understanding of that language and I then queried the
5 '142 patent to make sure that my understanding of the
6 claim language was consistent with the use of this
7 language in the patent.

8 It was consistent, and I note that DNA
9 sequencing also was used over 100 times in that
10 patent.

11 Q. So your determination of plain and -- strike that.

12 So the plain and ordinary meaning provided
13 in paragraph 29 of your declaration is not based on
14 the specification. Correct?

15 A. It's based on my understanding of the language.
16 Right.

17 Q. Thank you. Okay.

18 Let's go to page --

19 MS. KHANDURI: By the way, would you like
20 to take a break, or... if you -- if you want to --
21 let's take a break now --

22 THE WITNESS: Okay.

23 MS. KHANDURI: -- because it's about an
24 hour.

25 THE WITNESS: All right. Sounds good.

1 Thank you.

2 (Off the record at 9:57 a.m.)

3 (Back on the record at 10:19 a.m.)

4 BY MS. KHANDURI:

5 Q. Dr. Sherman, during the break, did you discuss any
6 substance of your testimony with your counsel?

7 A. No.

8 Q. Let's go to the '142 patent, which is Exhibit 1043,
9 and let's go to the claims.

10 A. Okay.

11 Q. So, Dr. Sherman, looking at Claim 5 -- are you there?

12 A. I am.

13 Q. Claim 5, Dr. Sherman, does not require any particular
14 level of efficiency for solid-phase amplification.
15 Correct?

16 MR. CHEUNG: Objection. Form.

17 A. Well, it has the words it has, and it has to work, so
18 that's my understanding, but there's no other
19 language other than this is the claim and it has to
20 work.

21 BY MS. KHANDURI:

22 Q. Okay. Okay. Let's go to page 29 of your declaration,
23 which is Exhibit 2008. On page 29 of your
24 declaration, Dr. Sherman, you provide a figure; is
25 that right?

1 A. A figure?

2 Q. Yes.

3 A. Of which -- excuse me, which page? Sorry.

4 Q. Page -- let's go to page 29.

5 A. Oh, I was -- I was -- sorry. I was --

6 Q. No worries.

7 A. I was looking at paragraph 29.

8 Q. Yeah, no worries. Page 29.

9 A. My apologies.

10 Q. Yeah. On page 29 of your declaration --

11 A. Uh-huh.

12 Q. -- you provide a figure.

13 A. Yes.

14 Q. Who created this figure, Dr. Sherman?

15 A. Well, I created the figure, and in my detailed
16 reading of the Stahl paper and digging into the SI, I
17 created this workflow.

18 Q. So it is your opinion that this figure depicts the
19 workflow of Stahl, Stahl's method?

20 A. That's right.

21 Q. But this figure is not in Stahl, which is
22 Exhibit 1016; is that right?

23 A. The figure's described from the description of Stahl
24 and the details in the paper and the supplementary
25 information. This is a visual depiction of those

1 details and instructions.

2 Q. So this visual depiction that we have on page 29 of
3 your declaration is not in Stahl.

4 A. It's not visually shown like this in Stahl, but the
5 words are there to create this visual depiction.

6 Q. And the visual depiction that we have on page 29,
7 which you testified you created, has eight steps.
8 Correct?

9 A. That's right.

10 Q. And for step 2 in this visual depiction, you
11 identify -- strike that.

12 You identify step 2 of this visual
13 depiction as "synthesize first-strand cDNA"; is that
14 right?

15 A. That's right.

16 Q. And under that step 2, you have depicted two
17 molecules. Right?

18 A. Well -- under step 2?

19 Q. Yes.

20 A. Well, I see three molecules. There's a black one,
21 and then the red one, and the blue one.

22 Q. Okay. The blue one is the collected mRNAs from the
23 tissue sample. Correct?

24 A. That's right.

25 Q. And then you said there are two additional molecules

1 under step 2, the black one and the red one.

2 A. That's right.

3 Q. Are you -- is your testimony that the black molecule
4 and the red molecule are not linked to each other?

5 A. Well, they're distinct from one another, as I show
6 here. Whether or not they're linked, they're
7 distinct.

8 Q. Are the black and the red, what you call molecules,
9 part of the same nucleotide sequence?

10 A. Well, you start with the black sequence, and then
11 there's a synthesis reaction that specifically
12 creates the red sequence. There's no creation of the
13 black sequence, there's only creation or synthesis of
14 the red sequence.

15 Q. My question, though, Dr. Sherman, is slightly
16 different. My question is, the black -- strike that.

17 My question, Dr. Sherman, is, the black
18 segment and the red segment are part of the same
19 nucleotide sequence. Right?

20 A. Well, I mean, I used different colors to denote that
21 they're distinct entities and, you know, I'm not --
22 I'm not sure, you know, what your point is, but
23 they're distinct entities that I'm denoting here
24 through the use of these different colors.

25 Q. The black sequence and the red sequence, are they part

1 of the same oligonucleotide?

2 A. Oligonucleotide?

3 Q. Yes.

4 A. Well, whatever -- I'm not quite sure what you mean,
5 but the -- as the figure depicts, and as is described
6 in Stahl, there's an attached sequence that you see
7 in black, and then there's a synthesis reaction that
8 generates a new sequence that is distinct from the
9 black sequence, which was there to begin with. So
10 the new part is in red, which is generated through a
11 DNA synthesis reaction.

12 So, you know, that's what this describes
13 and that's what -- that's what it is.

14 Q. I understand, Dr. Sherman, that you're saying --

15 A. Uh-huh.

16 Q. -- that the red part is the part that is synthesized
17 in the synthesis reaction --

18 A. Right.

19 Q. -- in step 2. I understand that.

20 A. Uh-huh.

21 Q. My question, though, is, the black and the red
22 sequence, they are part of the same oligonucleotide.
23 Correct?

24 A. I mean, I don't -- I don't know what you mean by
25 that. I mean, they're distinct components of what

1 becomes this black and red nucleic acid entity.

2 Q. Okay. So the red and the black sequences are a part
3 of one single entity. Correct?

4 A. Well, you can't put it that simply because I think it
5 would lead to misunderstandings. They're distinct
6 components of what visually here looks to be a single
7 entity, but they're -- they are distinct components,
8 have distinct roles, came about in different ways,
9 and so anything we say about it, we have to include
10 those parameters.

11 Q. Okay. So in the -- in step 2 of Stahl --

12 A. Uh-huh.

13 Q. -- this entity having the black sequence -- strike
14 that.

15 Let's go to step 3 of this depiction that
16 you have in -- I'll start over.

17 Let's go to step 3 of the depiction that
18 you have on page 29 of your declaration.

19 A. Okay.

20 Q. And you identify step 3 in this depiction as "cleave
21 capture probe"; is that correct?

22 A. Correct. That's right.

23 Q. What are you showing, Dr. Sherman, in this step 3?

24 A. That as opposed to step 2, where it's linked to a
25 solid surface from step 2 to step 3, there is a

1 change in the changes that what we're looking at has
2 been cleaved from the solid surface, so it goes into
3 solution.

4 Q. What is cleaved in step 3?

5 A. The cleavage occurs at the bottom of the black
6 segment which, in step 1, is called "attached DNA."

7 Q. Okay. And the attached DNA referred to under step 1
8 is the same as the capture probe noted in step 3 of
9 your figure?

10 A. It's the same except it's now been cleaved and is in
11 solution.

12 Q. Okay. Then going to step 4, which you have identified
13 as "synthesize second-strand cDNA" --

14 A. Right.

15 Q. -- what is happening in this step, Dr. Sherman?

16 A. So you can see that, in step 3, there was a blue
17 strand labeled messenger RNA, and it's a positive
18 strand; and in step 4, the cDNA that is comprised of
19 a red component, and then the original black
20 component, that was the DNA capture probe from
21 step 1. So now that's used for the synthesis of a
22 second-strand cDNA, which is a positive strand in
23 solution.

24 Q. So in step 4, the cDNA that is comprised of a red
25 component and the black component, that is the

1 template for the second-strand synthesis reaction?

2 A. It's a second-strand cDNA at step 4.

3 Q. I'm asking you, what is the template in the reaction
4 that's occurring in step 4?

5 A. Oh, it's the cDNA minus strand that I mention as the
6 black component and the red component.

7 Q. And talking about the black component, in step 1 of
8 this depiction, it includes a spatial barcode.

9 Correct?

10 A. The black component, yes, it does.

11 Q. The black component in step 2 includes a spatial
12 barcode?

13 A. In strand 2, as you can see, it is synthesized and
14 incorporates what is the template black component.
15 This is the second strand as opposed to the first
16 strand where that isn't happening. The first strand,
17 there's no incorporation. That's why I'm, you know,
18 separating the two. With the first strand, there's
19 no incorporation of that spatial barcode. In
20 strand 2, there is.

21 Q. Okay. So you are -- what you're saying, I think, is
22 that in step 4 the spatial barcode that is in the
23 black component is copied over into the second-strand
24 cDNA during the synthesis reaction.

25 A. That's what happens in step 4 --

1 Q. Okay.

2 A. -- not in step 1 --

3 Q. Okay.

4 A. -- or step 2.

5 Q. Okay.

6 A. There's no incorporation in the first-strand action.

7 It's already in the barcode. So it's not

8 incorporated.

9 Q. Okay. Focusing on the black components for now, the
10 black component that's in step 1 has spatial barcodes.

11 I think you testified to that before. Right?

12 A. Step 1 in the black component has that in place.

13 Q. And the black component in step 2 has the same
14 barcode. Right? Same barcode as -- that was in the
15 black component of step 1.

16 A. It is the same capture probe as step 1, so it does
17 have the same barcode.

18 Q. Then going to step 3, the black component shown under
19 step 3 has the same barcode that was in the black
20 component under step 1. Correct?

21 A. Right. Now at this stage it's been cleaved and it's
22 in solution, but it is now carryover from step 1.

23 Q. So let me understand that. Are you testifying that
24 the capture probe is cleaved --

25 A. Uh-huh.

1 Q. -- in step 3, but the black component that remains has
2 the spatial barcode that was present in the black
3 component of step 1?

4 A. Right. It's still there.

5 Q. Okay. Going to step 4, the -- I think it's brown, the
6 brown molecule under step 4 is the second-strand cDNA
7 that's synthesized. Correct?

8 A. It's the second-strand cDNA.

9 Q. Okay. And the second-strand cDNA has the sequence
10 complementary to the sequence of the spatial barcode
11 that was in the black component in step 4. Right?

12 A. So it will have the reverse complement of that
13 sequence that was in place in step 1 in the black
14 component that was not incorporated into the red
15 sequence in step 2. Cleaved in step 3, that cleaved
16 black-and-red nucleic acid fragment was used as the
17 template for second-strand cDNA synthesis to get the
18 positive strand.

19 Q. Okay. And that second-strand cDNA has a spatial
20 barcode.

21 A. It has the reverse complement of the original
22 sequence for a spatial barcode from step 1.

23 Q. Okay. Going back to step 1, the black attached DNA
24 that's under step 1, that also includes an oligo T
25 sequence. Correct?

1 A. Right. Yes. To capture the messenger RNA.

2 Q. And in step 4, the black component retains the oligo T
3 sequence that was in the black component in step 1.

4 Correct?

5 A. Well, it's a reverse complement of that, so... it's a
6 reverse complement of the sequence that's in the
7 black component.

8 Q. So you're saying the sequence that -- that is in the
9 black component in step 4 is the reverse complement of
10 the sequence that's in the black component in step 1?

11 A. Right. Well, it's minus strand cDNA plus strand
12 cDNA.

13 Q. My question, though, is about the minus strand.

14 A. Oh, yes. If you could ask that again. Maybe I
15 misheard you.

16 Q. So let's start over.

17 A. Okay.

18 Q. The black component --

19 A. Uh-huh.

20 Q. -- identified as attached DNA in step 1 --

21 A. Uh-huh.

22 Q. -- has oligo T sequence.

23 A. Oligo T, yes.

24 Q. The black component that's under step 4 retains the
25 oligo T sequence that was in the black component in

1 step 1.

2 A. It retains that. Yes.

3 Q. Okay. And the second-strand cDNA, which is the plus
4 strand you identified --

5 A. Right.

6 Q. -- under step 4 has the reverse complement of that
7 oligo T sequence.

8 A. Correct.

9 Q. And the reverse complement of oligo T sequence would
10 mean oligo base sequence.

11 A. That's right.

12 Q. So now going to step 5.

13 A. Okay.

14 Q. Could you explain what's happening in step 5?

15 A. Right. So as described in Stahl, and detailed in the
16 supplementary information, the brown strand here is
17 amplified to create the negative strand RNA through
18 an amplification reaction in solution.

19 Q. And the amplified RNA, called aRNA (-), have a spatial
20 barcode. Correct?

21 A. It would have the barcode sequence from -- yes, it
22 would.

23 Q. So the aRNAs, which are green molecules in your
24 depiction, they have the same spatial barcode as the
25 black component shown under Figure 5. Correct?

1 Sorry, strike that.

2 The green molecules, which are aRNAs under
3 step 5 --

4 A. Uh-huh.

5 Q. -- have the same spatial barcodes -- barcode as the
6 black component under step 5.

7 A. Well, not exactly because the black segment is DNA,
8 and as I show, the green fragment is RNA, so they're
9 actually different molecules.

10 Q. Okay. Going to step 6, could you explain what's
11 happening in step 6?

12 A. Right. So adapters are introduced onto the amplified
13 RNA molecules.

14 Q. Okay. Then going to step 7, what's happening in
15 step 7, Dr. Sherman?

16 A. So step 7 is basically now in order to preserve the
17 strandedness, that's what is occurring here, and
18 that's why it's so important to depict this visually
19 because it clarifies what's described in the
20 supplementary information text, and that is, this
21 whole scheme was conducted for the purpose of
22 stranded sequencing to preserve the strand --
23 positive strand that was originally captured in
24 step 1.

25 So 7 is now generating a cDNA product that

1 you can see is now the plus strand and that is
2 prepared for the step 8, which is amplifying and
3 adding the adapters that you usually do for an
4 Illumina platform and then conducting that Illumina
5 sequencing.

6 So this whole effort that -- it describes a
7 process that goes well beyond the conflated
8 understanding of Dr. Spellman, where none of this was
9 brought out. It's a really important part of Stahl.
10 It means that they're not working with this first
11 strand to create a library and sequence it. They're
12 going all the way through here, many steps down, as I
13 describe, for the eventual sequencing.

14 And post step 2, everything is in solution.

15 Q. So in your answer, Dr. Sherman, you mentioned, quote,
16 "preserve the strandedness." Could you explain what
17 you mean by that?

18 A. Yes. So there is a technology that was developed in
19 the mid-'20 teens to ascertain an understanding of
20 the handedness of the messenger RNA because there can
21 be directional differences that can reflect gene
22 expression differences or certain RNAs that may not
23 otherwise be captured in an authentic fashion like
24 micro RNAs.

25 So this stranded sequencing strategy was

50

1 created to ascertain what otherwise would perhaps be
2 hidden or not fully appreciated in terms of
3 quantification of the different types of messenger
4 RNAs and other RNAs.

5 So that's what Stahl did. And the reasons
6 to better understand the RNA, the quantification,
7 regulation, other rare types of RNAs like micro RNAs
8 that may otherwise not be captured. So that's what
9 they did here.

10 Q. So is the information about strandedness required to
11 be able to identify whether a particular sequence is
12 the sequence of the mRNA or whether it's the sequence
13 of its reverse complement? Is that the reason why
14 strandedness is important?

15 A. It depends on the experiment. It depends on what the
16 original scientific hypothesis is, like what --
17 what's driving the question. And in Stahl, what was
18 driving the question led them to use a stranded
19 sequencing method that they wanted to know what the
20 original -- the sequence of the original strand of
21 captured mRNA was. They wanted to know that, so they
22 went through this whole process.

23 It doesn't mean everyone needs to do it or
24 would do it. It really depends on the scientific
25 question. But in their case, the scientific question

1 led them to use this approach. Much longer, as you
2 can see.

3 Q. So when you say maintain the strandedness of -- strike
4 that.

5 So your opinion is that Stahl is performing
6 this stranded sequencing method so that it can
7 identify the sequence of the original mRNA.

8 A. Right. Right. Which means they cared about that
9 original messenger RNA and what its sequence was,
10 forcing them to go through this whole series of
11 steps. So they're dealing with not the original
12 synthetic cDNA, which is a minus strand, but what
13 they're sequencing way downstream through all these
14 solution-based amplifications and so on is a cDNA of
15 the positive strand which matches the original
16 captured messenger RNA.

17 Q. Okay. Okay. So going back to step 7 --

18 A. Uh-huh.

19 Q. -- the original -- strike that.

20 Under step 7, the orange molecules have the
21 same sequence as the -- strike that.

22 The orange molecules under step 7 have the
23 same sequence as the brown molecules under step 4.

24 Correct?

25 A. It's the second-strand cDNA positive strand. The

1 cDNA positive strand, in orange, has adapters linked
2 to it, which I don't show there, so it's actually
3 different and it's set up for Illumina sequencing, so
4 it's a -- it's a different molecule.

5 Q. Would you agree that the orange molecules under step 7
6 include the sequence of the brown molecules under
7 step 4?

8 A. Sorry, that -- that was distracting me. Can you ask
9 me again?

10 Q. I'll say it again. No worries.

11 Do the orange molecules under step 7
12 include the sequence of the brown molecules under
13 step 4?

14 A. So much of the sequence is the same, but as I
15 mentioned, there are adapters attached in preparation
16 for the Illumina sequencing.

17 Q. Okay. The --

18 A. But I would call it, you know, second-strand cDNA,
19 not -- it's not the synthetic product I show in red.
20 That's different.

21 Q. The orange molecules in step 7 --

22 A. Uh-huh.

23 Q. -- include the oligo A sequence that was in the
24 captured mRNA in step 1. Correct?

25 A. So as a homolog of the second-strand cDNA in brown,

1 it would have those sequences.

2 Q. And the orange molecules in step 7 would include a
3 reverse complement of the spatial barcode that was in
4 the black molecule in step 1. Correct?

5 A. So it would -- as a second-strand cDNA homolog it
6 would have the reverse complements of that sequence
7 from the negative strand, compared to the negative
8 strand.

9 Q. Okay. I know it gets -- it's getting very confusing.

10 A. No, it's -- I mean, it's...

11 Q. So let's -- let me try to clarify or make it easier
12 for both of us, to be honest.

13 Let's look at step 1 --

14 A. Uh-huh.

15 Q. -- and step 7.

16 A. Sure.

17 Q. The orange molecule in step 7 has a reverse complement
18 of the spatial barcode that was in the black molecule
19 identified as attached DNA. Correct?

20 A. So if you go through this, you know, the original
21 black sequence has its spatial barcode, it captures
22 the positive strand messenger RNA, there's a
23 first-strand synthesis which is the red component
24 that I've been describing, and then you go to the
25 second-strand synthesis in brown, which is the

1 positive strand cDNA, and if you go all the way to
2 the end now through all these steps, the cDNA would
3 have the reverse complement of the black sequence.

4 Q. Of the black sequence in step 1.

5 A. The reverse complement.

6 Q. I just want to make it clear just for the record.

7 I think what you said is that the orange
8 molecule in step 7 has a reverse complement of the
9 black -- strike that.

10 The orange molecule in step 7 has the
11 reverse complement of the spatial barcode in the black
12 sequence in step 1. Correct?

13 A. Well, yeah, I want to be very clear. The petitioner
14 and Dr. Spellman, they identify the initial sequence
15 DNA as the DNA of interest, and we're talking
16 about -- I want to be very clear. We're talking
17 about the second-strand cDNA, not the first strand.
18 So that's very different.

19 And when you go through this whole process,
20 which was, as I stated, Stahl was motivated to go
21 through this to preserve the original handedness of
22 the messenger RNA in the end product, so you can go
23 through all of this and you can, you know, work out
24 what's, you know, the original sequence, the reverse
25 complement.

1 When you go to the orange, as we've
2 discussed, the spatial barcode will be the reverse
3 complement.

4 Q. Okay. Yeah, that's all I was just trying to
5 understand.

6 A. Okay.

7 Q. Yeah. Thank you.

8 Then going to -- going to step 8 --

9 A. Okay.

10 Q. -- going back to step 8, which you have described in
11 your pictorial as "Amplify second cDNA product to add
12 sequencing adapters and sequence on Illumina
13 platform."

14 I read that correctly, Dr. Sherman?

15 A. Right.

16 Q. Could you just explain what's happening in the
17 amplification part of step 8?

18 A. Well, this is part of the Illumina sequencing
19 platform. So as opposed to what Stahl described for
20 a red component, which was not sequence, they just
21 added fluorescent nucleotides so they could image it.
22 In this depiction here, they go all the way through
23 to sequencing using the Illumina platform, and part
24 of that is amplification of the sequences to make a
25 lot of them so you get deep sequence information.

1 Q. So what is being amplified in step 8?

2 A. The cDNA is being amplified.

3 Q. So the second cDNA product that's in -- that was
4 generated in step 7 is being amplified in step 8; is
5 that correct?

6 A. That's right. So there's a step of adding the
7 adapters and then it can be amplified and go through
8 the Illumina platform.

9 Q. And does the amplification that happens in step 8
10 generate both the positive and the negative strands
11 from the orange molecule generated in step 7?

12 A. I don't know. I think they just want to amplify the
13 positive strand cDNA, so they may just be amplifying
14 the negative strand to only get the positive strand
15 cDNA because that's what they want. But it's -- but
16 whatever they're doing here, they're going through
17 the actual strand preservation method.

18 Q. Let's go to page 22 of your declaration.

19 A. Page 22?

20 Q. Yeah.

21 A. Okay.

22 Q. Okay. On page 22, in the bottom half of the top
23 paragraph, you state, quote, "The sequencing library
24 was then sequenced using an Illumina sequencing
25 platform."

1 A. Right.

2 Q. And then you have a quote from the Stahl reference,
3 which is, "Finished libraries were diluted to 4
4 nanomolar and sequenced on the Illumina NextSeq
5 platform using paired-end sequencing according to the
6 manufacturer's protocol."

7 Do you have an understanding of "paired-end
8 sequencing"?

9 A. Yes.

10 Q. What's your understanding?

11 A. So Illumina works by making short fragments of
12 sequences, and they're captured on a solid surface
13 and they make these bridge molecules, and the
14 sequencing happens on those -- on those molecules.

15 Q. How is the sequencing library generated in paired-end
16 sequencing -- strike that.

17 How is the sequencing library generated for
18 paired-end sequencing?

19 A. Through amplification.

20 Q. And does that amplification for sequencing library
21 generation include generating both the positive and
22 the negative strands from the template?

23 A. Well, in this particular instance, since they were
24 preserving the strandedness they were focusing on
25 amplifying the positive strand cDNA and then

1 sequencing that. And I -- you know, the details of,
2 you know, that process are in the Illumina sequencing
3 method.

4 Q. Right. My question, though, Dr. Sherman, is that --
5 my question is, does the amplification for sequencing
6 library generation for paired-end sequencing include
7 generating both the positive and the negative strands
8 from the template?

9 A. Well, the template is the -- is this green amplified
10 RNA negative strand, and it's amplifying then the
11 orange strand. So it's giving a lot of that cDNA,
12 which is the positive strand, and that's what's being
13 sequenced.

14 Q. So are you testifying that in step 8, the
15 amplification reaction uses the green molecules as
16 templates?

17 A. Well, you see the green to orange, and then there's
18 amplification of that cDNA to make a lot of it to
19 sequence. So they had to pilot -- I mean, it's
20 described in here. They had to pilot that reaction
21 to get -- to get it, essentially, standardized, and
22 then they made the positive strand cDNA for
23 sequencing.

24 Q. What is the template that is used in the amplification
25 reaction of step 8 in the pictorial that you have on

1 page 9?

2 A. Well, my understanding is that they amplify the green
3 to get a lot of the cDNA positive strand. That's
4 what they're interested in.

5 Q. So then your description of step 8 is incorrect, would
6 you say?

7 A. No. They're amplifying that. I mean, they're
8 amplifying to get a lot of that cDNA positive strand.

9 Q. So you're testifying that the step that's shown --
10 strike that.

11 Are you testifying that the reaction that's
12 shown in step 7 is also occurring in step 8 during the
13 amplification?

14 A. Well, yes, step 7 is they, you know, sort of piloted
15 the whole process to make sure they had the right
16 conditions and they were getting the right
17 amplification levels, and then they scaled that up
18 for the final step to get that cDNA positive strand.

19 Q. So let me make sure I understand.

20 A. Sure.

21 Q. Why are you depicting three different pairs of
22 molecules under step 7?

23 A. Uh-huh.

24 Q. Can you explain that to me?

25 A. Oh, that just shows that it continues from 6. I

1 showed 3 and 6, which denotes essentially from step
2 5, "generate amplified RNA," okay, that produces
3 green, amplified RNA negative strand in step 5.

4 Step 6, "ligate adapters to amplified RNA."
5 Okay, so that's shown, essentially, those three
6 strands that are denoting amplification. So the
7 adapters are added, those are the little black
8 segments at the top there, and then 7 shows the, sort
9 of, pilot amplification to get the conditions
10 optimized. And once that's done, it goes to step 8.

11 Q. So your opinion is that, in step 7, there is
12 amplification. Agreed?

13 A. Well, it's a pilot experiment. Nothing's done with
14 that. It's just, essentially, used by the -- by
15 Stahl to establish conditions for the scaleup library
16 construction.

17 Q. So is amplification happening in step 7 of the
18 pictorial that you have on page 29?

19 A. Well, there is -- there are test amplifications going
20 on. It's a pilot. Okay? It's a -- to get the
21 conditions established for the library construction,
22 the larger scale construction of the library.

23 Q. Okay. So you're testifying that there is a pilot
24 amplification occurring in step 7?

25 A. Yes, it's in the -- it's in Stahl. It's described in

1 Stahl.

2 Q. Okay. Okay. So there is pilot amplification in
3 step 7 that generates the orange molecules; is that
4 correct?

5 A. Right.

6 Q. And then in step 8, what is happening?

7 A. So step 7 is to establish the conditions using a
8 pilot scale amplification to get the conditions
9 right, the right concentration, the right amount of
10 enzyme, the right temperature, all these parameters
11 that are required.

12 Once they establish that, which is
13 described in Stahl, once that's established, they then
14 scale up for the step 8, which is "amplify second cDNA
15 product," and then they sequence.

16 Q. And for amplifying the second cDNA product, your
17 testimony is that they are generating the second cDNA
18 product?

19 A. Right. The cDNA plus strand. Right.

20 Q. Are they generating the negative strand in step (c) --
21 are they generating a negative strand in step 8's
22 amplification?

23 A. Well, that would not serve their goal of stranded
24 sequencing to have those strands.

25 Q. So Stahl is not generating the negative strand in the

1 amplification in step 8.

2 A. Well, this is stranded sequencing, so my
3 understanding is that they're generating the sequence
4 for the plus strand because that will match and
5 they'll be able to establish the -- address the
6 questions that they're interested in that are
7 demanded by stranded sequencing. That's why they did
8 this.

9 Q. So, again, Dr. Sherman, in step 8, the amplification
10 is not generating the negative strand. Correct?

11 A. I mean, that's my understanding if you're going
12 through this process for stranded sequencing.

13 Q. And is your understanding that the library that is
14 generated for paired-end sequencing does not include
15 the negative strand?

16 A. In order to preserve the strandedness, you would have
17 to focus on sequencing the single strand for those
18 short reads.

19 Q. So is your understanding that the library that is
20 generated for paired-end sequencing outside of the
21 Stahl's method does not include the negative strand?

22 A. Oh, outside of Stahl. I mean, normally it involves
23 both strands. You want both strand information in
24 Illumina, but here they wanted the single strand.

25 Q. Okay. So typically the library generated for

1 paired-end sequencing, outside of Stahl's method,
2 includes both the negative and the positive strand.
3 Right?

4 A. Well, normally they wouldn't go through this process.
5 Right? Illumina sequencing, you isolate DNA or cDNA
6 and you sequence both strands. Right. You want
7 that.

8 Q. So --

9 A. If you're doing what we might consider typical
10 Illumina sequencing. But here they're going through
11 this whole process. They're not -- they're
12 sequencing the cDNA minus strand in red, they're
13 using it for imaging. They're going all the way
14 through to determine the exact sequence of that cDNA
15 positive strand, so they're -- what I -- that's my
16 understanding that's why they're doing this.
17 Otherwise, why would you do this work? So that's
18 what they're doing. And in order to preserve it, you
19 can sequence a single strand.

20 Q. So your opinion is that the paired-end sequenced --
21 strike that.

22 The sequencing library that is generated --
23 I'll start over. Sorry.

24 So your opinion is that in Stahl's method,
25 the sequencing library that is generated for

1 paired-end sequencing does not include the negative
2 strand. Correct?

3 A. Well, if they want to preserve the strandedness, they
4 have to get the sequence of the positive strand only.
5 Right? That's what they're interested in. So
6 whatever they're doing, they're preserving that
7 strand sequence so they can match it with the
8 messenger RNA.

9 Q. Dr. Sherman, you're not answering the question that
10 I'm asking, so let me ask it again.

11 The sequencing library that's generated in
12 Stahl's method --

13 A. Right.

14 Q. -- for paired-end sequencing --

15 A. Okay.

16 Q. -- does not include negative strand. Correct?

17 MR. CHEUNG: Objection. Form.

18 A. Whatever they're doing here, they are able to
19 determine the sequence of that positive strand of the
20 cDNA. So that's my understanding and that's what --
21 that's why they're doing stranded sequencing to
22 obtain that sequence.

23 BY MS. KHANDURI:

24 Q. What molecules are included in the sequencing library
25 that's generated in Stahl's method?

1 A. What DNA molecules?

2 Q. Yes.

3 A. Well, we -- I show it right here in this graphic
4 depiction, so we can go through it again
5 step-by-step.

6 Q. So you agree that the sequencing library that's
7 generated in step 8 of the pictorial on page 29 of
8 your declaration include molecules that have the
9 sequence of the positive strand shown in orange in
10 your pictorial. Correct?

11 A. Right. It's the sequence of the positive strand
12 cDNA.

13 Q. Are you able to say whether the library that is
14 generated in step 8 of the pictorial on page 29 of the
15 declaration include molecules that have sequence of
16 the negative strand depicted as green molecule in your
17 pictorial?

18 A. Well, the green molecules are RNA.

19 Q. Okay. Are you able to say whether the sequencing
20 library that's generated in step 8 of the pictorial on
21 page 29 of your declaration include molecules that
22 have the sequence that is reverse complement of the
23 molecules shown in orange in your pictorial?

24 A. I can't say one way or another. I don't see those
25 details in the paper. But given why they did this,

1 they were interested in the positive strand cDNA, and
2 their sequencing method would have enabled them to
3 obtain the sequence of that strand to match the
4 original messenger RNA.

5 Q. And then after the sequencing library is sequenced in
6 step 8 of the pictorial on page 29, how does Stahl's
7 method determine whether it is the sequence of the
8 original mRNA?

9 A. Well, I mean, it's shown here how they go through the
10 entire process, starting with step 1, capturing the
11 messenger RNA, and the messenger RNA is captured
12 while it's still attached to the solid surface.

13 You can see that there's a synthesis
14 reaction to get the minus cDNA which is generated from
15 that original captured messenger RNA, so you have the
16 cleavage so everything goes into solution. The
17 messenger RNA minus strand is detached. The
18 second-strand cDNA is then generated from what you see
19 here, the black and the red, so it's the plus strand,
20 and so they're preserving that original messenger RNA
21 positive strand by using this approach.

22 Q. Okay. Dr. Sherman, you mentioned that step 7 of the
23 pictorial on page 29 is a pilot amplification; is that
24 correct?

25 A. Right.

1 Q. And you said that this pilot amplification is
2 described in Stahl; is that correct?

3 A. Right.

4 Q. I am handing to you Stahl, which is Exhibit 1016.

5 ENTERED INTO THE RECORD:

6 PREVIOUSLY MARKED EXHIBIT 1016

7 11:30 a.m.

8 BY MS. KHANDURI:

9 Q. And if you look on page -- pages 6 and 7 of the Stahl
10 reference, it provides cDNA library collaboration or
11 sequencing.

12 A. Right.

13 Q. Could you tell me where in Stahl the pilot
14 amplification of step 7 depicted in your pictorial on
15 page 29 is shown or described?

16 A. So I have to find it in the supplementary.

17 Q. Sure, take your time.

18 A. So on page 7 of Stahl -- so like in -- approximately
19 in the middle of the page... so let's see...

20 So a total reaction volume of 10
21 microliters. Do you see that? Containing 1xKAPA HiFi
22 HotStart ReadyMix?

23 Q. Yes, I see it.

24 A. 2 microliters of purified cDNA amplified by qPCR with
25 the following protocol, and it gives the protocol.

1 After determining the amount of cycles needed, the
2 samples were amplified in a total reaction of
3 25 microliters.

4 I'm looking for, "After determining the
5 amount of cycles needed based on the qPCR, the samples
6 were amplified in a total reaction volume of
7 25 microliters."

8 So do you see that sentence?

9 Q. Yes, I see that.

10 A. "After determining the amount of cycles needed." So
11 that is what I'm talking about, the pilot reaction.

12 Q. So just so I understand, Dr. Sherman, in your opinion,
13 the pilot amplification depicted in step 7 of your
14 pictorial on page 29 is described on page 7 of Stahl,
15 and the sentence that describes it says, "After
16 determining the amount of cycles needed based on the
17 qPCR, the samples were amplified in a total reaction
18 volume of 25 microliters."

19 A. Correct.

20 Q. So that one single sentence --

21 A. Yes.

22 Q. -- describes --

23 A. That's right.

24 Q. -- step 7 of your pictorial?

25 A. After determining the amount of cycles needed. It's

1 a pilot reaction.

2 Q. And what is described in the sentence prior to that,
3 which starts with, "A total reaction volume of 10
4 microliter," and ends with "72 degree centigrade for
5 30 seconds"?

6 A. "A total reaction volume of 10 microliters
7 containing," which I described, "1xKAPA HiFi HotStart
8 ReadyMix...and 2 microliters purified cDNA were
9 amplified by qPCR." And then it goes on to give the
10 exact conditions for that, for the pilot, and then it
11 says, "After determining the amount of cycles
12 needed."

13 So nothing was done with those. It was
14 basically a pilot reaction to essentially instruct
15 Stahl how to scale up to make the actual library.

16 Q. And where in Stahl is the amplification step mentioned
17 in step 8 of your pictorial described?

18 A. Well, it says after determining the amount of cycles
19 needed, the cycles were amplified in a total reaction
20 volume of 25 microliters to make a library, and then
21 the libraries were purified as described previously.
22 It's all there.

23 Q. So are you saying -- and correct me if I'm wrong --
24 are you saying that the sentence, "After determining
25 the amount of cycles needed based on the qPCR, the

1 samples were amplified in a total reaction volume of
2 25 microliters," that sentence describes both step 7
3 and step 8 amplifications of your pictorial on
4 page 29?

5 A. Well, it describes the pilot reaction transitioning
6 into the library.

7 MS. KHANDURI: Okay, let's take a break.

8 (Off the record at 11:40 a.m.)

9 (Back on the record at 12:23 p.m.)

10 BY MS. KHANDURI:

11 Q. Okay, Dr. Sherman, during the break did you speak with
12 your counsel about the substance of your testimony?

13 A. No.

14 Q. So going back to the Stahl reference, which is
15 Exhibit 1016 --

16 A. Right.

17 Q. -- and going back to page 6 -- sorry, going back to
18 page 7.

19 A. Right.

20 Q. And before the break, you testified that the sentence,
21 quote, "After determining the amount of cycles needed
22 based on the qPCR, the samples were amplified in a
23 total reaction volume of 25 microliters," end quote,
24 on page 7 of Stahl, describes both steps 7 and 8 of
25 your pictorial; is that right?

1 MR. CHEUNG: Objection. Form.

2 A. So I'll go back to step 1 so we get the whole
3 picture.

4 So the black sequence is attached to the
5 solid surface, and it enables capture of messenger RNA
6 through a poly-T -- poly-T tail because messenger RNA
7 has a poly-A tail. There is then a synthesis
8 reaction, and that's shown in 2, cleavage off the
9 solid-phase, which is 3, synthesis of the
10 second-strand cDNA which is a positive strand in
11 brown. The brown strand then becomes the template for
12 amplified RNA, which is the negative strands. That
13 negative strand is used to attach adapter sequences
14 and is then used to generate the second cDNA product
15 in preparation for the library, which is a -- sort of
16 a transition between 7 and 8.

17 The investigators had to pilot the creation
18 of the library, which is what's described on page 7,
19 and which is why they're describing the -- in the
20 sentence, "After determining the amount of cycles
21 needed based on the qPCR, the samples were amplified
22 in a total reaction volume of 25 microliters."

23 So once they piloted the amplification to
24 get all the parameters done correctly to assure that
25 they would actually generate a suitable library, that

1 was then conducted in a 25-microliter reaction.

2 And then they go on to describe what they
3 did with the library, which is step 8.

4 And just as a reminder, this was done, all
5 these steps were done for stranded sequencing to be
6 able to sequence and understand the positive messenger
7 RNA that was captured, originally captured.

8 BY MS. KHANDURI:

9 Q. So then the qPCR that is mentioned on page 7 of Stahl
10 is performed between step 7 and step 8 of your
11 pictorial of page 29?

12 A. Yes. Basically it's a very important step to
13 establish the conditions for making the library.

14 Q. So to be clear, the qPCR mentioned on page 7 of Stahl
15 is performed between steps 7 and 8 of the pictorial on
16 page 29.

17 A. That's how I view it, yeah.

18 Q. So where in Stahl is step 7 described?

19 A. I'm trying to get my orientation here.

20 So on page 21, I write, "A reverse
21 transcription reaction then generates second cDNA
22 products (depicted in orange) from the amplified RNA
23 (step 7)."

24 And I go on, "Samples were placed on
25 ice" -- samples were -- "Samples were heated at 65

73

1 degrees C for five minutes and then placed on ice,"
2 which you see in my report there were dot-dot-dot for
3 some of that intermediate text, and then
4 "8 microliters reverse transcription mix was added to
5 a final content," and then dot-dot-dot, "500
6 micromolar of each dNTP, 1 millimolar reverse
7 transcription-primer, 10 units per microliter
8 Superscript III and 2 units per microliter of
9 RNaseOUT." And then it goes on.

10 So that step -- as I denote, that's step 7.

11 Q. Okay. So just so it's clear on the record,
12 Dr. Sherman, I'm just going to point to the language
13 on Stahl's page 7 that I think you testified as
14 describing step 7 of your pictorial.

15 The text in the Stahl reference that
16 describes step 7 of your pictorial on page 29 of your
17 declaration is on page 7 of Stahl.

18 A. Did you say page 29?

19 Q. Of your pictorial.

20 A. Okay.

21 Q. So let me start again. I know there are so many
22 numbers, so I'll start over.

23 A. Sure.

24 Q. The text in Stahl that describes step 7 of the
25 pictorial on page 29 of your declaration is on page 7

1 of Stahl's supplemental material, and it states the
2 following: "Samples were heated at 65 degrees Celsius
3 for 5 minutes and then placed on ice, 8 microliter
4 reverse transcription mix was added to a final content
5 of 1x First Strand Buffer, 0.05 molar DTT, 500
6 micromolar of each dNTP, 1 millimolar RT-primer, 10
7 units per microliter Superscript III and 2 units per
8 microliter RNaseOUT.

9 "Samples were incubated at 50 degrees
10 Celsius for 1 hour before placed on ice and the
11 samples were subsequently purified using Agencourt
12 RNAClean XP beads according to the protocol previously
13 described," end quote.

14 Is that correct?

15 A. Well, I mean, you've read more than I have, but my
16 statement on page 21 ends at "RNaseOUT." Right?

17 Q. Okay. So your testimony is that step 7 of your
18 pictorial on page 29 of your declaration is described
19 on page 7 in the first sentence of the quote that I
20 read just now; is that correct?

21 A. Well, that's what I have in my declaration.

22 Q. Okay. And then, in your opinion, step 8 -- strike
23 that.

24 In your opinion, the amplifying second cDNA
25 product to add sequencing adapters is described on

1 page 7 of Stahl in the following sentence: "After
2 determining the amount of cycles needed based on the
3 qPCR, the samples were amplified in a total reaction
4 volume of 2 [sic] microliters." Correct?

5 MR. CHEUNG: Objection. Form.

6 A. Let me just check.

7 BY MS. KHANDURI:

8 Q. I think -- I'll --

9 A. So where did you start again? A total reaction
10 volume of 10 microliters?

11 Q. I'll just restate my question, Dr. Sherman.

12 In your opinion, the amplified second cDNA
13 product to add sequencing adapters portion of step 8
14 of your pictorial on page 29 is described in the
15 following sentence on page 7 of Stahl's supplemental
16 material, quote: "After determining the amount of
17 cycles needed based on the qPCR, the samples were
18 amplified in a total reaction volume of
19 25 microliters," end quote.

20 Correct?

21 A. That's right.

22 Q. The molecules, Dr. Sherman, that are generated in
23 step 8 of your pictorial on page 29 have sequencing
24 adapters. Correct?

25 A. That's right.

1 Q. The orange molecules depicted under step 7 of your
2 pictorial do not have the sequencing adapters.
3 Correct?

4 A. Well, they have. As you can see, they go all the way
5 up to the adapter sequence, so they have the reverse
6 complement of the adapter sequence at that point.

7 Q. Is your opinion that the adapters shown under step 7
8 of your pictorial are the sequencing adapters noted
9 under step 8 of your pictorial?

10 A. It's not 100 percent clear to me if they add
11 additional adapters to the end or if they take that
12 reverse complement sequence into account and use
13 those as the adapters. That's just not clear to me.

14 Q. Okay. Let's go to Stahl, Exhibit 1016, page 6 of the
15 supplemental materials, and we are looking at the last
16 paragraph on page 6 of the supplemental materials.

17 A. Okay.

18 Q. In the middle of that paragraph --

19 A. Uh-huh.

20 Q. -- there is a sentence beginning with, "The remaining
21 sample and 2.5 microliter Ligation adapter (IDT) was
22 added to a final concentration of" .01 -- "0.71
23 micromolar."

24 A. I see that.

25 Q. And does that sentence start to describe step 6 of

1 your pictorial where adapters are added to the
2 amplified RNA molecules?

3 A. I believe so, yes.

4 Q. And the adapters that are described in the sentence
5 entered into record from page 6 of Stahl's
6 supplemental material are the same adapters that are
7 depicted in -- under step 7 of the pictorial?

8 A. That's right.

9 Q. So would you say that the adapters in -- strike that.

10 Would you say the adapters shown under
11 step 7 of the pictorial are different from the
12 sequencing adapters that are added in step 8?

13 A. I mean, it looks like, from the top of 7, if you look
14 three lines down [as read]: The samples were
15 purified using Agencourt RNAClean XP beads according
16 to the protocol previously described and mixed with
17 1 microliter RT-primer (IDT) to a final concentration
18 0.83 millimolar of each dNTP.

19 So it looks to me that they used a reverse
20 transcriptase primer from this company IDT to generate
21 that cDNA positive strand in orange.

22 And, you know, whether they used that
23 adapter sequence, and they'd know what it -- they'd
24 know what it was, of course, or whether they added new
25 adapters, it's not clear to me.

1 Q. Okay. Let's look a little bit further down from where
2 you were on page 7 --

3 A. Sure.

4 Q. -- of Stahl's supplemental material.

5 A. Uh-huh.

6 Q. And it is the sentence right before the sentence we
7 were talking about earlier, which was, "After
8 determining the amount of cycles."

9 A. Okay. Right before that?

10 Q. Yeah.

11 A. Okay.

12 Q. The sentence right before that.

13 A. Uh-huh.

14 Q. And it starts with, "A total reaction volume of
15 100" -- strike that.

16 "A total reaction volume of 10 microliters
17 containing," and it ends with "72 degrees Celsius for
18 30 seconds." Do you see that sentence, Dr. Sherman?

19 A. Yes.

20 Q. And in that sentence, there is a mention of the
21 following entities: InPE1.0, PCR Index, InPE2.0. Do
22 you see that, Dr. Sherman?

23 A. Uh-huh. Right.

24 Q. In your opinion, are those the sequencing adapters
25 that were added during the amplification in step 8 of

1 your pictorial?

2 A. I think that -- I think they are. Yes.

3 Q. Okay. So going back to your pictorial --

4 A. Uh-huh.

5 Q. -- step 8 of the pictorial -- strike that.

6 In step 8 of your pictorial, sequencing
7 adapters are added to the orange second cDNA product
8 during amplification. Correct?

9 A. Right.

10 Q. And those sequencing adapters were not in the orange
11 second cDNA product depicted under step 7 of your
12 pictorial. Correct?

13 A. No, they were added -- they were added after. We
14 just read that. Yeah.

15 Q. They were added after, in step 8. Correct?

16 A. Right.

17 Q. So the molecules that were sequenced in step 8 are
18 different from the molecules shown as orange in --
19 strike that.

20 The molecules that were sequenced in step 8
21 of your pictorial are different from the orange
22 molecules depicted under step 7 of your pictorial.
23 Correct?

24 A. Yeah, they're different in that they have adapters.

25 Q. So then you take back your statement that Stahl isn't

1 clear about the sequencing adapters. Correct?

2 A. Now that we've read it together and I see them, I
3 agree that adapters were put on again at that stage,
4 yes.

5 Q. Going back to step 8 of your pictorial --

6 A. Uh-huh.

7 Q. -- where does Stahl say that only the positive strand
8 is generated during amplification of step 8?

9 A. I am not aware that Stahl actually describes that.
10 Stahl is silent on that piece, as far as I'm aware.
11 But I'm not sure that it matters because they're
12 going to have sequencing information and they're
13 going to be able to correlate that second-strand cDNA
14 product back to the positive messenger RNA.

15 Q. How would -- how would Stahl's authors correlate the
16 sequencing information back to the messenger --
17 messenger RNA identified as positive strand under
18 step 1 of your pictorial?

19 A. Because they're doing all of this for stranded
20 sequencing. Otherwise, they would have sequenced the
21 negative strand cDNA, which they didn't do. That's
22 really the key issue here. They did not sequence the
23 original cDNA negative strand in red. They used that
24 for imaging.

25 They went on because they wanted to do

1 stranded sequencing, they wanted to capture the
2 information from the original messenger RNA. And the
3 way they did that was to go through this whole process
4 that we've been discussing where they used that
5 original synthesized product that reflects the
6 sequence of the captured messenger RNA, so that red
7 product, they used that to go all the way down to the
8 end to correlate with the original positive strand
9 messenger RNA for stranded sequencing.

10 Q. How would Stahl's authors correlate the information
11 obtained from sequencing back to the original positive
12 strand messenger RNA?

13 A. Because they've developed their experiment to show
14 that. That's why they're doing it. Otherwise, they
15 would have sequenced the negative strand cDNA, which
16 they didn't do. So they're capturing the messenger
17 RNA and they're going all the way to the end to
18 obtain a positive strand cDNA as opposed to a
19 negative strand cDNA, and that is being done to
20 capture the original sequence of the positive strand,
21 the messenger RNA.

22 Q. Is that because the sequence of the positive strand
23 messenger RNA would have a poly-A tail -- or poly-A
24 sequence?

25 A. I mean, it does have a -- it has a poly-A sequence,

1 that's how it's captured on the black probe fragment,
2 so it captures the messenger RNA, which is a positive
3 strand, and they go all the way to the end to
4 sequence a cDNA that has the positive strand sequence
5 as opposed to sequencing a cDNA that has a negative
6 stranded sequence.

7 I think we can all agree that that's what
8 they're doing here. That's what they show. We've
9 gone through every step, 1 through 8, and they're
10 capturing a second-stranded cDNA, not a first-strand
11 cDNA, and they did it for a reason. They did it to
12 capture the sequence of the original positive strand
13 messenger RNA.

14 They went through a lot of work to do that,
15 and we read the supplementary information, all the
16 detail to get through each one of these steps that
17 I've depicted here, and they're doing it for a reason.
18 That reason is to capture the sequence in a
19 second-strand positive cDNA which will reflect the
20 original captured messenger RNA, which is a positive
21 strand.

22 Q. I'm trying to understand something that you testified
23 earlier, so let me -- let me state your testimony from
24 before.

25 A. Sure.

1 Q. My question was, "Going back to step 8 of your
2 pictorial, where does Stahl say that only the positive
3 strand is generated during amplification of step 8."

4 A. Uh-huh.

5 Q. And your response was, "I am not sure that Stahl
6 actually describes that, but I'm not sure that it
7 matters because they are going to have sequencing
8 information and they are going to be able to correlate
9 the second-strand cDNA product back to the positive
10 messenger RNA."

11 A. Uh-huh.

12 Q. So my question is, Dr. Sherman, why did you say, "I am
13 not sure that it matters whether Stahl says that only
14 positive strand is generated during amplification or
15 not"?

16 MR. CHEUNG: Objection. Form.

17 A. Because at the end of this you can get a lot of
18 sequencing information, but the point is, once they
19 have all that data it may be both strands, but it --
20 it's a reflection of the originally captured positive
21 strand messenger RNA. So that's the important
22 conclusion of this long process that they describe in
23 the paper, which wasn't noted by Spellman.

24 And Spellman conflated a first-strand
25 synthesis with -- and sequencing with what turned out

1 to be a very long process here that they conducted
2 that we've read through and been through in detail.
3 And at the end of the day, what they sequence is going
4 to be a reflection of the authentic originally
5 captured positive strand messenger RNA.

6 So I may not have been clear before, but
7 that's what they did and that's why they did it, and
8 we've just been through all the details about how they
9 did it.

10 Q. So if the data generated, the sequencing data
11 generated in Stahl has both strands, how is that a
12 reflection of the originally captured positive --
13 positive strand messenger RNAs?

14 A. Because they know which strand is the original
15 positive cDNA. They would know that.

16 Q. And how would they know that?

17 A. Based on the adapter sequence.

18 Q. Are you saying the adapter sequence in step 6?

19 A. In step -- right. So that sequence is preserved.
20 And, you know, the reality is, I'm not sure it
21 matters because what matters -- I mean, they can have
22 both strands and they have both strand sequences, and
23 why are they doing stranded sequencing? They're
24 doing stranded sequencing to essentially capture the
25 nature of that positive messenger RNA.

1 And that's the important thing. The
2 important thing is what's there, and they will
3 sequence that and from that they can essentially know
4 what it is, how much of it is there, and that's the
5 important aspect of this experiment.

6 Q. Does Stahl mention stranded RNA sequencing?

7 A. He does not mention it, but he describes it. Because
8 we've been through it. That's what he is describing.
9 And at this time -- and I include some exhibits --
10 this was state of the art in the field to capture the
11 messenger RNA and preserve the strand sequencing and
12 capture that sequence.

13 So even though they don't state that as
14 such, that's what they're doing. It's right there.

15 Q. What specific description in Stahl indicates to you
16 that Stahl is doing stranded RNA sequencing?

17 A. Because if he wasn't doing stranded RNA sequencing he
18 would have just sequenced the original negative
19 strand cDNA. You just go to step 2 or step 3 and you
20 sequence. Why would he go -- why would they go all
21 the way through to step (a) if they weren't doing
22 stranded sequencing. That's what they were doing.
23 Their supplementary information would have been a lot
24 shorter.

25 And they didn't sequence the first strand.

1 They sequenced what, in essence, is the second-strand
2 cDNA, and Spellman and the petitioners are focused on
3 that first strand and the information from that first
4 strand, and that's not what Stahl describes. There
5 was no sequencing in the first strands. It's
6 sequencing of the second strand.

7 Q. Did you review any of the references that are cited in
8 Stahl?

9 A. I don't recall. I mean, what I reviewed is in my --
10 what I've listed in my exhibits. Some of them are
11 from Stahl and we can look at them.

12 Q. If any of the references describe -- if any of the
13 references cited in Stahl were important for your
14 opinions provided in your declaration, you would have
15 cited them. Right?

16 A. Right.

17 MS. KHANDURI: Let's take a break. It's
18 about an hour.

19 THE WITNESS: Okay.

20 (Off the record at 1:10 p.m.)

21 (Back on the record at 1:29 p.m.)

22 MS. KHANDURI: We have no further
23 questions. We'll pass the witness. Thank you.

24 THE WITNESS: All right. Thank you.

25 MR. CHEUNG: Can we take a short break?

1 MS. KHANDURI: Sure.

2 (Off the record at 1:29 p.m.)

3 (Back on the record at 1:33 p.m.)

4 EXAMINATION

5 BY MR. CHEUNG:

6 Q. Dr. Sherman, do you recall testifying earlier as
7 regards to your depiction of Stahl's workflow such as
8 the one in paragraph 46 of your declaration?

9 A. Paragraph 46?

10 Q. That's right.

11 A. Right. Yes.

12 Q. In paragraph 46, do you identify the parts in Stahl's
13 supplementary information that you used to generate
14 the figure of Stahl's workflow in paragraph 46?

15 A. Yes, I did.

16 Q. Is there any portion of paragraph 46 that you would
17 like to change or amend?

18 A. No.

19 Q. Do you recall testifying earlier in regards to
20 sequencing adapters?

21 A. Right.

22 Q. I'd direct you to page 7 in Stahl's supplementary
23 information. Let me know when you're there.

24 A. I'm there.

25 Q. Do you recall earlier in your conversation with

1 counsel where you talked about the entities identified
2 around the middle of the page as InPE 1.0, InPE 2.0,
3 and PCR Index?

4 A. Yes.

5 Q. And you agree that those are sequencing adapters for
6 Illumina sequencing; is that right?

7 A. That's right.

8 Q. If I can direct you to page 8 of the supplementary
9 information, are those entities we just talked about
10 described on this page?

11 A. Yes, they are.

12 Q. So is it your opinion that Stahl provides the
13 sequences of each of those entities in its paper?

14 A. Yes. Correct. Under the Ligation Adapter heading.

15 Q. If you can turn back to page 7 of the supplementary
16 information, do you see the last sentence on the page
17 where it says, "Finished libraries were diluted to 4
18 nanomolar and sequenced on the Illumina NextSeq
19 platform using paired-end sequencing according to the
20 manufacturer's protocol"?

21 Do you see that sentence?

22 A. I do. Yes.

23 Q. Does Stahl describe what the manufacturer's protocol
24 for the Illumina NextSeq platform anywhere?

25 A. No, those details are not included here.

1 Q. Would a POSA be able to find out what these
2 manufacturer's protocols are?

3 A. Yes, they would.

4 MR. CHEUNG: No further questions.

5 MS. KHANDURI: Two-minute break, quickly.

6 (Off the record at 1:38 p.m.)

7 (Back on the record at 1:40 p.m.)

8 MS. KHANDURI: Okay, no more questions.

9 Thank you, Dr. Sherman, for your time.

10 THE WITNESS: Okay. Thank you.

11 (Proceedings concluded at 1:40 p.m.)

12

13

14

15

16

17

18

19

20

21

22

23

24

25

CERTIFICATE OF NOTARY

STATE OF MICHIGAN)

) SS

COUNTY OF OAKLAND)

I, ALISON WEBSTER, certify that the
deposition of DAVID SHERMAN, Ph.D. was taken before
me via videoconference on the date hereinbefore set
forth; that the foregoing questions and answers
were recorded by me stenographically and reduced to
computer transcription; that this is a true, full,
and correct transcript of my stenographic notes so
taken; and that I am not related to, nor of counsel
to, either party nor interested in the event of
this cause.

Alison C. Webster

ALISON C. WEBSTER, CSR-6266, RPR, RMR, CRR, RDR
Notary Public, Oakland County, Michigan
My commission expires: May 1, 2029

	142 7:25 8:2 9:1,2,7,11 11:12 12:15 13:16 14:10 19:15 29:7 31:6 33:16,23 34:8 35:5 36:8	
\$		4
\$700 9:24	19 19:20	4 42:12,18,24 43:2,4,22,25 45:5,6,11 46:2,9,24 47:6 51:23 52:7,13 57:3 88:17
(	1:10 86:20	46 87:8,9,12,14,16
(a) 85:21	1:29 86:21 87:2	
(b) 30:16	1:33 87:3	5
(c) 26:3,10 27:16 28:21,25 29:4,17,22 30:8,16,20 31:9,11,21 32:1,3 61:20	1:38 89:6	5 36:11,13 47:12,14,25 48:3,6 60:2,3 74:3
(d) 26:3,22,24 27:2 28:23,25 29:5,17, 23 30:8,20 31:9 32:11	1:40 89:7,11	50 12:10 74:9
	1x 74:5	500 73:5 74:5
0	1xkapa 67:21 69:7	
0.05 74:5	2	6
0.71 76:22	2 38:10,12,16,18 39:1 40:19 41:11,24, 25 43:11,13,20 44:4,13 45:15 49:14 67:24 69:8 71:8 73:8 74:7 75:4 85:19	6 48:10,11 59:25 60:1,4 67:9 70:17 76:14,16,25 77:5 84:18
0.83 77:18	2.0 88:2	65 72:25 74:2
01 76:22	2.5 76:21	68 9:10
1	20,000 10:6	689 8:22 9:2,8 12:16
1 26:4,11,22,24 27:16 28:25 29:5,19, 23 30:9,16,20 31:9,11,22 32:1,4,11 42:6,7,21 43:7 44:2,10,12,15,16,20, 22 45:3,13,22,23,24 46:3,10,20 47:1 48:24 52:24 53:4,13 54:4,12 66:10 71:2 73:6 74:6,10 77:17 80:18 82:9	2008 10:14,16 12:2 36:23	7
1(c) 27:24	2018 22:15 23:18 24:6 25:2	7 48:14,15,16,25 51:17,20,22 52:5,11, 21 53:2,15,17 54:8,10 56:4,11 59:12, 14,22 60:8,11,17,24 61:3,7 66:22 67:9,14,18 68:13,14,24 70:2,18,24 71:16,18 72:9,10,14,15,18,23 73:10, 13,14,16,17,24,25 74:17,19 75:1,15 76:1,7 77:7,11,13 78:2 79:11,22 87:22 88:15
1(d) 27:24	2020 22:15	71 10:24
1.0 88:2	2024 11:2	72 69:4 78:17
10 67:20 69:3,6 73:7 74:6 75:10 78:16	2025 4:2	
100 33:16 34:4 35:9 76:10 78:15	20th 11:2	8
1016 37:22 67:4,6 70:15 76:14	21 72:20 74:16	8 49:2 55:8,10,17 56:1,4,9 58:14,25 59:5,12 60:10 61:6,14 62:1,9 65:7,14, 20 66:6 69:17 70:3,24 71:16 72:3,10, 15 73:4 74:3,22 75:13,23 76:9 77:12 78:25 79:5,6,15,17,20 80:5,8 82:9 83:1,3 88:8
1043 11:12 29:12 31:8 36:8	22 19:22 20:8,11 22:5 56:18,19,22	8's 61:21
1044 11:15,18	25 68:3,7,18 69:20 70:2,23 71:22 75:19	9
10:19 36:3	25-microliter 72:1	9 59:1
10x 4:18 5:6,7 8:9 9:15 14:16,19 19:10	29 34:12,14,25 35:13 36:22,23 37:4,7, 8,10 38:2,6 41:18 60:18 65:7,14,21 66:6,23 67:15 68:14 70:4 72:11,16 73:16,18,25 74:18 75:14,23	
10x's 14:18	3	
11:30 67:7	3 41:15,17,20,23,25 42:4,8,16 44:18, 19 45:1,15 60:1 71:9 85:19	
11:40 70:8	30 4:2 69:5 78:18	
12:23 70:9	35 26:2,5,8,9 32:19,20 33:21 34:8 35:1	
14 11:4,5,9 12:5		

9:11 10:17 9:46 29:13 9:57 36:2 A a.m. 10:17 29:13 36:2,3 67:7 70:8 ability 17:19 24:22 account 76:12 accurately 6:6 acid 16:6 18:9 41:1 45:16 acids 16:5 acquired 8:12 action 44:6 active 15:11 actual 16:12 56:17 69:15 adapter 71:13 76:5,6,21 77:23 84:17, 18 88:14 adapters 48:12 49:3 52:1,15 55:12 56:7 60:4,7 74:25 75:13,24 76:2,7,8, 11,13 77:1,4,6,9,10,12,25 78:24 79:7, 10,24 80:1,3 87:20 88:5 add 55:11 74:25 75:13 76:10 added 55:21 60:7 73:4 74:4 76:22 77:1,12,24 78:25 79:7,13,15 adding 49:3 56:6 additional 38:25 76:11 address 62:5 advise 7:16 affirm 4:6 Agencourt 74:11 77:15 agree 19:14 25:9,13 27:15 30:14,16 31:21 52:5 65:6 80:3 82:7 88:5 Agreed 60:12 AIDS 17:18 aligned 13:17 alters 17:12 amazing 16:20 amend 87:17 amount 9:25 12:16 61:9 68:1,5,10, 16,25 69:11,18,25 70:21 71:20 75:2, 16 78:8	amplification 36:14 47:18 55:17,24 56:9 57:19,20 58:5,15,18,24 59:13,17 60:6,9,12,17,24 61:2,8,22 62:1,9 66:23 67:1,14 68:13 69:16 71:23 78:25 79:8 80:8 83:3,14 amplifications 51:14 60:19 70:3 amplified 47:17,19 48:12 56:1,2,4,7 58:9 60:2,3,4 67:24 68:2,6,17 69:9,19 70:1,22 71:12,21 72:22 75:3,12,18 77:2 amplify 55:11 56:12 59:2 61:14 amplifying 49:2 56:13 57:25 58:10 59:7,8 61:16 74:24 analysis 16:11,15 34:23 and/or 19:23 Ann 5:5 answering 6:19 64:9 apologies 37:9 application 19:24 20:15,17 25:13 apply 20:12 34:1,23 appreciated 50:2 approach 20:21 25:21 51:1 66:21 approaches 19:18 21:1,16,21 approximately 12:7,23 67:18 Arbor 5:5 arna 47:19 arnas 47:23 48:2 array 18:3,6 art 23:17 24:6,10 25:2,17 33:13 35:3 85:10 ascertain 49:19 50:1 aspect 20:24 21:7 22:4 85:5 assays 19:25 20:18 assume 23:22 assure 71:24 attach 71:13 attached 40:6 42:6,7 45:23 46:20 52:15 53:19 66:12 71:4 authentic 49:23 84:4 authors 80:15 81:10 aware 80:9,10	B back 5:10 28:3 36:3 45:23 51:17 55:10 70:9,14,17 71:2 79:3,25 80:5, 14,16 81:11 83:1,9 86:21 87:3 88:15 89:7 background 20:19 ballpark 10:5,8 barcode 21:21 27:19 43:8,12,19,22 44:7,14,17,19 45:2,10,20,22 47:20, 21,24 48:5 53:3,18,21 54:11 55:2 barcodes 27:9,11 28:1 44:10 48:5 base 47:10 based 34:8,10 35:13,15 68:5,16 69:25 70:22 71:21 75:2,17 84:17 basically 18:17 19:6 30:22 48:16 69:14 72:12 beads 74:12 77:15 begin 12:9 40:9 beginning 76:20 big 25:8 billing 9:23 bind 17:2 21:18 binding 15:20,22 binds 17:23 bit 78:1 black 38:20 39:1,3,8,10,13,16,17,25 40:7,9,21 41:1,2,13 42:5,19,25 43:6, 7,10,11,14,23 44:9,10,12,13,15,18,19 45:1,2,11,13,23 46:2,3,7,9,10,18,24, 25 47:25 48:6,7 53:4,18,21 54:3,4,9, 11 60:7 66:19 71:4 82:1 black-and-red 45:16 blue 38:21,22 42:16 board's 11:20,23 bottom 42:5 56:22 break 7:7,8,11 35:20,21 36:5 70:7, 11,20 86:17,25 89:5 breaks 7:4,6 bridge 57:13 broad 21:15 brought 49:9 brown 45:5,6 47:16 51:23 52:6,12,25
--	---	--

53:25 71:11 Bruker 5:7 8:12,15 9:15,16 19:1 Bruker's 5:6 18:23 Buffer 74:5 C calculated 10:2 12:12 call 39:8 52:18 called 4:21 16:22 27:9 42:6 47:19 capture 18:3,6,9 21:7,9,11,12,17,20 41:21 42:8,20 44:16,24 46:1 71:5 81:1,20 82:12,18 84:24 85:10,12 captured 48:23 49:23 50:8,21 51:16 52:24 57:12 66:11,15 72:7 81:6 82:1, 20 83:20 84:5,12 captures 53:21 82:2 capturing 66:10 81:16 82:10 cared 51:8 carryover 44:22 case 9:21 10:12 18:21 50:25 caveat 7:9 cdna 38:13 42:13,18,22,24 43:2,5,24 45:6,8,9,17,19 46:11,12 47:3 48:25 51:12,14,25 52:1,18,25 53:5 54:1,2, 17 55:11 56:2,3,13,15 57:25 58:11, 18,22 59:3,8,18 61:14,16,17,19 63:5, 12,14 64:20 65:12 66:1,14,18 67:10, 24 69:8 71:10,14 72:21 74:24 75:12 77:21 79:7,11 80:13,21,23 81:15,18, 19 82:4,5,10,11,19 83:9 84:15 85:19 86:2 cell 16:18 17:16 18:19 cells 15:6,10 17:17 18:12,14,16,19, 20 Celsius 74:2,10 78:17 centigrade 69:4 change 13:7 42:1 87:17 check 75:6 Cheung 13:24 31:14 33:24 36:16 64:17 71:1 75:5 83:16 86:25 87:5 89:4 circumstance 22:19 circumstances 22:13 25:3,12 cited 11:17 12:2 86:7,13,15	claim 26:4,11,22,24 27:16,20,24 28:6,25 29:5,19,23 30:9,16,20 31:9, 11,22 32:1,4,11,14 33:3,6,9,21 34:1, 15,21,24,25 35:6 36:11,13,19 claims 32:7 36:9 clarification 6:24 clarifies 48:19 clarify 53:11 clear 54:6,13,16 72:14 73:11 76:10, 13 77:25 80:1 84:6 cleavage 42:5 66:16 71:8 cleave 41:20 cleaved 42:2,4,10 44:21,24 45:15 collaboration 67:10 colleague 4:19 15:13 collected 26:17 27:3,17,24 29:1,20, 25 30:10 38:22 collecting 18:9 colors 39:20,24 commonly 22:14 23:17 company 77:20 compare 19:4 compared 53:7 compensated 9:20 complement 45:12,21 46:5,6,9 47:6,9 50:13 53:3,17 54:3,5,8,11,25 55:3 65:22 76:6,12 complementary 45:10 complements 53:6 complete 6:19,20 17:15 complex 17:3,24 complicated 17:25 component 42:19,20,25 43:6,7,10, 11,14,23 44:10,12,13,15,18,20 45:1, 3,11,14 46:2,3,7,9,10,18,24,25 47:25 48:6 53:23 55:20 components 40:25 41:6,7 44:9 compounds 15:19 comprised 42:18,24 concentration 61:9 76:22 77:17 concluded 89:11 conclusion 83:22	Concord 13:24 condition 22:12 conditions 21:1,3,4,6 22:21 59:16 60:9,15,21 61:7,8 69:10 72:13 conducted 48:21 72:1 84:1 conducting 49:4 confirm 10:25 33:14 confirmed 33:18 conflated 49:7 83:24 confusing 53:9 considered 11:5 consistent 34:4 35:6,8 construction 32:14 60:16,21,22 contacted 9:2,7,8,10,11 content 8:1 73:5 74:4 context 32:14 continues 59:25 controlling 15:17 conversation 87:25 conversations 6:12 copied 43:23 core 14:24 correct 5:9,12 7:20 9:9 11:7,21 14:1, 9 19:11,15,16,18 20:16 25:2 26:13, 16,20,25 27:1,7,19 28:10 29:6,20 32:5 35:14 36:15 38:8,23 40:23 41:3, 21,22 43:9 44:20 45:7,25 46:4 47:8, 20,25 51:24 52:24 53:4,19 54:12 56:5 61:4 62:10 64:2,16 65:10 66:24 67:2 68:19 69:23 74:14,20 75:4,20,24 76:3 79:8,12,15,23 80:1 88:14 correctly 20:1 31:18,19 32:25 55:14 71:24 correlate 80:13,15 81:8,10 83:8 counsel 6:25 7:3,14,15 9:12 12:22 13:17 36:6 70:12 88:1 court 6:11,16 create 38:5 47:17 49:11 created 37:14,15,17 38:7 50:1 creates 39:12 creation 39:12,13 71:17 critical 30:23
--	---	--

cure 15:12,16 cycles 68:1,5,10,16,25 69:11,18,19, 25 70:21 71:20 75:2,17 78:8 D data 83:19 84:10 David 4:1,18,20 5:4 day 84:3 dealing 51:11 decision 11:20,21,23 declaration 8:2 10:12,21 11:4,6,10, 14,18 12:2,5,8,15,16,20,21,25 13:3,5, 8,10,15,16 14:8 19:22 22:5 24:25 26:2 32:19 33:22 34:12 35:13 36:22, 24 37:10 38:3 41:18 56:18 65:8,15,21 73:17,25 74:18,21 86:14 87:8 deep 55:25 definition 19:19 definitions 32:9 degree 69:4 degrees 73:1 74:2,9 78:17 demand 22:25 demanded 62:7 denote 39:20 73:10 denotes 60:1 denoting 39:23 60:6 depends 21:2,6 22:3,8,12 24:2 50:15,24 depict 48:18 depicted 38:16 65:16 67:14 68:13 72:22 76:1 77:7 79:11,22 82:17 depicting 59:21 depiction 37:25 38:2,5,6,10,13 41:15,17,20 43:8 47:24 55:22 65:4 87:7 depicts 37:18 40:5 depo 13:12 deposed 5:8,13 7:21 8:1,20,23 deposition 4:1 5:10,14 7:3 13:14,20 14:3,8 depositions 5:21 Derek 13:24	describe 49:13 72:2 76:25 83:22 86:12 88:23 describes 40:12 49:6 68:15,22 70:2, 5,24 73:16,24 80:9 83:6 85:7 86:4 describing 53:24 71:19 73:14 85:8 description 37:23 59:5 85:15 design 19:24 20:14,17,21,23 21:3 designed 21:18 designing 20:24,25 21:7 22:4 detached 66:17 detail 82:16 84:2 detailed 37:15 47:15 details 14:25 37:24 38:1 58:1 65:25 84:8 88:25 detect 17:15,17 determination 35:11 determine 16:2,17 33:8,20 34:23 63:14 64:19 66:7 determining 68:1,4,10,16,25 69:11, 18,24 70:21 71:20 75:2,16 78:8 develop 15:11,15 developed 49:18 81:13 differences 49:21,22 digging 37:16 diluted 57:3 88:17 direct 15:22 87:22 88:8 directed 23:6 directional 49:21 directly 17:2,24 disclose 18:1 discover 15:15 discovered 15:12 discuss 24:25 36:5 discussed 12:21 55:2 discussing 12:24 81:4 discussion 8:21,25 9:12 disease 15:17 distinct 39:5,7,21,23 40:8,25 41:5,7, 8 distracting 52:8 DNA 22:14 23:6,10,11,19,21 24:5,9,	11,13,24 25:1,6,15,22,24 26:12,20,25 27:6,21,23 28:2,8,10,11 31:12,23 32:5,23 33:7,10 34:17 35:8 40:11 42:6,7,20 45:23 46:20 48:7 53:19 54:15 63:5 65:1 DNA-DEPENDENT 25:1,15,24 dntp 73:6 74:6 77:18 document 10:19 documents 7:18 12:4 13:15 dot-dot-dot 73:2,5 downstream 51:13 driving 50:17,18 drug 15:11,15 16:9 17:8,10,12,14,18, 20,23 drugs 15:20 17:2 DTT 74:5 duly 4:22 E earlier 5:8 8:5 78:7 82:23 87:6,19,25 early 8:21 easier 53:11 effect 30:7 efficacy 31:12,15 efficiency 31:23,25 32:7 36:14 effort 17:10,11 49:6 elaborate 21:11 enable 17:14 21:22 enabled 33:13 66:2 enables 71:5 end 10:24 54:2,22 70:23 74:13 75:19 76:11 81:8,17 82:3 83:17 84:3 ends 69:4 74:16 78:17 engaged 8:23 engineered 22:20 entered 6:13 10:15 29:11 67:5 77:5 entire 66:10 entities 39:21,23 78:21 88:1,9,13 entity 41:1,3,7,13 enzyme 22:11 61:10
---	---	--

enzymes 22:14 24:18 essence 86:1 essentially 58:21 60:1,5,14 69:14 84:24 85:3 establish 60:15 61:7,12 62:5 72:13 established 60:21 61:13 estimate 10:5 event 28:14,15,17,19 eventual 49:13 exact 15:20 63:14 69:10 EXAMINATION 4:25 87:4 examined 4:24 examples 20:6,9,10 exclude 29:5,23 exclusion 30:5 excuse 22:15 37:3 execute 21:5 exercise 5:19 Exhibit 10:14,16 11:12 29:12 31:8 36:8,23 37:22 67:4,6 70:15 76:14 exhibits 11:17 13:17 85:9 86:10 experience 19:24 33:12 experiment 21:3 24:2 50:15 60:13 81:13 85:5 experimental 20:20 22:25 experimentalist 21:23 experiments 17:4 expert 5:6 9:14 15:14 expertise 21:5 22:10 23:1 explain 47:14 48:10 49:16 55:16 59:24 explanation 6:25 expression 17:8 49:22 extreme 22:21 F facility 14:24 fact 16:25 fall 8:21 fashion 49:23	field 85:10 figure 36:24 37:1,12,14,15,18,21 40:5 42:9 47:25 87:14 figure's 37:23 filed 8:4,8,12 final 59:18 73:5 74:4 76:22 77:17 finally 12:1 find 67:16 89:1 fine 8:17 Finished 57:3 88:17 firm 4:16 first-strand 38:13 44:6 53:23 82:10 83:24 fluorescent 55:21 focus 62:17 focused 86:2 focusing 44:9 57:24 forcing 51:10 Form 31:14 33:24 36:16 64:17 71:1 75:5 83:16 found 17:20 Fox 4:17 fragment 45:16 48:8 82:1 fragments 57:11 freshly 15:8 frozen 15:7,8 fully 50:2 G gene 49:21 generate 56:10 60:2 71:14,25 77:20 87:13 generated 40:10 56:4,11 57:15,17 62:14,20,25 63:22,25 64:11,25 65:7, 14,20 66:14,18 75:22 80:8 83:3,14 84:10,11 generates 26:12,25 27:21 28:8,10, 11 33:7 40:8 61:3 72:21 generating 48:25 57:21 58:7 61:17, 20,21,25 62:3,10 generation 57:21 58:6	genomic 20:12 genomics 4:18 14:13 15:24 19:18 21:1,16,20 gentleman 13:22 gentlemen 13:23 Geomx 19:2,5,12 get all 71:24 give 4:7 10:5 21:14 24:3 25:15 29:7 69:9 giving 20:6 58:11 global 25:5 goal 61:23 Goldstein 4:17 good 4:12,13 13:7 35:25 graphic 65:3 green 47:23 48:2,8 58:9,15,17 59:2 60:3 65:16,18 guess 12:9 guidelines 5:20 H half 56:22 hand 4:5 10:11 handedness 49:20 54:21 handing 67:4 handled 14:25 happening 42:15 43:16 47:14 48:11, 14 55:16 60:17 61:6 happy 24:3 heading 88:14 hear 31:18 heard 31:19 heated 72:25 74:2 hidden 50:2 hide 16:23 17:19 Hifi 67:21 69:7 high 19:15,17 high-level 21:4 HIV 15:12,14 16:22,23,24 17:2,3,16, 17,19
--	---	--

Holman 4:18 homolog 52:25 53:5 honest 53:12 Hotstart 67:22 69:7 hour 9:24 35:24 74:10 86:18 hours 12:7,10,14,23 14:6 Howard 5:4 human 15:6 hypothesis 50:16 I ice 72:25 73:1 74:3,10 idea 17:14 identified 16:21 42:12 46:20 47:4 53:19 80:17 88:1 identify 38:11,12 41:20 50:11 51:7 54:14 87:12 identifying 34:16 identity 16:4,12 IDT 76:21 77:17,20 III 73:8 74:7 illumina 24:12 25:20,22,24 49:4 52:3,16 55:12,18,23 56:8,24 57:4,11 58:2 62:24 63:5,10 88:6,18,24 image 55:21 imagine 20:20 21:3 imaging 63:13 80:24 immediately 24:15,17 immune 16:24 17:15,16,20 impact 16:9,21 impacts 17:8 importance 16:24 important 48:18 49:9 50:14 72:12 83:21 85:1,2,5 86:13 include 20:25 21:7,21 22:6 41:9 52:6,12,23 53:2 57:21 58:6 62:14,21 64:1,16 65:8,15,21 85:9 included 17:3 64:24 88:25 includes 17:24 19:17 43:8,11 45:24 63:2 including 7:3	incorporate 27:18 incorporated 26:20 27:5 28:2 44:8 45:14 incorporates 43:14 incorporation 43:17,19 44:6 incorrect 59:5 incubated 74:9 Index 78:21 88:3 infected 17:16,17 information 21:23,24,25 22:3 23:23 37:25 47:16 48:20 50:10 55:25 62:23 80:12,16 81:2,10 82:15 83:8,18 85:23 86:3 87:13,23 88:9,16 initial 54:14 Inpe 88:2 Inpe1.0 78:21 Inpe2.0. 78:21 instance 57:23 institution 11:20,23 instruct 69:14 instructions 38:1 instrument 15:1 instruments 14:16 intense 23:24 interchangeably 8:15 27:12 interest 54:15 interested 59:4 62:6 64:5 66:1 intermediate 73:3 interrupt 6:21 intervals 7:7 introduced 48:12 investigation 23:24 investigators 71:17 invoiced 10:1 involved 8:4,8 19:10 involves 62:22 involving 7:25 IPR 7:25 8:2,3,6,8,12,18 9:2,3,7,8,11 10:1,22 11:15 12:15,16 IPRS 9:15	isolate 63:5 issue 80:22 J January 4:2 K Kessler 4:17,19 key 80:22 Khanduri 4:12,14,15 5:1 10:18 29:15 31:16 34:5 35:19,23 36:4,21 64:23 67:8 70:7,10 72:8 75:7 86:17, 22 87:1 89:5,8 kind 22:18,19,20 23:3 34:23 kinds 23:11 L labeled 42:17 landscape 25:8 language 30:1,4,6 33:9,21 34:1,15, 21,24 35:1,4,6,7,15 36:19 73:12 larger 24:18 60:22 late 8:22 law 4:16 lawyer 13:2 layer 18:14,16,17 lead 41:5 learn 8:18 led 50:18 51:1 lengths 21:8,9 level 19:14,17 23:1 31:12,22,25 32:6 36:14 levels 17:12 59:17 libraries 57:3 69:21 88:17 library 49:11 56:23 57:15,17,20 58:6 60:15,21,22 62:13,19,25 63:22,25 64:11,24 65:6,13,20 66:5 67:10 69:15,20 70:6 71:15,18,25 72:3,13 ligate 60:4 Ligation 76:21 88:14 limitation 27:20 28:7 33:4,6
---	--	--

limitations 24:22 lines 77:14 linked 39:4,6 41:24 52:1 list 11:5 26:15,17,19 listed 11:8 12:4 20:8 86:10 locate 17:5 located 14:24 locating 16:1 location 16:2,4,17 17:13 22:1 location-identifying 26:19 27:5,8, 12 28:1 long 14:5 83:22 84:1 longer 51:1 looked 33:22 lot 33:17 55:25 58:11,18 59:3,8 82:14 83:17 85:23 lots 22:22 23:11 M made 58:22 maintain 51:3 make 25:5 30:24 34:3 35:5 53:11 54:6 55:24 57:13 58:18 59:15,19 69:15,20 makes 22:16 making 57:11 72:13 manipulate 19:25 20:4 manufacturer's 57:6 88:20,23 89:2 marked 10:14,16 29:12 67:6 match 62:4 64:7 66:3 matches 51:15 material 30:22,23 74:1 75:16 77:6 78:4 materials 11:5,8 12:1 76:15,16 matter 4:7 7:25 11:21,24 matters 80:11 83:7,13 84:21 meaning 32:14,22 33:3,9,14,19,21 34:6,7,20,24 35:12 means 6:5 33:4 34:11 49:10 51:8 medical 15:13	meet 12:19 13:2,19 27:3 meeting 14:4,5 meetings 14:2 mention 43:5 78:20 85:6,7 mentioned 18:22 20:25 22:4 23:13 49:15 52:15 66:22 69:16 72:9,14 messenger 17:8 42:17 46:1 49:20 50:3 51:9,16 53:22 54:22 64:8 66:4, 11,15,17,20 71:5,6 72:6 80:14,16,17 81:2,6,9,12,16,21,23 82:2,13,20 83:10,21 84:5,13,25 85:11 met 5:10,14 13:17,21,23,24 method 15:1 37:19 50:19 51:6 56:17 58:3 62:21 63:1,24 64:12,25 66:2,7 methods 14:13 22:9 Michigan 5:5 14:17 micro 49:24 50:7 microliter 69:4 73:7,8 74:3,7,8 76:21 77:17 microliters 67:21,24 68:3,7,18 69:6, 8,20 70:2,23 71:22 73:4 75:4,10,19 78:16 micromolar 73:6 74:6 76:23 mid-'20 49:19 middle 67:19 76:18 88:2 millimolar 73:6 74:6 77:18 mine 15:13 minus 43:5 46:11,13 51:12 63:12 66:14,17 minutes 73:1 74:3 misheard 46:15 misunderstandings 41:5 mix 73:4 74:4 mixed 77:16 molar 74:5 molecule 16:6,16,18,23 39:3,4 45:6 52:4 53:4,17,18 54:8,10 56:11 65:16 molecules 16:3,5,9,21 18:10 24:14 38:17,20,25 39:8 47:23 48:2,9,13 51:20,22,23 52:5,6,11,12,21 53:2 57:13,14 58:15 59:22 61:3 64:24 65:1,8,15,18,21,23 75:22 76:1 77:2 79:17,18,20,22 morning 4:12,13 13:6	motivated 54:20 mrna 50:12,21 51:7 52:24 66:8 mrnas 17:13 38:22 N nanomolar 57:4 88:18 Nanostring 8:4,9,13,15 9:18 Nanostring's 14:16 nature 84:25 necessarily 21:5 needed 68:1,5,10,16,25 69:12,19,25 70:21 71:21 75:2,17 Nef 16:22,24 17:2,3,23,24 negative 47:17 53:7 56:10,14 57:22 58:7,10 60:3 61:20,21,25 62:10,15,21 63:2 64:1,16 65:16 71:12,13 80:21,23 81:15,19 82:5 85:18 Nextseq 57:4 88:18,24 nice 4:15 note 20:7 35:8 noted 32:7 33:15 42:8 76:8 83:23 Nothing's 60:13 November 11:2 nucleic 16:5,6 18:9 41:1 45:16 nucleotide 21:18 39:9,19 nucleotides 55:21 number 12:14 numbers 73:22 O oath 5:25 object 7:14 Objection 31:14 33:24 36:16 64:17 71:1 75:5 83:16 obtain 64:22 66:3 81:18 obtained 81:11 obvious 24:16 occurring 43:4 48:17 59:12 60:24 occurs 42:5 October 5:11,14,16 8:24
--	--	--

offer 15:16

oligo 45:24 46:2,22,23,25 47:7,9,10 52:23

oligonucleotide 27:18 29:6,24,25 30:18 31:3 40:1,2,22

oligonucleotides 26:17 27:4,25 29:2,20 30:4,10

opinion 23:16 26:10,22 32:21 33:2 37:18 51:5 60:11 63:20,24 68:12 74:22,24 75:12 76:7 78:24 88:12

opinions 11:9 34:14 86:14

opposed 15:16 41:24 43:15 55:19 81:18 82:5

optimized 60:10

orange 51:20,22 52:1,5,11,21 53:2, 17 54:7,10 55:1 56:11 58:11,17 61:3 65:9,23 72:22 76:1 77:21 79:7,10,18, 21

order 48:16 62:16 63:18

ordinary 32:13,22 33:3,8,14,19,20 34:6,7,20,24 35:12

organism 22:20

orientation 72:19

origin 23:13

original 42:19 45:21 50:16,20 51:7,9, 11,15,19 53:20 54:21,24 66:4,8,15,20 80:23 81:2,5,8,11,20 82:12,20 84:14 85:18

originally 48:23 72:7 83:20 84:4,12

origins 23:17

overlap 6:21

P

p.m. 70:9 86:20,21 87:2,3 89:6,7,11

pages 67:9

paired-end 57:5,7,15,18 58:6 62:14, 20 63:1,20 64:1,14 88:19

pairs 59:21

paper 37:16,24 65:25 83:23 88:13

paragraph 11:4,5,9 12:5 19:20,22 20:8,11 22:5 26:2,5,8,9 32:19,20 33:21 34:8,12,14,25 35:1,13 37:7 56:23 76:16,18 87:8,9,12,14,16

parameters 41:10 61:10 71:24

part 17:2,24 27:22 39:9,18,25 40:10, 16,22 41:2 49:9 55:17,18,23

parts 87:12

pass 86:23

past 15:12

patent 7:25 11:12 13:16 14:10 19:15 29:8 31:6 33:15,23 34:2,9 35:5,7,10 36:8

patents 8:22

PCR 78:21 88:3

penalty 6:2

pending 7:9

people 17:18

percent 76:10

performed 72:10,15

performing 30:2 32:23 33:11 51:5

perjury 6:2

permitted 7:2

person 33:12 35:2

petitioner 54:13

petitioners 86:2

Ph.d. 4:1,20

phosphoramidite 30:25 31:3

pictorial 55:11 58:25 60:18 65:7,10, 14,17,20,23 66:6,23 67:14 68:14,24 69:17 70:3,25 72:11,15 73:14,16,19, 25 74:18 75:14,23 76:2,8,9 77:1,7,11 79:1,3,5,6,12,21,22 80:5,18 83:2

picture 71:3

piece 80:10

pilot 58:19,20 60:9,13,20,23 61:2,8 66:23 67:1,13 68:11,13 69:1,10,14 70:5 71:17

piloted 59:14 71:23

place 5:2 44:12 45:13

plain 32:13,21 33:3,8,14,18,20 34:6, 7,20,24 35:11,12

plate 18:17

platform 49:4 55:13,19,23 56:8,25 57:5 88:19,24

playing 8:25

plurality 30:3 32:22,23 33:10 34:16

plurality]' 34:17

point 20:22 39:22 73:12 76:6 83:18

poly-a 71:7 81:23,25

poly-t 71:6

polymerase 22:19,22 25:7,16,22,24

polymerases 22:6,14,16 23:4,6,10, 11,14,16,19,20 24:5,7,9,11,19 25:1

polynucleotide 19:25 20:5

portion 75:13 87:16

POSA 19:14,19,23 20:13,19 21:10 22:23 23:23 24:16 26:10,23 27:15,20 28:6 29:4,22 30:20 32:17,21 33:5 34:1 89:1

POSA's 21:12,16 26:3 34:15

positive 42:17,22 45:18 48:23 51:15, 25 52:1 53:22 54:1 56:10,13,14 57:21,25 58:7,12,22 59:3,8,18 63:2, 15 64:4,19 65:9,11 66:1,21 71:10 72:6 77:21 80:7,14,17 81:8,11,18,20, 22 82:2,4,12,19,20 83:2,9,14,20 84:5, 12,13,15,25

post 49:14

potential 16:10 25:13

Pratibha 4:14

prep 13:12

preparation 52:15 71:15

prepare 12:19,20,21 13:14,19 14:2

prepared 11:9 12:24 15:8 49:2

preparing 11:6 12:5,7 13:3 14:8

present 12:22 45:2

preservation 56:17

preserve 48:16,22 49:16 54:21 62:16 63:18 64:3 85:11

preserved 84:19

preserving 57:24 64:6 66:20

pretty 21:15

previous 23:14

previously 10:16 29:12 67:6 69:21 74:12 77:16

primarily 13:21

primary 18:20

primer 77:20

principles 5:21

prior 23:17 24:10 25:17 69:2

probe 21:13,17,20 41:21 42:8,20
44:16,24 82:1

probes 18:6,9 21:8,9,11

proceed 4:11 12:13 20:22 23:1

proceeding 5:7 8:19,25 27:9

proceedings 89:11

process 35:2 49:7 50:22 54:19 58:2
59:15 62:12 63:4,11 66:10 81:3 83:22
84:1

produces 60:2

product 19:3,8 28:16,19 30:24 48:25
52:19 54:22 55:11 56:3 61:15,16,18
71:14 74:25 75:13 79:7,11 80:14
81:5,7 83:9

products 14:13,18,19 18:23,25
26:12,20,25 27:6,22,23 28:2,8,10,12
31:13,23 32:5,23 33:7,10 34:17 72:22

professional 9:16

project 15:11,25 16:21

promising 15:19

proprietary 18:2

protein 16:12,22 17:6,9

proteomic 16:15

proteomics 15:24

protocol 57:6 67:25 74:12 77:16
88:20,23

protocols 89:2

provide 26:2 33:2 34:8 36:24 37:12

provided 35:12 86:14

providing 34:14,20

public 6:14

published 16:25

purified 67:24 69:8,21 74:11 77:15

purpose 23:25 48:21

purposes 23:22

put 32:8 41:4 80:3

Q

qpcr 67:24 68:5,17 69:9,25 70:22
71:21 72:9,14 75:3,17

quantification 32:7 50:3,6

queried 35:4

question 6:19,24 7:9,10 21:15 23:2,
6 25:5 28:8,15 29:16,17 31:19,20
39:15,16,17 40:21 46:13 50:17,18,25
58:4,5 64:9 75:11 83:1,12

questions 6:7 7:14,15 13:12 15:18
62:6 86:23 89:4,8

quickly 89:5

quote 49:15 56:23 57:2 70:21,23
74:13,19 75:16,19

quoted 33:21 34:25 35:1

quotes 33:4

R

raise 4:5

rare 50:7

rate 9:23

reaction 26:11,16,24 27:2,17,21,22
28:7,10,11,18 29:1,5,19,23 30:3,9,17,
23 33:7,19 39:11 40:7,11,17 43:1,3,
24 47:18 58:15,20,25 59:11 66:14
67:20 68:2,6,11,17 69:1,3,6,14,19
70:1,5,23 71:8,22 72:1,21 75:3,9,18
78:14,16

reaction' 33:11

reaction.' 32:24

reactions 22:7

read 11:8 20:1 28:3 30:6 32:17,25
33:4 34:21 55:14 74:15,20 77:14
79:14 80:2 82:15 84:2

reading 37:16

reads 62:18

Readymix 67:22

Readymix...and 69:8

reagent 22:11

reality 84:20

reason 50:13 82:11,17,18

reasonable 7:6,7

reasons 50:5

recall 8:24 9:23,25 12:23 14:21 15:4
86:9 87:6,19,25

recently 16:25

recognize 10:19

record 5:3 6:13 10:15 29:11 36:2,3
54:6 67:5 70:8,9 73:11 77:5 86:20,21
87:2,3 89:6,7

records 10:4

red 38:21 39:1,4,8,12,14,18,25 40:10,
16,21 41:1,2 42:19,24 43:6 45:14
52:19 53:23 55:20 63:12 66:19 80:23
81:6

reference 57:2 67:10 70:14 73:15

references 86:7,12,13

referred 42:7

referring 23:25

reflect 49:21 82:19

reflection 83:20 84:4,12

reflects 81:5

regulation 50:7

relating 8:2

relationships 9:16,19

relevant 19:15

rely 12:4

remainder 27:23

remaining 76:20

remains 45:1

reminder 72:4

report 73:2

reporter 6:11,16

represent 4:17

request 6:18 7:10

require 5:20 22:10 26:24 27:16,21,
24,25 28:7 29:1,19 30:9,17 31:11,22
33:6 36:13

required 50:10 61:11

requirement 22:25 26:16,18

requirements 26:15 27:3

requires 26:11 27:2 31:24 32:2,4

research 14:12 15:9 18:4 19:5

reside 5:4

residence 5:3

respect 32:9

response 23:2 83:5

restate 75:11

restoration 17:15
results 18:2 19:4 27:23
retains 46:2,24 47:2
reverse 45:12,21 46:5,6,9 47:6,9
50:13 53:3,6,17 54:3,5,8,11,24 55:2
65:22 72:20 73:4,6 74:4 76:5,12
77:19
reverses 17:19
review 12:3 13:5 14:10 19:19 86:7
reviewed 11:12,14,17,20,23 13:15
14:7 86:9
RNA 17:8 24:19 42:17 46:1 47:17,19
48:8,13 49:20 50:6 51:9,16 53:22
54:22 58:10 60:2,3,4 64:8 65:18 66:4,
11,15,17,20 71:5,6,12 72:7,22 77:2
80:14,17 81:2,6,9,12,17,21,23 82:2,
13,20 83:10,21 84:5,25 85:6,11,16,17
RNACLEAN 74:12 77:15
RNAS 49:22,24 50:4,7 84:13
RNASEOUT 73:9 74:8,16
role 9:1 17:23
roles 41:8
RT-PRIMER 74:6 77:17
rules 5:20

S

sample 15:4,7 18:16,17,18 38:23
76:21
samples 15:8 68:2,5,17 70:1,22
71:21 72:24,25 74:2,9,11 75:3,17
77:14
scale 60:22 61:8,14 69:15
scaled 59:17
scaleup 60:15
scenario 21:14
scheme 48:21
school 15:13
scientific 50:16,24,25
second-strand 42:13,22 43:1,2,23
45:6,8,9,17,19 47:3 51:25 52:18,25
53:5,25 54:17 66:18 71:10 80:13
82:19 83:9 86:1
second-stranded 82:10
seconds 69:5 78:18

segment 39:18 42:6 48:7
segments 60:8
selection 22:6
sense 17:7
sentence 20:4,11 28:3,9 33:2,5 68:8,
15,20 69:2,24 70:2,20 71:20 74:19
75:1,15 76:20,25 77:4 78:6,12,18,20
88:16,21
separate 9:5
separating 43:18
sequence 21:18,22 39:9,10,12,13,
14,19,25 40:6,8,9,22 41:13 45:9,10,
13,15,22,25 46:3,6,8,10,22,25 47:7,9,
10,21 49:11 50:11,12,20 51:7,9,21,23
52:6,12,14,23 53:6,21 54:3,4,12,14,
24 55:12,20,25 58:19 61:15 62:3
63:6,14,19 64:4,7,19,22 65:9,11,15,
22 66:3,7 71:4 72:6 76:5,6,12 77:23
80:22 81:6,20,22,24,25 82:4,6,12,18
84:3,17,18,19 85:3,12,20,25
sequenced 56:24 57:4 58:13 63:20
66:5 79:17,20 80:20 81:15 85:18 86:1
88:18
sequences 19:25 20:5 26:19 27:5,8,
12 28:1 41:2 53:1 55:24 57:12 71:13
84:22 88:13
sequencing 24:12,13,14,19 25:20,
22,25 35:9 48:22 49:5,13,25 50:19
51:6,13 52:3,16 55:12,18,23 56:23,24
57:5,8,14,15,16,17,18,20 58:1,2,5,6,
23 61:24 62:2,7,12,14,17,20 63:1,5,
10,12,22,25 64:1,11,14,21,24 65:6,19
66:2,5 67:11 72:5 74:25 75:13,23
76:2,8 77:12 78:24 79:6,10 80:1,12,
16,20 81:1,9,11 82:5 83:7,18,25
84:10,23,24 85:6,11,16,17,22 86:5,6
87:20 88:5,6,19
sequencing.' 34:17
series 51:10
serve 61:23
serving 9:14
set 52:3
Sherman 4:1,4,9,12,20 5:4 7:19
10:11,19 13:12 14:12 18:22 19:14
20:25 22:4 27:15 28:4,8,23,25 29:16
30:8 31:11,21 36:5,11,13,24 37:14
39:15,17 40:14 41:23 42:15 48:15
49:15 55:14 58:4 62:9 64:9 66:22
68:12 70:11 73:12 75:11,22 78:18,22
83:12 87:6 89:9

short 57:11 62:18 86:25
shorter 85:24
show 15:22 39:5 48:8 52:2,19 65:3
81:13 82:8
showed 60:1
showing 41:23
shown 38:4 44:18 47:25 59:9,12
60:5 65:9,23 66:9 67:15 71:8 76:7
77:10 79:18
shows 59:25 60:8
SI 37:16
sic 75:4
signature 10:25 11:1
signed 11:2
silent 80:10
similar 9:1 13:12 26:22
simply 15:16 41:4
single 28:14,15,19 41:3,6 62:17,24
63:19 68:20
single-synthesis 27:17 28:9,11
sitting 13:22
situation 21:2 22:8 24:21
skill 19:14,17 33:13 35:3
slightly 39:15
solid 18:18 41:25 42:2 57:12 66:12
71:5
solid-phase 24:5,8,9,20,23 25:1,7,
16 36:14 71:9
solution 42:3,11,23 44:22 47:18
49:14 66:16
solution-based 23:21 51:14
sort 17:3 20:20 21:14 22:9 23:20
32:8 59:14 60:8 71:15
Sounds 35:25
spatial 14:13 15:24 16:17 17:13
19:17 20:12 21:1,16,20,21 22:1 27:9,
11,19 28:1 43:8,11,19,22 44:10 45:2,
10,19,22 47:19,24 48:5 53:3,18,21
54:11 55:2
spatially 17:5
speak 7:2 70:11
specialized 22:10 23:22,25
specific 15:1 32:8 85:15

specifically 20:6 30:1 39:11
specification 33:22 34:9 35:14
speculating 12:11 13:1
Spellman 49:8 54:14 83:23,24 86:2
Spellman's 11:14,18 13:16 14:7
spend 12:7
spent 12:14,16,24
spring 19:9
stage 44:21 80:3
Stahl 37:16,19,21,23 38:3,4 40:6
 41:11 47:15 49:9 50:5,17 51:5 54:20
 55:19 57:2 60:15,25 61:1,13,25 62:22
 67:2,4,9,13,18 68:14 69:15,16 70:14,
 24 72:9,14,18 73:15,17,24 75:1 76:14
 79:25 80:7,9,10 83:2,5,13 84:11 85:6,
 15,16 86:4,8,11,13 88:12,23
Stahl's 37:19 62:21 63:1,24 64:12,25
 66:6 73:13 74:1 75:15 77:5 78:4
 80:15 81:10 87:7,12,14,22
stand 13:10
standard 22:9 23:20
standardized 58:21
start 39:10 41:16 46:16 63:23 73:21,
 22 75:9 76:25
starting 30:22,23 66:10
starts 19:20 69:3 78:14
state 5:2,20,21 19:22 26:8 56:23
 82:23 85:10,13
stated 54:20
statement 25:6 74:16 79:25
states 6:2 74:1
stay 31:6
STENOGRAPHER 4:4,10
step 26:10,22,24 27:2,16 28:21,23
 29:22 30:8,16,20 31:9,11,21 32:1,3,
 11 38:10,12,16,18 39:1 40:19 41:11,
 15,17,20,23,24,25 42:4,6,7,8,12,15,
 16,18,21,24 43:2,4,7,11,22,25 44:2,4,
 10,12,13,15,16,18,19,20,22 45:1,3,5,
 6,11,13,15,22,23,24 46:2,3,9,10,20,
 24 47:1,6,12,14 48:3,6,10,11,14,15,
 16,24 49:2,14 51:17,20,22,23 52:5,7,
 11,13,21,24 53:2,4,13,15,17 54:4,8,
 10,12 55:8,10,17 56:1,4,6,9,11 58:14,
 25 59:5,9,12,14,18,22 60:1,3,4,10,11,
 17,24 61:3,6,7,14,20,21 62:1,9 65:7,
 14,20 66:6,10,22 67:14 68:13,24

69:16,17 70:2,3 71:2 72:3,10,12,18,
 23 73:10,14,16,24 74:17,22 75:13,23
 76:1,7,9,25 77:7,11,12 78:25 79:5,6,
 11,15,17,20,22 80:5,8,18 82:9 83:1,3
 84:18,19 85:19,21
step-by-step 65:5
steps 26:3 28:25 29:4,17 31:9 38:7
 49:12 51:11 54:2 70:24 72:5,15 82:16
Sterne 4:17,19
story 17:25
strand 42:17,18,22 43:5,13,15,16,18,
 20 45:18 46:11,13 47:4,16,17 48:22,
 23 49:1,11 50:20 51:12,15,25 52:1
 53:7,8,22 54:1,17 56:13,14,17 57:25
 58:10,11,12,22 59:3,8,18 60:3 61:19,
 20,21,25 62:4,10,15,17,21,23,24
 63:2,12,15,19 64:2,4,7,16,19 65:9,11,
 16 66:1,3,17,19,21 71:10,11,13 74:5
 77:21 80:7,17,21,23 81:8,12,15,18,
 19,20,22 82:3,4,12,21 83:3,14,21
 84:5,13,14,22 85:11,19,25 86:3,4,6
stranded 48:22 49:25 50:18 51:6
 61:23 62:2,7,12 64:21 72:5 80:19
 81:1,9 82:6 84:23,24 85:6,16,17,22
strandedness 48:17 49:16 50:10,14
 51:3 57:24 62:16 64:3
strands 56:10 57:22 58:7 60:6 61:24
 62:23 63:6 71:12 83:19 84:11,22 86:5
strategy 49:25
strike 8:7 9:10 16:1 18:14 20:23 26:8
 29:24 31:17 32:2 34:6 35:11 38:11
 39:16 41:13 48:1 51:3,19,21 54:9
 57:16 59:10 63:21 74:22 77:9 78:15
 79:5,19
strong 19:23
studying 15:21
subgroup 16:13
submitted 10:21 11:15 12:17
subsequently 17:9 74:11
substance 36:6 70:12
successful 15:16
suitable 71:25
summer 8:22
Superscript 73:8 74:7
supplemental 74:1 75:15 76:15,16
 77:6 78:4
supplementary 37:24 47:16 48:20

67:16 82:15 85:23 87:13,22 88:8,15
surface 41:25 42:2 57:12 66:12 71:5
suspect 16:11
swear 4:6
sworn 4:22 5:18
synthesis 22:6 23:21 24:5,8,10,20
 25:2,7,16 26:11,16,24 27:2,21,22
 28:7,16 29:1,5,19,23 30:3,9,17 31:1,3
 32:2,24 33:7,11,16,19 39:11,13 40:7,
 11,17 42:21 43:1,24 45:17 53:23,25
 66:13 71:7,9 83:25
synthesize 38:13 42:13
synthesized 40:16 43:13 45:7 81:5
synthesizes 28:19
synthesizing 31:12,23 32:4,22 33:9
synthetic 51:12 52:19
system 16:24 17:15,17,20
systems 19:4

T

T4 25:23,24
tail 71:6,7 81:23
talk 14:18 22:18
talked 88:1,9
talking 43:7 54:15,16 68:11 78:7
target 15:20,21 16:3,5,6,10,12 17:10
 21:19,24 22:1,2
targets 16:13
technician 14:25
techniques 20:6,8,12,13,15
technology 49:18
teens 49:19
temperature 61:10
template 26:18 27:18 29:6,25 30:10,
 18,21,22 31:4 43:1,3,14 45:17 57:22
 58:8,9,24 71:11
templates 27:4,25 29:2,20 58:16
term 30:21
terms 8:22 14:25 21:2 27:11 50:2
test 60:19
testified 4:24 5:16 28:21 30:8 38:7
 44:11 70:20 73:13 82:22

testify 4:22 6:6

testifying 5:24 44:23 58:14 59:9,11
60:23 87:6,19

testimony 4:6 9:20 36:6 39:3 61:17
70:12 74:17 82:23

testing 17:12

text 48:20 73:3,15,24

thing 7:13 85:1,2

things 22:23

thought 35:3

Thursday 4:2

time 5:10 6:18 7:8 9:3 12:16 13:18
33:15 67:17 85:9 89:9

times 9:5 33:16 34:4 35:9

tissue 15:4 18:18,20 38:23

today 4:15 5:18 6:11,17 7:22 8:4,8,
20 9:13 18:1

tolerate 22:21

top 56:22 60:8 77:13

total 9:25 67:20 68:2,6,17 69:3,6,19
70:1,23 71:22 75:3,9,18 78:14,16

transcribing 6:12,16

transcript 6:13

transcriptase 77:20

transcription 72:21 73:4 74:4

transcription-primer 73:7

transcriptional 16:10,15

transcripts 17:7

transition 71:16

transitioning 70:5

trial 5:16

truth 4:7,8,22,23

truthfully 6:6

turn 88:15

turned 83:25

Two-minute 89:5

type 14:21 15:4 21:22 22:11 24:9
25:20

types 24:8,13,14 25:3 50:3,7

typical 63:9

typically 21:9,20 62:25

U

Uh-huh 16:7 25:19 28:5,22 33:8
37:11 40:15,20 41:12 44:25 46:19,21
48:4 51:18 52:22 53:14 59:23 76:19
78:5,13,23 79:4 80:6 83:4,11

understand 5:24 6:5,9,14,23 7:4,16,
17,21 8:3,9,13 16:8 20:13,21 22:10
26:10,23 27:13,16 29:4,22 30:21
32:17 33:13 34:2 40:14,19 44:23 50:6
55:5 59:19 68:12 72:6 82:22

understanding 7:24 8:11 17:22
19:23 20:14,20 21:10,12,17 22:24
26:3 30:25 32:13,16 33:18 34:1,10,15
35:4,5,15 36:18 49:8,19 57:7,10 59:2
62:3,11,13,19 63:16 64:20

understood 27:20 28:6,15 32:21
33:6

unique 22:11

United 6:2

units 73:7,8 74:7

University 14:17

V

validate 15:21

validation 17:10

versus 5:7

view 21:4 72:17

Visium 14:20,21 15:5,9 16:16 17:5
18:3 19:8

Visium's 19:8

visual 37:25 38:2,5,6,10,12

visually 38:4 41:6 48:18

volume 67:20 68:6,18 69:3,6,20
70:1,23 71:22 75:4,10,18 78:14,16

W

wait 6:18,20

Walter 13:25

wanted 19:4 50:19,21 62:24 80:25
81:1

ways 15:23 41:8

word 22:16 23:19 33:15

words 32:17 36:17 38:5

work 12:12 25:4,5,9 31:24 32:8,10
36:17,20 54:23 63:17 82:14

workflow 37:17,19 87:7,14

working 17:18,22,25 49:10

works 57:11

worries 37:6,8 52:10

wow 10:6

write 20:4,5 72:20

wrong 31:19 69:23

X

XP 74:12 77:15

Y

year 5:8,11

years 15:13

yesterday 13:21,22