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

- - - - - x
10X GENOMICS, INC., :
Petitioner, : Case No. IPR2023-01298
v. :
NANOSTRING TECHNOLOGIES, : U.S. Patent No.
INC., : 11,377,689 B2
Patent Owner. :
- - - - - X

Deposition of PAUL T. SPELLMAN, Ph.D.
Conducted Virtually
Thursday, December 19, 2024
12:05 p.m. EST

Job No.: 565127
Pages 1 - 115
Reported by: Debra A. Whitehead

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

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

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A P P E A R A N C E S

ON BEHALF OF PETITIONER:

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ALSO PRESENT:

KIERAN MORRISON, A/V Technician

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C O N T E N T S

EXAMINATION OF PAUL T. SPELLMAN, Ph.D.	PAGE
By Mr. Cheung	5
By Ms. Khanduri	112

EXHIBITS MARKED IN TODAY'S SESSION
(none marked)

EXHIBITS MARKED IN PRIOR SESSIONS

DEPOSITION EXHIBIT	PAGE
Exhibit 1001 U.S. Patent 11,377,689 B2	81
Exhibit 1005 (Not Described)	34
Exhibit 1008 '386 Application	71
Exhibit 1009 '487 Application	41
Exhibit 1055 Reply Declaration of P. Spellman	83

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P R O C E E D I N G S

PAUL T. SPELLMAN, Ph.D.,

having been duly sworn, testified as follows:

EXAMINATION BY COUNSEL FOR PATENT OWNER

BY MR. CHEUNG:

Q Dr. Spellman, good morning.

A Good morning.

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

A Paul Thomas Spellman. 10807 Rochester
Avenue, R-O-C-H-E-S-T-E-R, Los Angeles,
California, 90024.

Q And did you prepare for today's
deposition?

A Yes.

Q What did you do to prepare for today's
deposition?

A Met with counsel, reviewed my
declarations, reviewed documents in -- that have
been introduced into the case as exhibits, read
opposing counsel's positions that were provided to
me by -- that are in the record already, as well

1 as the deposition and transcript of Dr. Sherman.

2 Q How long did you spend in total on this
3 preparation?

4 A I believe about 30 or 40 hours.

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

7 A I did.

8 Q When did you meet with counsel?

9 A Within the past two weeks.

10 Q Who did you meet with?

11 A Dr. Khanduri, Dr. Longsworth, Mr. Holman,
12 and Mr. Sterne. I may have applied doctors or
13 missed doctors to some of those individuals.
14 Apologies.

15 Q How long in total was your meeting with
16 counsel?

17 A I did not keep track explicitly. I'd
18 have to check my billing records.

19 Q Can you provide an estimate?

20 A More than ten hours, less than 30 hours.

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

1 A I don't recall.

2 Q Is it more than ten hours?

3 A Yes.

4 Q Is it more than 20 hours?

5 A Probably. I'd have to check my billing
6 records.

7 Q In preparing for your deposition today,
8 did you review your reply declaration, marked
9 Exhibit 1055?

10 A Yes.

11 Q Did you review Dr. Sherman's deposition,
12 marked Exhibit 1056?

13 A Yes.

14 Q Did you review Dr. Sherman's declaration,
15 marked Exhibit 2006?

16 A I believe so, yes.

17 Q Did you review your first declaration,
18 marked Exhibit 1002?

19 A Yes.

20 Q Did you review the Board's Institution
21 Decision, marked Paper Number 14?

22 A Yes.

1 Q And are you familiar with the substance
2 of those documents we just talked about?

3 A Some of them closely, some of them at a
4 high level.

5 Q But you're able to speak to the content
6 of those documents today.

7 Is that right?

8 A I believe so.

9 Q Dr. Spellman, are you familiar with the
10 synthesis of oligonucleotides?

11 A Roughly speaking, yes.

12 Q And how are synthetic oligonucleotides
13 synthesized?

14 A Normally there's a phosphoramidite
15 chemistry that's the predominant one used. The
16 exact chemistry is not something I'm expert at.
17 But it allows you to synthesize chains from
18 individual nucleotide bases in a single-stranded
19 manner to produce long chains, longer chains of
20 nucleotides that are synthetic single-strand DNA.

21 Q Were synthetic oligonucleotides readily
22 available by 2018?

1 A Yes.

2 Q Can synthetic oligonucleotides be
3 prepared with a fluorescent label?

4 A There are a variety of complex
5 chemistries that are utilized in synthesizing
6 oligonucleotides. The easiest oligonucleotides to
7 synthesize are those that mirror DNA most exactly.
8 There it is not uncommon in the art to use
9 modified nucleotides that have extra features to
10 them.

11 In general, these extra features are more
12 complicated and more expensive to utilize. It is
13 common to synthesize them, although the costs and
14 constraints on what is possible are more
15 complicated with more complicated
16 oligonucleotides.

17 Q Were synthetic oligonucleotides with a
18 fluorescent label readily available for purchase
19 from a commercial vendor by 2018?

20 A In 2018 one could order oligonucleotides
21 with fluorescent labels attached in specific
22 places. I am not sure if they could be

1 arbitrarily labeled with -- so with a generic
2 label somewhere, absolutely; with specific labels
3 in specific places, I'm not sure.

4 Q By 2018 were synthetic oligonucleotides
5 prepared with an affinity label readily available
6 for ordering from a commercial vendor?

7 A Given the caveats that I described for
8 fluorescents, specific affinity labels were known
9 and commercially available. The most common one
10 would be biotin. More esoteric affinity labels
11 may or may not have been commercially available.
12 So it could depend specific on the fluoro in the
13 case of the previous answer or the affinity group
14 in the case of the current answer.

15 Q So of the different types of affinity
16 labels, biotin was the one most readily available
17 for purchase when part of synthetic
18 oligonucleotides.

19 Is that right?

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

22 A That is the one that I am most familiar

1 with. It may not have been the most common. It
2 has excellent properties for lots of other steps
3 and so would be a -- a POSA would commonly choose
4 biotin. I'm not sure about the market penetration
5 or which one was most ordered.

6 Q By 2018 were synthetic oligonucleotides
7 with a cleavable linker commercially available for
8 purchase?

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

11 A I presume so, although I had never
12 ordered them. So I can't actually be certain.

13 Q Did you have any reason to believe that
14 oligonucleotides with cleavable linkers were not
15 available for purchase in 2018?

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

18 A Photocleavable linkers are a far less
19 common technology. They are not nearly as well
20 utilized as fluorescents or biotin. And I am
21 unsure how readily they were available
22 commercially, at scale, et cetera.

1 Q Is it your understanding that no vendors
2 sold oligonucleotide with cleavable linkers by
3 2018?

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

6 A I have no knowledge whether or not they
7 were broadly commercially available to incorporate
8 into traditional oligonucleotides. Photocleavable
9 linkers had been broadly used in the industry, but
10 I don't -- so in many situations. But whether or
11 not they were commercially available as
12 oligonucleotides for sale in pre-made
13 oligonucleotides, I have no knowledge. And I have
14 never utilized them. Nor do I know anyone outside
15 of very specific chemistry projects or the large
16 companies that utilized them in their commercial
17 products who had access to them. But that may be
18 erroneous.

19 Q Are you familiar with techniques for the
20 spatial detection of nucleic acids?

21 MS. KHANDURI: Objection. Form.

22 A Broadly, yes.

1 Q Given a human tissue section, what is the
2 potential number of nucleic acids that can be
3 detected?

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

6 A Don't think the question is answerable.

7 Q Can you provide an estimate of how many
8 potential nucleic acids there may be in a human
9 tissue section?

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

12 A I believe you're leaving out a
13 substantial fraction of the question that would be
14 necessary to answer that question.

15 Q What additional information would you
16 require to answer that question?

17 A The number of cells in the tissue, the
18 size of the tissue, whether or not you're
19 constraining yourself to RNA or DNA, whether or
20 not you're constraining yourself to mRNA or all
21 RNAs, whether or not you're measuring T RNAs. A
22 vast number of possibilities that I don't think a

1 POSA would understand your question.

2 Q Given a human tissue section on a
3 standard microscope slide taken from a human, can
4 you give an estimate on the potential number of
5 nucleic acids including DNA and RNA that can be
6 detected on that tissue section?

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

9 A So it -- again, you haven't told me the
10 size of the tissue, the thickness of the tissue,
11 the cellular density of the tissue. You haven't
12 determined whether or not you want to know the
13 total number of mRNAs, the total number of tRNAs,
14 the total number of ribosomal RNAs, the total
15 number of different isoforms of various different
16 RNAs, nor have you told me whether or not you want
17 to count individual chromosomes, mitochondrial
18 DNA, or a variety of other factors that I could
19 continue to list.

20 Q Dr. Spellman, what is the typical size of
21 a tissue section?

22 MS. KHANDURI: Objection. Form.

1 A Tissues are sectioned anywhere from low
2 numbers of microns to tens or more microns,
3 depending on the application.

4 Q For use in spatial application, what is a
5 typical size of a tissue section?

6 MS. KHANDURI: Objection. Form.

7 A Again, the answer is small numbers of
8 microns to tens of microns, rarely more than a
9 hundred microns, or maybe occasionally more than a
10 hundred microns in certain applications, but that
11 would be less common.

12 Q On a tissue section that is tens of
13 microns, how many potential cells could there be
14 in that tissue section?

15 MS. KHANDURI: Objection. Scope.
16 Relevance.

17 A A person of ordinary skill in the art
18 would know what type of cells they were looking
19 at, and there is a wide variety of sizes of cells,
20 as well as thicknesses of cells, in specific
21 spaces.

22 A rule of thumb might be that a cell has

1 a diameter of about 10 microns, but that diameter
2 is not constant and can vary from as little as,
3 you know, the parts of neurons can be hundreds of
4 nanometers. And there are cells that can be 20,
5 30, or more microns in diameter.

6 Q In a typical cell that is tens of microns
7 sized, how many nucleic acids can be within the
8 cell?

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

11 A I still can't answer the question based
12 on my previous comments regarding what you are
13 referring to as nucleic acids.

14 Q In a cell that is tens of microns size,
15 what is the number of mRNA molecules inside that
16 cell?

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

19 A Experiments done in the I believe 1980s
20 suggested that the typical number of mRNA
21 transcripts in a human cell was approximately
22 300,000. I believe that number is broadly

1 accurate but highly dependent upon a variety of
2 different factors.

3 Q Given a typical human tissue section,
4 what is the expected number of cells in that
5 section?

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

8 A Again, it would depend upon the size of
9 the section in both width and length, the depth of
10 the section, and the type of cells that are
11 present in that tissue.

12 Q What is the typical length and width of a
13 tissue section?

14 A I don't know that there is one.

15 Q What are the different widths and lengths
16 of tissue section that are commonly used?

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

19 A The smallest tissue sections that I think
20 would be commonly used would be 1 or 2 millimeters
21 by 1 or 2 millimeters. It is not uncommon to have
22 tissue sections as large as several centimeters by

1 several or many centimeters. So perhaps 2
2 centimeters by 5 or 7 centimeters would be amongst
3 the larger tissue sections.

4 Q What is the typical length and width of a
5 tissue section used for spatial detection?

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

8 A Again, I don't believe there is one.

9 Q How about in the context of the So-456
10 reference?

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

13 A I'd have to read the specification
14 closely.

15 Q So you haven't performed that analysis
16 before the deposition today.

17 Is that correct?

18 MS. KHANDURI: Objection. Form. Scope.

19 A I have not.

20 Q Does the size of the tissue section used
21 in the method in So-456 affect any of your
22 opinions in your declarations?

1 MS. KHANDURI: Objection. Scope.
2 Relevance.

3 A So-456 specifies many factors about the
4 tissue and provides a set of methods that would
5 work on specific types of tissues and specific
6 sets of sizes of tissues.

7 The -- a POSA reading that would have a
8 set of parameters that would be compatible with
9 So-456, and that does not change my interpretation
10 of So-456.

11 Q But sitting here today, you are not aware
12 of the tissue sizes that So-456 specifies?

13 MS. KHANDURI: Objection. Form.

14 A I am not aware of any relevant constraint
15 between the millimeters to centimeter-sized scales
16 that we have talked about that would or would not
17 be compatible with So-456. Specific pieces of
18 thicknesses would be constrained by So-456 based
19 on the specific NC2 biochemistry described.

20 Q How would the thickness of the tissue
21 sample affect the NC2 biochemistry described in
22 So-456?

1 MS. KHANDURI: Objection. Relevance.
2 Scope.

3 A Can I open my declaration? I have a copy
4 with me. Or should I use the electronic one
5 provided, or do you want it on the screen?

6 Q Whatever works for you, Dr. Spellman.

7 A So in my reply declaration, in Paragraph
8 13 I described how So-456 discloses methods for
9 treating a tissue sample. Those methods would --
10 and the methods in Paragraphs 152 and 153 require
11 the ability to do in situ biochemistry as a POSA
12 would understand. And the constraints of the NC2
13 biochemistry described in 152 and 153, as well as
14 other methods that a POSA would know, require
15 certain thicknesses of tissue. And the
16 preparation of those samples is something
17 well-known in the art.

18 Q Dr. Spellman, can you repeat the
19 paragraph numbers?

20 A Paragraphs 152 and 153 of So-456.

21 Q When you talk about constraints, are you
22 talking about a maximum thickness of the tissue

1 sample?

2 A In situ biochemistry has both maximum and
3 minimum thicknesses that are compatible with the
4 goals of the in situ biochemistry.

5 Q Do you know the compatible range of
6 tissue section thicknesses?

7 MS. KHANDURI: Objection. Form.

8 A It is common to use thinner sections,
9 between 3 and 10 microns, for in situ histo -- in
10 situ biochemistry proposals. The hazard of using
11 too thin a section is that you miss parts of the
12 cells, given the thickness of the cells. So one
13 is balancing the ability to do in situ
14 biochemistry with the goal of getting cells
15 present in the sample.

16 So one is generally choosing tissue
17 sections in the range of 5 or 10 microns.

18 Q And what happens if that tissue section
19 is thicker than 10 microns?

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

22 A As the thickness of the tissue increases,

1 it becomes more difficult to work with in a
2 variety of different factors.

3 Q Given the method in So-456, what would
4 happen if you start with a tissue section that is
5 thicker than 10 microns?

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

8 A A POSA would have to determine how to
9 best implement the method -- how to best use the
10 method described in 45 -- in So-456 to achieve
11 their objectives.

12 Q But it is your opinion that a POSA would
13 know how to deal with such a thick tissue sample.
14 Is that right?

15 MS. KHANDURI: Objection. Form.

16 A I don't think I described it quite that
17 way. I think that the POSA would read the
18 relevant literature and the method, the in situ
19 biochemistry method they wished to utilize, and
20 apply that method in a consistent manner.

21 Q So without performing additional
22 research, a POSA might not know how to utilize a

1 tissue section that is too thick?

2 MS. KHANDURI: Objection. Form.

3 A That's not at all what I said.

4 What I said was that a POSA would read
5 relevant literature to get guidance on how to
6 perform specific in situ methods that met their
7 requirements.

8 Q In the context of an amplification
9 reaction, are you familiar with the term
10 "amplicon"?

11 A Yes.

12 Q Based on your understanding, what is an
13 amplicon?

14 A Amplicons are small segments of DNA that
15 have been preferentially replicated to produce
16 many copies that are bound at specific ends --
17 that have -- end at specific places that are
18 targeted during the replication process.

19 Q Is an amplicon double-stranded or
20 single-stranded?

21 A The common use of the phrase "amplicon"
22 would be double-stranded, but specific individuals

1 in specific contexts may refer to an amplicon as
2 being single-stranded.

3 As an example, during PCR one melts the
4 two strands and one would still call the melted
5 strands amplicons.

6 Q In the context of an amplification
7 reaction, what is a template?

8 A The template is the initial DNA molecule
9 that is being used as a source, and it is the
10 copies of that initial DNA molecule that are used
11 in later cycles of an amplification reaction.

12 Q Based on your understanding, a template
13 is a copy.

14 Is that right?

15 MS. KHANDURI: Objection. Form.

16 A It is common in the art for the
17 explanation of exponential replication during PCR
18 to describe the first and second copies of DNA as
19 further templates into subsequent rounds of the
20 replication reaction.

21 So although it is common to refer to the
22 original DNA molecule as a template, it is not

1 uncommon, when talking about the reaction itself,
2 to talk about copies of the original molecule as
3 templates for further rounds of reaction. And a
4 POSA would think about the reaction and where the
5 use -- whether or not a specific strand of DNA is
6 a template or being replicated or something else.

7 Q Are the molecules that are templates for
8 further rounds of amplification themselves
9 amplicons of the original template molecule?

10 MS. KHANDURI: Objection. Form.

11 A In PCR specifically the first cycle of
12 PCR is unbounded. And that first strand of
13 replicated DNA would not generally be considered
14 an amplicon because it doesn't -- it would be very
15 unlikely to end at the same place as the reverse
16 primer; and, therefore, it would in all likelihood
17 be longer than the targeted amplicons, which are
18 the defined -- or are designed to have -- can be
19 designed to have specific endpoints.

20 Q So in PCR is the sequence of the
21 amplicons the same as the sequence of the original
22 template molecule?

1 MS. KHANDURI: Objection. Scope.

2 A Depending on how the PCR is designed,
3 because PCR is a workhorse technology, the
4 sequence of the amplicons do not necessarily have
5 the sequence of the template molecule.

6 Q Typically when referring to amplicons,
7 does that include the original template molecule?

8 A In the case of four five -- sorry, in the
9 case of PCR broadly, where the ends are not
10 controlled, that is unlikely.

11 However, in the So-456 reference, the
12 initial template molecule for in situ
13 amplification is bounded by the extension ligation
14 reaction and is exactly the same sequence as the
15 derived amplicon copies, and is indistinguishable
16 from those replicated copies. And it would be
17 a -- perfectly appropriate to count the first
18 molecule that is the template seed into the
19 amplification reaction as an amplicon. And in
20 fact, it will be, because at the final end of the
21 in situ amplification, it will be double-stranded
22 mixed with a copy of itself, a reverse copy of

1 itself.

2 Q So in the So-456 method, is there a way
3 to distinguish between the original molecules and
4 those that are copied from the amplification
5 reaction?

6 A Not inherently. To the best of my
7 knowledge, no.

8 Q And that's because they have the exact
9 same sequence.

10 Is that right?

11 A That is what So-456 describes.

12 Q During the amplification reaction in
13 So-456, what is your understanding of how many
14 copies are generated?

15 A So-456 is neutral on the topic of how
16 many copies to generate, to the best of my
17 understanding.

18 Q Typically when performing PCR, how many
19 copies of the original template molecule are
20 generated?

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

1 A Performing PCR, which is different than
2 what's done in So-456, can occur for as few as two
3 to five cycles of PCR producing four to 30 copies
4 of the amplicons, assuming high efficiency, which
5 is not guaranteed, or as many as two to the 30th
6 copies.

7 So PCR is a workhorse technology, is
8 designed by a -- is utilized by a POSA to achieve
9 innumerable objectives in molecular biology. It
10 is the workhorse technology of molecular biology.

11 Q Do you agree that PCR can generate
12 billions of amplicons from each original template
13 module?

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

16 A The number of copies of an amplicon that
17 are generated is a function of the number of
18 cycles utilized. Two to the 30th is approximately
19 1 billion, so that is not inconsistent with what
20 is achievable with PCR. But it depends on how
21 it's implemented, the availability of nucleotides.
22 It is not uncommon for PCRs to run out of

1 nucleotides.

2 In multiplex PCRs, the number of copies
3 of each target dramatically falls. And in those
4 situations in which you have done a billion
5 copies, it is actually somewhat uncommon because
6 that typically utilizes a single input copy, and
7 more commonly one is using tens, hundreds,
8 thousands, or even millions of copies of the input
9 DNA as template.

10 So the answer is very broad and very
11 complicated.

12 Q In multiplex PCR, is it common to
13 generate millions of copies of the original
14 molecules?

15 MS. KHANDURI: Objection. Scope.
16 Relevance.

17 A PCR performed in a tube in solution, not
18 uncommon. Again, very different than the So-456
19 reference.

20 Q Are you familiar with Illumina
21 next-generation sequencing?

22 A Yes.

1 Q How many molecules can be sequenced at
2 once on an Illumina sequencing platform by 2017?

3 MS. KHANDURI: Objection. Relevance.

4 A I don't recall the exact number in 2017.
5 If you brought up the commercially available
6 sequencers in 2017, I could give you a better
7 estimate. But I don't keep a timeline of when
8 specific instruments were commercially available.

9 Q Did you investigate the capability of an
10 Illumina sequencer as you prepared your
11 declaration in this case?

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

14 A I am broadly knowledgeable about the
15 capabilities of Illumina sequencers. And if you
16 asked about a specific number of sequences capable
17 of being generated, I could give you, you know,
18 relatively accurately whether or not that was
19 possible in 2018. I just don't want to answer
20 definitively circa 2018.

21 Q Based on your understanding, how many
22 molecules can be sequenced at once on an Illumina

1 HiSeq X Ten instrument?

2 MS. KHANDURI: Objection. Scope.

3 Relevance. Form.

4 A My recollection is that it is between a
5 hundred million and 1 billion, perhaps as many as
6 5 billion. They -- even that instrument continued
7 to upgrade over time, and so I can't give you an
8 exact number of what it was capable of in 2017
9 without looking it up.

10 Q Is that number you just provided to the
11 number of unique molecules that are sequenced
12 simultaneously on the HiSeq X Ten instrument?

13 MS. KHANDURI: Objection. Form.

14 Relevance. Scope.

15 A To be precise, the Illumina sequencing
16 technologies are not single-molecule sequencers.
17 So the way they function is a little more
18 complicated than unique molecules.

19 Roughly speaking, that instrument should
20 have been capable of doing -- of producing about 1
21 billion sequences of roughly 150 base pairs in
22 length on each end of the input molecule.

1 Q And if the original sample was composed
2 entirely of mRNA, how many molecules would that 1
3 billion fragments represent?

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

6 A I'm not sure the answer can be provided
7 in the way the question is asked.

8 To the best of my knowledge, the Illumina
9 sequencer is not capable of directly sequencing
10 mRNA.

11 Q If mRNA was reverse transcribed in cDNA
12 and sequenced on the Illumina HiSeq X Ten
13 instrument, how many molecules can be
14 simultaneously sequenced?

15 MS. KHANDURI: Objection. Relevance.
16 Form. Scope.

17 A Broadly speaking, the Illumina sequencers
18 circa 2017 would have produced roughly 1 billion,
19 the current number is 25 billion. But roughly 1
20 billion unique sequences. A POSA would be
21 unlikely to achieve that, but possible in certain
22 situations.

1 Generally a POSA would have made -- made
2 cDNA that was compatible with the Illumina
3 sequencers. And it would have been quite common
4 to PCR that cDNA, which tends to produce what are
5 called PCR duplicates. So the one generally does
6 not count the PCR duplicates when assigning unique
7 molecules, but some individuals do.

8 So if they got 1 billion sequences out,
9 that would be up to 1 billion cDNAs.

10 Q In forming your opinions did you apply
11 the definitions in So-456?

12 MS. KHANDURI: Objection. Form.

13 A Definitions of what?

14 Q The definition of terms within So-456.

15 MS. KHANDURI: Objection. Form.

16 A Sorry. Did I -- did I read So-456 in the
17 context of itself?

18 Q Correct, in the context of a definition
19 provided for the terms within itself?

20 MS. KHANDURI: Objection. Form.

21 A Yes.

22 Q Did you understand that So-456 includes a

1 definition for amplicon?

2 A Can we bring it up?

3 Q If you can bring up Exhibit 1005, at
4 Paragraph 121.

5 (Exhibit 1005, previously marked, not
6 attached.)

7 A Paragraph 121. Is that correct?

8 Q Yes, Paragraph 121.

9 A Yes.

10 Q Do you agree that amplicon refers to the
11 product of copying the nucleic acid, wherein the
12 product has a nucleotide sequence that is the same
13 or complementary to at least a portion of the
14 nucleotide sequence of the nucleic acid?

15 A Can you please repeat your question?

16 Q If I can direct you to the first sentence
17 in that paragraph.

18 Do you agree that amplicon refers to the
19 product of copying the nucleic acid, wherein the
20 product has a nucleotide sequence that is the same
21 as or complementary to at least a portion of the
22 nucleotide sequence of the nucleic acid?

1 A I mean, that's what it says.

2 Q So in the context of So-456, you agree
3 that that is the definition that should be applied
4 to the term "amplicon."

5 Is that right?

6 A That's what it says.

7 Q In the context of So-456, do you agree
8 that an amplicon can be a single copy of a
9 particular nucleotide sequence?

10 MS. KHANDURI: Objection. Form.

11 A That's what it says.

12 Q In the context of So-456, do you agree
13 that a first amplicon can be a complementary copy
14 of a target nucleic acid?

15 A Again, that's what it says.

16 Q Now I can direct you to Paragraph 122.

17 A Yes.

18 Q In the context of So-456, do you agree
19 that there can be at least 10,000 copies of a
20 template from amplification reaction?

21 A Paragraph 122 says as few as one and as
22 many as 10,000 copies.

1 Q Dr. Spellman, are you saying the maximum
2 number of copies is 10,000?

3 MS. KHANDURI: Objection. Form.

4 A My apologies. It says at least one and
5 as many as at least 10,000.

6 Q So do you agree that there can be at
7 least 10,000 copies of a template from an
8 amplification reaction?

9 MS. KHANDURI: Objection. Form.

10 A Paragraph 122 instructs a POSA to modify
11 their replication technology to influence
12 amplification yield and control the number of
13 copies as they see fit from as -- at one copy to
14 as many as 10,000 or more copies.

15 Q In So-456, how many probes does the
16 method start with?

17 MS. KHANDURI: Objection. Form.

18 Foundation.

19 A What is your definition of the word
20 "probe"?

21 Q Dr. Spellman, you opined on Figure 9 of
22 So-456 in this case.

1 Is that correct?

2 A Yes.

3 Q In Figure 9 of So-456, there is a step
4 where probes are introduced to the sample.

5 Is that right?

6 A So-456 uses probes in a different context
7 than other documents in this case, and I just want
8 to be clear about what use of probe you're using.

9 Q In Figure 9 of So-456, in that method how
10 many probes are introduced to the sample?

11 MS. KHANDURI: Objection. Form.

12 A When you say "probes," do you need -- do
13 you mean the number of unique molecules, the
14 number of unique types of molecules, or something
15 else?

16 Q I'm referring to the number of probe
17 molecules that are introduced in the method.

18 A The unique --

19 MS. KHANDURI: Objection. Form.

20 A The unique number of physical molecules,
21 not the number of different types of molecules?

22 Q Correct.

1 MS. KHANDURI: Objection. Form.

2 A Sorry, I'm looking for the section where
3 it would describe the ...

4 Pardon me. Let me go to my declaration.

5 I don't believe it specifies the exact
6 number of molecules of each of the -- of the DNA
7 sequences that bind to the template.

8 Q Based on your understanding of the method
9 in So-456, can you provide an estimate of how many
10 unique molecules of probes would be used?

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

13 A Off the top of my head, I'd have to read
14 the literature more closely.

15 Q Did you perform that analysis as part of
16 this case?

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

19 A I examined the So-456 reference. I
20 presumed it was enabled. And I considered whether
21 or not I thought it was a reasonable thing that a
22 POSA could practice. And so in that context I

1 did.

2 But I did not perform a specific analysis
3 as to the number of molecules of each
4 oligonucleotide I might use.

5 Q Based on your understanding of So-456,
6 can you provide an estimate on the proportion of
7 probes that hybridize to the captured probes?

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

10 A I have not considered that. The
11 specification describes a -- as few as one cycle
12 of amplification, and as many as 10,000. And I
13 believe it would be, therefore, a function of what
14 worked best for the POSA in that application. But
15 presumably as few as -- it could be a very high
16 fraction, given that they propose a small number
17 of cycles.

18 Q When you say a "high fraction," what
19 would that be in percentage?

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

22 A If a POSA were going to implement this,

1 they -- and use a small number of cycles of
2 amplification, it would have to be above 10
3 percent binding for it to be useful.

4 But again, a POSA would choose that
5 number appropriately.

6 Q Is there a maximum percentage of binding
7 that a POSA can realistically expect?

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

10 A When collecting the amplicons, which
11 include the original extended and ligated
12 molecule, I don't know that there is an intrinsic
13 limit on what fraction of molecules are collected.

14 My impression would be that the POSA
15 would choose a number of cycles that allowed the
16 system to work well.

17 Q Of the molecules that are captured by the
18 array in So-456, what percentage of them are
19 subsequently sequenced?

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

22 A The molecules captured on the array,

1 which include the original extended and ligated
2 probe -- probes, and which functionally meet the
3 definition of amplicon because they are copies of
4 the parent strand, once bound to the capture
5 probes of the array and extended should have quite
6 high yield, better than 50 percent, although I
7 don't know that to be sure.

8 MR. CHEUNG: We've been going a little
9 over an hour. Would you like a short break?

10 THE WITNESS: Sure.

11 MR. CHEUNG: Okay. Let's go off the
12 record.

13 (A recess was taken.)

14 BY MR. CHEUNG:

15 Q Dr. Spellman, if I can direct you to
16 Exhibit 1009, which is the '487 application. And
17 let me know when you're at Paragraph 233.

18 (Exhibit 1009, previously marked, not
19 attached.)

20 A This is on Page 52?

21 Q This is on Page 52, correct.

22 A Yes, I'm at Paragraph 233.

1 Q Please review the paragraph, and let me
2 know when you're ready.

3 A Yes, I've read 233.

4 Q What is your understanding of an
5 intermediary oligonucleotide as described in
6 Paragraph 233?

7 A There's a figure that I think illustrates
8 it fairly well. It's a synthetic DNA sequence
9 that bridges the photocleavable probe of the
10 specification with the target nucleic acid as
11 shown in Figure 14 of the specification
12 application.

13 Q Do you understand that the intermediary
14 oligonucleotide comprises a nucleic acid backbone
15 and is capable of binding a target nucleic acid?

16 A Yes.

17 Q Do you understand that the intermediary
18 oligonucleotide is a probe?

19 A The specification describes it that way,
20 that it -- that a POSA could think of it as a
21 probe. But it has different properties than the
22 set of things that are generally considered

1 probes.

2 And in Figure 14 the probe is labeled,
3 and the intermediate oligonucleotide is called an
4 intermediary oligonucleotide. It functionally has
5 different behaviors. And in the context of the --
6 of the system it is not of the same class as the
7 photocleavable probes, or cleavable probes shown
8 as probe.

9 Q But you do not disagree that Paragraph
10 233 states, "It could be said that the
11 intermediary oligonucleotide is a probe as defined
12 herein"?

13 A The specification does say that, yes.

14 Q What do you understand the economical
15 flexibility to be in the assay design described in
16 Paragraph 233?

17 A So the way 233 is structured, it proposes
18 nucleotides that lack the cleavable elements
19 because those elements are expensive, and
20 therefore it shifts those into reusable probes
21 that have target binding domains that can be
22 readdressed to the target nucleic acid using the

1 intermediate oligonucleotide that binds to the
2 target binding domain of the probe and the target
3 nucleic acid.

4 Q Does the paragraph state that the probe
5 is more expensive than the intermediary
6 oligonucleotide because the probe has a cleavable
7 linker in it?

8 A The paragraph says, This allows
9 economical and rapid flexibility in an assay
10 design, as the target (present in a sample)
11 -specific components of the assay are included in
12 inexpensive and widely available synthetic DNA
13 oligonucleotides rather than the more expensive
14 probes."

15 The principal difference between the
16 synthetic DNA oligonucleotides and the more
17 expensive probes are the photocleavable elements,
18 or other cleavable elements.

19 It does not note that synthetic DNA
20 oligonucleotide is modified in any way. It
21 describes it as inexpensive and widely available.

22 Q Does it states in Paragraph 233 why the

1 probes are more expensive?

2 MS. KHANDURI: Objection. Scope.

3 Relevance.

4 A Explicitly, no. It implies that the
5 differences between what the probes are and the
6 synthetic DNA oligonucleotides, the indirect
7 hybridization pieces, the principal difference
8 between them is the cleavable linker.

9 Q The last sentence of Paragraph 233, what
10 is your understanding of why there is an infinite
11 variety of target nucleic acids present in a
12 sample in different experiments?

13 A Sorry, I'm not sure I understand your
14 question.

15 Q Do you see the sentence which says,
16 "Therefore, a single set of indirectly binding
17 probes can be used to detect an infinite variety
18 of target nucleic acids present in a sample in
19 different experiments simply by replacing the
20 target specific synthetic oligonucleotide portion
21 of the assay"?

22 Do you see that sentence?

1 A Yes.

2 Q What is your understanding in that
3 sentence when it refers to "an infinite variety of
4 target nucleic acids present in a sample in
5 different experiments"?

6 A It is restating the advantage of the
7 intermediary oligonucleotide, which is cheap and
8 reprogrammable -- you can synthesize a large
9 number of them at will -- with the more expensive
10 probes which can then be made in bulk once, and
11 then be reprogrammed to the different target
12 nucleic acids that you might be interested in
13 measuring.

14 So it is simply the economic
15 consequence -- well, the practical consequence of
16 the economic argument favored above.

17 Q What do you understand the "rapid
18 flexibility in assay design" to be -- that is
19 described in Paragraph 233?

20 A If one had a set of probes that were
21 cleavable, one could order a set of intermediary
22 oligonucleotides that would bind to the probes and

1 allow them to bind to new places, new nucleic
2 acids, that -- relatively straightforwardly.

3 Q So based on your understanding, is the
4 "rapid flexibility in assay design" referring to
5 the speed with which you can replace the
6 intermediary oligonucleotide from one experiment
7 to the next?

8 MS. KHANDURI: Objection. Form.

9 A I'm not sure how to answer that. A user
10 would have to choose a new set of targets, have
11 those targets validated, link those targets to the
12 probe binding sequence that one wished to assign,
13 order those, validate that they worked properly.
14 And so it's -- and presumably do so on the scale
15 of hundreds or thousands or tens of thousands.

16 It would be cheaper, and speed and cost
17 are often related in this case. Things that are
18 laborious and tedious tend to cost more than
19 things that are fast and easy.

20 Q So based on your understanding, the
21 advantage of employing an intermediary
22 oligonucleotide which is economical and rapid

1 flexibility in an assay design, both advantages
2 refer to the same thing, which is cost.

3 Is that your opinion?

4 MS. KHANDURI: Objection. Form.

5 A I'm -- it explicitly says economical and
6 rapid flexibility. So it's tying them together.

7 Sometimes one has things that are fast
8 but expensive. And here it's saying that it's
9 both faster and cheaper to use this. So I
10 guess -- I guess it is both.

11 Q The advantage of rapid flexibility, is
12 that due to the speed with which the intermediary
13 oligonucleotide can be synthesized?

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

16 A Potentially. It describes the
17 intermediary oligonucleotide as inexpensive and
18 widely available synthetic DNA oligonucleotides,
19 rather than the more expensive probes. So it is
20 tying them together, economical and rapid.

21 Q So based on your understanding, is there
22 a speed advantage to employing an intermediary

1 oligonucleotide?

2 MS. KHANDURI: Objection. Form.

3 A Potentially. It ties them together.

4 Q So is it your opinion that potentially
5 there is no speed advantage to employing an
6 intermediary oligonucleotide?

7 MS. KHANDURI: Objection. Form.

8 A It -- the written description here tells
9 a POSA that it is faster and cheaper. That --
10 beyond that, I cannot elaborate.

11 The instruction to the POSA is that it is
12 faster and cheaper.

13 Q To clarify, Paragraph 233 does not state
14 a reason why using an intermediary oligonucleotide
15 is faster.

16 Is that right?

17 MS. KHANDURI: Objection. Form.

18 A It implies that they're inexpensive and
19 widely available, suggesting that the probes are
20 harder to make and perhaps more tedious to make.

21 It does not explicitly say that the
22 expensive probes. It says the DNA -- synthetic

1 DNA oligonucleotides rather than the more
2 expensive probes. It does not explicitly say that
3 the expensive probes are slower to manufacture.
4 It's implies, because it says that it is
5 economical and rapid to do this -- to do the
6 widely available ones. But it's not a -- but it
7 only applies cost to the expensive probe, and not
8 time to the expensive probes.

9 Q In Figure 9 of So-456, is it your opinion
10 that the original ligated probes that were bound
11 to the target analytes are collected along with
12 their amplified copies?

13 A I'm going to So-456, and to Figure 9 to
14 have it in front of me.

15 In Figure 9 the first step, 810, involves
16 binding Molecules 920 and 925 to their template
17 DNA. And in doing so, allowing the formation --
18 the Step 815 to occur, which is an extension
19 reaction, copying information from Molecule 910
20 into the Product 950. 950, the extension product
21 that copies information from 910, producing a
22 first copy of 910, is then ligated shut to create

1 a single-stranded molecule labeled 950. That
2 Molecule 950 then undergoes additional rounds of
3 replication after the first round of -- of
4 information copying from the template Molecule
5 910.

6 Those molecules all identified as 950 as
7 copies of 910 that are bound by the externally
8 added sequences 935 and 945 are captured onto the
9 array 110 at Site 935.

10 Q At Step 820 of Figure 9, are you saying
11 that there is only one replication cycle?

12 A As we discussed earlier, after the first
13 round of replication in Step 815 where the --
14 where the extension copying step happens, there is
15 at least one additional round of replication
16 indicated in 820.

17 The text describes, as we discussed, at
18 least up to 10,000 copies can be created.

19 Q Can there be more than 10,000 copies
20 created at Step 820?

21 A The specification describes at least up
22 to 10,000 and as few as one.

1 Q Does the specification provide an upper
2 limit to the number of copies that can be
3 generated?

4 A No.

5 Q So it could be a million copies.

6 Is that right?

7 A My understanding is that the constraints
8 around upper limits and lower limits in these
9 situations are evaluated by a POSA in context.
10 And a POSA would read it and understand that
11 10,000 is achievable, and more than 10,000 is
12 possible. And a POSA would then evaluate that.

13 Given that the numbers presented are one,
14 five, ten, 100, 1,000, 2,000, 3,000, I don't
15 believe that a POSA would extrapolate from 10,000
16 to a million, but it's not precluded.

17 Q To clarify, a million copies is possible.

18 Is that right?

19 A It is not --

20 MS. KHANDURI: Objection. Form.

21 A -- precluded.

22 Q So in Figure 9, Step 825, when molecules

1 are collected by hybridizing to the captured
2 probe, is it your opinion that both the original
3 ligated probes and their copies are collected?

4 A Step 825 shows Molecule 950, which is
5 represented by the first copy of the template as
6 shown in Step 815, as well as derived copies of
7 the template as shown in Step 820, binding to the
8 capture array.

9 Q Is it your opinion that the capture of
10 the original ligated probes meets the collecting
11 claim step in the '689 patent?

12 A Yes.

13 Q Is it your opinion that the capture of
14 the copies of the original ligated probe meets the
15 collecting claim step in the '689 patent?

16 A I'm going to my declaration.

17 On Page 73 of my original declaration,
18 Paragraph 137, I state, "Accordingly, So-456
19 method includes capturing whole ligated probes
20 formed by ligating the primary probe pairs that
21 diffuse from and are captured across the whole
22 tissue sample all at the same time."

1 Q Dr. Spellman, so in your opinion, does
2 the capture of the copies of the original ligated
3 probes that are generated during the amplification
4 reaction, do those molecules meet the collecting
5 claim step in the '689 patent?

6 A As I --

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

9 A I will reiterate that my declaration
10 identifies in Paragraph 137 that So-456 method
11 includes capturing whole ligated probes formed by
12 ligating the primary probe pairs that diffuse from
13 and are captured across the whole tissue sample
14 all at the same time.

15 Q So you're not able to say, sitting here
16 today, whether capture of the copies of the
17 original ligated probe meets the collecting claim
18 step in the '689 patent.

19 Is that right?

20 MS. KHANDURI: Objection. Form.
21 Misrepresents testimony.

22 A So the declaration is my testimony, the

1 entire declaration. And I specifically identify
2 that -- in Paragraph 137 that the method includes
3 capturing whole ligated probes that have been
4 amplified as part of the method. Form -- whole
5 ligated probes formed by ligating the primary
6 probe pairs.

7 Q Dr. Spellman, in Paragraph 137 when you
8 talk about capturing whole ligated probes formed
9 by ligating the primary probe pairs, are you
10 referring exclusively to the original ligated
11 probes?

12 A In Paragraph 137 I am referring to the
13 original ligated probes.

14 Q In Paragraph 137 are you referring to the
15 copies of the whole ligated probes in any way?

16 A The original Molecule 950 formed by
17 copying Molecule 910 creating the first copy of
18 the amplicon that will be captured in Step 825,
19 hence in 137 I am explicitly referring to the very
20 first copy of the amplicon formed by the extension
21 ligation reaction.

22 Q So to clarify, you are not referring to

1 the copies of the original ligated probes that are
2 generated during the amplification reaction at
3 Step 820.

4 Is that correct?

5 A That is not what I said.

6 Q Can you explain to me how Paragraph 137
7 refers to the copies of the original ligated
8 probes?

9 A What I stated was that at Step 815, the
10 first copy of the amplicon of the target region of
11 910 is created by the extension ligation reaction
12 that creates the molecule -- the first copy of
13 amplicon 950 -- 950. And that Molecule 950 then
14 undergoes subsequent rounds of amplification. And
15 in 137 I am explicitly referring to the first copy
16 of the Amplicon 950 created by the extension
17 ligation reaction.

18 Q Dr. Spellman, the Molecule 950 at Step
19 815 is an amplicon.

20 Is that right?

21 A The Molecule 950 is created by copying
22 information from Molecule 910 as required under

1 the term "amplicon," creating a single copy of
2 910, and that it is ligated closed.

3 Q Dr. Spellman, if you could go up to
4 Paragraph 135 of your original declaration,
5 Exhibit 1002?

6 A Paragraph 135, yes.

7 Q Do you see an annotated Figure 9 at
8 Paragraph 135?

9 A Sorry, Paragraph 135 on Page 72. Yes?
10 Figure 9 on Page 172? Confirm?

11 Q Yes. Are these your annotations?

12 A Yes.

13 Q Do you agree with these annotations?

14 A I'm not sure I understand the question.

15 Q Sitting here today, is there any reason
16 for you to change any of these annotations?

17 A Using -- the words on Page 72 are my own,
18 not the language of the '456 specification, which
19 uses a very specific definition.

20 And the language used on Page 72 is my
21 own language, rather than the language consistent
22 with '456, which would, in that context, the first

1 extension product copied from 910 would be an
2 amplicon.

3 Q Do you see in the annotation that
4 corresponds to Step 820 where you have added the
5 words "amplifying DNA molecule 950, ligated
6 probes, to produce Amplicon 950"?

7 A Yes.

8 Q Do you see the next annotation which
9 corresponds to Step 825 of Figure 9 where you
10 added the words "capturing Amplicons 950 at
11 capture sites 105"?

12 A Yes.

13 Q So at this step of capturing Amplicons
14 950 at capture site 105, are you saying that
15 copies of the original ligated probes generated at
16 Step 820 is captured?

17 A The -- my declaration in Paragraph 135
18 explicitly states, These Amplicons 950, i.e.,
19 ligated probes of the claim, are captured onto the
20 capture site 105."

21 My declaration equates the first amplicon
22 copy 950 synthesized by the extension ligation

1 reaction with any derived copies of 950
2 synthesized at Step 820.

3 Q So to use your language, "derived copies
4 of 950," does the capture of these derived copies
5 950 satisfy the collecting claim step in the 698
6 patent?

7 MS. KHANDURI: Objection. Form.

8 A As we've --

9 MS. KHANDURI: Scope. Relevance.

10 A Paragraph 137 says, "So's '456 method
11 includes capturing whole ligated probes formed by
12 ligating the primary probe pairs, capturing them
13 on the whole tissue sample at the same time."

14 Paragraph 137 is the whole ligated probes
15 of Step 815 which are the first copy of 910.

16 Q My question to you is a little different.

17 Are you able to give me a yes or no on
18 whether the capture of the derived copies of 950,
19 the ones generated at Step 820, do those meet the
20 collecting claim step of the '689 patent?

21 MS. KHANDURI: Objection. Scope.

22 Relevance.

1 A I don't believe I comment on that in my
2 clarification.

3 Q So you're not able to say one way or the
4 other today.

5 Is that right?

6 A I don't believe I comment on that in my
7 declaration, and I'm not prepared to form an
8 opinion about that right now.

9 Q Do you recall you stated at your previous
10 deposition that you are not a lawyer?

11 A I am not a lawyer.

12 Q So today you are still not a lawyer.

13 Is that correct?

14 A Still correct.

15 Q Given that you are not a lawyer, you
16 don't understand what incorporation by reference
17 is.

18 Is that right?

19 A I have been informed on what
20 incorporation by reference, and I can read from my
21 reply declaration if you'd like.

22 Q No. That's okay. So you relied on

1 attorneys to tell you what incorporation by
2 reference is.

3 Is that right?

4 A Let me go to my reply declaration.

5 In Paragraph 97 I have a discussion of
6 incorporating by reference, and my being informed
7 about it.

8 Q At Paragraph 97 of your reply
9 declaration, Exhibit 1055, you state that, and I
10 quote, "I understand that the '386 application is
11 not effectively incorporated into the '487
12 application."

13 Is that right?

14 A That is correct.

15 Q Is that a statement of your opinion?

16 A I was informed by counsel, and I
17 understand that that is true.

18 Q So that is an assumption that you
19 obtained from counsel.

20 Is that correct?

21 A It's a piece of information I obtained
22 from counsel.

1 Q Do you have your own independent
2 understanding of why the '386 application is not
3 effectively incorporated into the '487
4 application?

5 A Only what is written in Paragraph 97.

6 Q And what is written in Paragraph 97?

7 A I can read it, if you'd like.

8 Q Sure. Go ahead.

9 A "Second, Dr. Sherman relies on
10 disclosures in U.S. Patent Application Number
11 14/946386 that Dr. Sherman represents is
12 incorporated by reference into the '487
13 application in Paragraph 64, 216, and 227,
14 reference 2006, Paragraph 96, reference 1009
15 Paragraph 64, 216, 227. I note that the '487
16 application purports to incorporate U.S.
17 2014946386 and not U.S. Patent Application Number
18 14/946386. I understand that the '386 application
19 is not effectively incorporated into the '487
20 application."

21 Q Is your understanding of why the '386
22 application is not effectively incorporated into

1 the '487 application entirely from your
2 conversation with counsel?

3 A Yes.

4 Q Moving on to Paragraph 98.

5 You state that, "Even if the '386
6 application were properly incorporated into the
7 '487 application, it is incorporated by
8 disclosures of the sequencing methods."

9 Is that right?

10 A That's what's written.

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

13 Q Is that also an assumption you obtained
14 from attorneys?

15 A In this case I can go to the U.S. 2014 --
16 sorry, the U.S. Patent Application 14/946386 and
17 see that it is referring to sequencing methods,
18 and it's -- and it's about incorporating
19 enzyme-free methods of sequencing. And I can see
20 that the '487 application discusses this
21 application in the context of sequencing.

22 Q So this opinion that the '386 application

1 is incorporated for disclosures of sequencing
2 methods, that is your opinion.

3 Is that right?

4 A If we go to the '487 application,
5 Paragraph 216 is the first reference to this, to
6 the term U.S. 2014/946386. It says, "A hybridized
7 product produced in Step 4 can be sequenced using
8 an enzyme-free method of sequencing. Enzyme-free
9 methods of sequencing have been described."

10 This paragraph instructs a POSA that they
11 can use enzyme-free methods to sequence the
12 products. And that if they want to find out about
13 that, they should go to this other reference.

14 Q Dr. Spellman, I'm going to need a yes or
15 no from you on whether your opinion that the '386
16 application is incorporated for disclosures of
17 sequencing methods, it's your opinion independent
18 from what you obtained from counsel?

19 MS. KHANDURI: Objection. Form.

20 A As I said, a POSA, reading this
21 description, would understand that they should use
22 the methods in U.S. 2014/946386 for sequencing.

1 Q So that is your opinion. You're opining
2 on this.

3 Is that correct?

4 A That is correct.

5 Q At Paragraph 216 of the '487 application,
6 which is Exhibit 1009, do you see the last phrase
7 where it says, "Each of which is incorporated
8 herein by reference in its entirety"?

9 A Yes.

10 Q Do you agree that reference in its
11 entirety refers to the entire '386 application?

12 A The entire documents referenced in
13 Paragraph 216 are included for the purpose of
14 enzyme-free methods of sequencing.

15 Q And we can go to Paragraph 227 of the
16 '487 application, Exhibit 1009.

17 A Yes.

18 Q Do you see here it also has the last
19 phrase, which says, "Each of which is incorporated
20 herein by reference in its entirety"?

21 A Again, 227 is directed towards
22 enzyme-free methods of sequencing that have been

1 described in these two citations. And it says a
2 POSA should follow instructions in those
3 applications for enzyme-free sequencing.

4 Q Did you perform an analysis of which
5 portion of the '386 application is incorporated
6 into the '487 application before you submitted
7 your reply declaration?

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

10 A The '487 application directs a POSA to
11 study this in the context of enzyme-free methods
12 of sequencing.

13 Q Did you form an analysis of which portion
14 of the '386 application discusses enzyme-free
15 methods of sequencing?

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

18 A The entire application '386, as I
19 understand it, is directed towards methods of --
20 enzyme-free methods of sequencing.

21 Q So your testimony today is that the
22 entire '386 application is incorporated into the

1 '487 application?

2 MS. KHANDURI: Objection. Objection.

3 Form.

4 A Paragraph 227 and the preceding paragraph
5 both state that the entire reference is
6 incorporated in its entirety in the context of
7 enzyme-free methods of sequencing.

8 Q Is it your testimony that there are no
9 portions of the '386 application which are not
10 about enzyme-free methods of sequencing?

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

13 A I would have to read the methods very
14 closely to be confident of that.

15 Q Sitting here today, are you aware of any
16 portions of the '386 application which are not
17 about enzyme-free methods of sequencing?

18 MS. KHANDURI: Objection. Scope.
19 Relevance.

20 A At this moment, I cannot identify
21 sections of the U.S. 2014386 that are not
22 referring to enzyme-free methods of sequencing.

1 Q Based on your understanding, the entire
2 '386 application is about enzyme-free methods of
3 sequencing.

4 Is that right?

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

7 A Paragraph 227 and the paragraph we looked
8 at before, instruct a POSA to look at '386 for
9 enzyme-free methods of sequencing for written
10 descriptions of enzyme-free methods of sequencing.

11 A POSA is not directed to look at
12 anything else. There may be other components of
13 that application, but the paragraph referenced
14 here and the preceding one we looked at don't
15 point a POSA there for any other reason.

16 Q Prior to today, did you review the '386
17 application to identify which portions are not
18 directed to enzyme-free methods of sequencing?

19 MS. KHANDURI: Objection. Form. Scope.
20 Relevance.

21 A No.

22 Q If I can direct you to Paragraph 125 to

1 127 of your reply declaration, which is Exhibit
2 1055.

3 A Paragraph 125 to 127, Pages 61, 62?

4 Q That's right.

5 A Yes.

6 Q You're not providing an opinion on
7 whether the '607 application, Exhibit 2009, is
8 incorporated by reference into the '487
9 application. Correct?

10 A Can you repeat your question?

11 Q You are not providing an opinion on
12 whether the '607 application, Exhibit 2009, is
13 incorporated by reference into the '487
14 application. Correct?

15 A I do not believe that I render an opinion
16 on that.

17 Q If you can go to Paragraph 133 to 137,
18 also on your reply declaration.

19 A Yes.

20 Q You are also not providing an opinion on
21 whether the '774 application, Exhibit 2010, is
22 incorporated by reference into the '487

1 application. Correct?

2 A I see nothing in my declaration that
3 comments on whether or not the '774 is properly
4 included.

5 Q So to clarify, you are not rendering an
6 opinion on whether the '774 application is
7 incorporated by reference into the '487
8 application. Correct?

9 A I do not believe that I have rendered an
10 opinion.

11 Q And if you can turn to Paragraph 142 of
12 your reply declaration.

13 A Yes.

14 Q You are not providing an opinion on
15 whether the '111 application, Exhibit 2012, is
16 incorporated by reference into the '487
17 application. Correct?

18 A I do not have any section of my document
19 at Page 70-71 that renders an opinion on that.

20 Q If you can bring up Exhibit 2008, which
21 is the '386 application. And let me know when
22 you're at Paragraph 11.

1 (Exhibit 1008, previously marked, not
2 attached.)

3 A Paragraph 11 on Page 2? Paragraph --
4 yeah.

5 Q I think Paragraph 11 is on --

6 A Oh, it's Page 45. It's numbered Page 2
7 of the patent, but it's Page 45 of the PDF.

8 Q Right. Okay, I think we're on the same
9 page.

10 Please review Paragraph 11 and let me
11 know when you're done.

12 A I have read it once briefly.

13 Q Do you agree that Paragraph 11 describes
14 a enzyme-free method of sequencing?

15 A I believe I've read the document -- the
16 section, and I believe it describes a method for
17 sequencing and no mention of enzymes.

18 Q So do you agree that the method described
19 in this paragraph is incorporated by reference
20 into the '487 application?

21 MS. KHANDURI: Objection. Scope. Form.

22 A I'd have to cross-apply the various

1 identifiers. I don't have the -- if you want to
2 bring up the -- point me to where in the '487 it
3 references this, I'd be happy to check.

4 Q I believe we are looking at Paragraph 216
5 and Paragraph 227 of the '487 application, which
6 is Exhibit 1009.

7 A So in Paragraph 227 it lists two things,
8 U.S. 2014/946386 and U.S. 15/819151. I don't see
9 this -- I have open U.S. 2016/0194701. So I don't
10 see that reference there.

11 Q Assuming that Paragraphs 216 and 227 of
12 the '487 application refers to Exhibit 2008, is
13 Paragraph 11 incorporated by reference into the
14 '487 application?

15 MS. KHANDURI: Objection. Objection.
16 Scope. Relevance. Form.

17 A I don't understand the question, Counsel.
18 Let me close some documents, which might make this
19 a little easier for me.

20 MS. KHANDURI: While Dr. Spellman is
21 doing that, can we take a break soon? It's been
22 more than an hour.

1 MR. CHEUNG: Just a few more minutes to
2 finish this line of question.

3 MS. KHANDURI: Sure.

4 A Okay, I have the '487 application open.
5 The Paragraph 227, it references two documents,
6 U.S. 2014/946386 and U.S. 15/819151. Neither of
7 those appear to be U.S. 2016/0194701, so I don't
8 think so.

9 Q My question is, assuming that Paragraph
10 216 at 227 of the '487 application refers to the
11 '386 application at Exhibit 2008, does Paragraph
12 11 of Exhibit 2008, is it incorporated into the
13 '487 application as an enzyme-free method of
14 sequencing?

15 MS. KHANDURI: Objection. Scope.
16 Relevance. Form.

17 A You are instructing me to interpret U.S.
18 2014/946386 to be equivalent to 2016/0194701 A1?

19 Q I'm instructing you to equate Exhibit
20 2008 with U.S. 2014/946386 in Paragraph 227 of the
21 '487 application.

22 A Gotcha. Okay. Yes. I'm now -- I have

1 linked Exhibit 2008 to the '386 string in my head.
2 Yes.

3 Q Under such an assumption, would Paragraph
4 11 in Exhibit 2008 be incorporated by reference
5 into the '487 application?

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

8 A A person of ordinary skill in the art
9 would have come to this application, '701, Exhibit
10 2008, titled Enzyme and Amplification-Free
11 Sequencing, found that that was consistent to the
12 Paragraph 227 directing them to enzyme-free
13 methods of sequencing having been described as
14 shown in 227, and would then incorporate this
15 entire reference in the context of enzyme-free
16 methods of sequencing, of which Paragraph 11
17 appears to be an example.

18 Q Do you agree that Exhibit 2008 discloses
19 sequencing probes?

20 A Exhibit 2008 describes -- in Paragraph 11
21 describes a first population of sequencing probes.

22 Q Do you agree that the sequencing probes

1 hybridized to a target nucleic acid?

2 A Paragraph 11 says, "The method comprises
3 steps of hybridizing a first population of
4 sequencing probes to a target nucleic acid."

5 Q So do you agree that Exhibit 2008
6 discloses sequencing probes that hybridize to a
7 target nucleic acid?

8 A In Paragraph 11 they are mobilized on a
9 substrate. There's a set of conditions there, but
10 yes.

11 Q If I can direct you to Paragraph 12 of
12 Exhibit 2008.

13 Do you agree that Exhibit 2008 discloses
14 de-hybridizing sequencing probes from the target
15 nucleic acid?

16 MS. KHANDURI: Objection. Form.

17 A Yes, I've had a chance to read Paragraph
18 12. What's your question again?

19 Q Do you agree that Exhibit 2008 discloses
20 de-hybridizing sequencing probes from the target
21 nucleic acid?

22 A In the context of sequencing DNA without

1 enzymes, Paragraph 12 describes embodiments where
2 more than one population of probes are used and
3 de-hybridizing sequencing probes, i.e. those
4 probes used in the process of sequencing, of a
5 first population, is performed. And then later on
6 a second population.

7 Q In the context of the application itself,
8 do you agree that Exhibit 2008 discloses
9 denaturization?

10 MS. KHANDURI: Objection. Form.

11 A It hasn't explicitly used those terms in
12 Paragraphs 11 or 12 that I see.

13 MS. KHANDURI: Counsel, how much longer
14 would you go on? Can we take a break?

15 MR. CHEUNG: Just a few more minutes.

16 Q So would that be a yes or no,
17 Dr. Spellman?

18 A It describes a dehybridization.

19 Q And your opinion is dehybridization
20 different from denaturization?

21 A Yes. Denaturation is a broader term than
22 dehybridization.

1 Q So is it correct to say dehybridization
2 is a subset of denaturation?

3 A I would have to think about it. The use
4 of denaturation and the use of dehybridization,
5 they're not synonyms. And I'm not sure that
6 dehybridization is always a subset of
7 denaturation. I haven't given it a great deal of
8 thought.

9 I suspect there are cases in which
10 dehybridization would not be denaturation.

11 Q Are there cases where dehybridization can
12 be considered denaturation?

13 A Probably.

14 Q Can you provide an example where both the
15 terms "denaturation" and "dehybridization" can be
16 applied?

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

19 A "Dehybridization" is a very specific
20 phrase that has substantial connotation.

21 I'm -- normally one would use
22 dehybridization to describe a controlled process

1 by which something one had previously
2 intentionally bound to what would normally be a
3 nucleic acid, although someone -- some individuals
4 may use it in other contexts -- and then one --
5 one wanted to remove that molecule after one had
6 attached it to -- you know, to two DNA strands
7 binding to one another.

8 It's -- it is surely a phrase that one
9 would understand. But ways in which they would
10 distinguish it from denaturization could be quite
11 complicated.

12 Denaturization is quite a bit broader
13 concept and has much broader implications and
14 consequences; whereas dehybridization is normally
15 used in the context of something that a person is
16 doing, controlled reaction.

17 I think that's the best answer I can give
18 you.

19 Q Can two nucleic acids being separated and
20 no longer hybridized be described both as
21 dehybridization and denaturation?

22 A If I have two oligonucleotides bound to

1 one another and I cause them to separate, could I
2 describe that both as dehybridization and
3 denaturation? In that context they would both
4 have -- they would have dehybridized, if I had
5 previously hybridized them to one another. That's
6 sort of the context of dehybridization, is that
7 you previously made it bound. And the -- I think
8 a POSA would say that one method for
9 dehybridization could be denaturation. But I
10 don't think they're synonyms even there, because
11 one could have used an enzyme, for example, to
12 separate the two strands, or one could have
13 systematically degraded one of the strands,
14 dehybridizing it by destroying it. And I don't
15 think that's an incompatible use of
16 dehybridization.

17 Q If you had two nucleic acids bound to
18 each other and the temperature was increased such
19 that the two strands are no longer bound to each
20 other, would that be considered dehybridization?

21 MS. KHANDURI: Objection. Form.

22 A Then I think there is a connotation of

1 having intentionally previously bound the strands
2 together. So one would normally say in PCR that
3 the first step of PCR is denaturation. One
4 normally would put in double-stranded DNA, and one
5 wants to separate the two strands, it would be
6 uncommon in that use case to describe that as
7 dehybridization.

8 But if one had previously annealed two
9 DNA sequences together for some reason, and then
10 put them into PCR, one might have performed
11 dehybridization, and therefore it may or may not
12 be synonymous in that very specific context.

13 MS. KHANDURI: Can we take a break?

14 MR. CHEUNG: Let's take a break here.

15 Yeah, let's go off the record.

16 (A recess was taken.)

17 BY MR. CHEUNG:

18 Q Dr. Spellman, during break did you speak
19 with anyone?

20 A No.

21 Q If you can bring up Exhibit 1001, which
22 is the '689 patent, and go to the claims.

1 A In the files that I was sent this
2 morning, I don't have Exhibit 1001.

3 Q Okay.

4 A/V TECHNICIAN: I don't have it either,
5 Counsel.

6 MR. CHEUNG: Let me see if I can rectify
7 that quickly. Let me find the link.

8 (A discussion was held off the record.)

9 (Exhibit 1001, previously marked, not
10 attached.)

11 A Yes, I have Exhibit 1001.

12 Q Do you see that Claim 1E requires, quote,
13 "Performing an extension reaction that
14 incorporates at least one nucleic acid sequence
15 that identifies the second location of the tissue
16 sample into each of the nucleic acid probes or
17 portion thereof collected in Step C, thereby
18 forming a second plurality extension products that
19 comprise the nucleic acid probes or probes
20 thereof, collected in Step C and D, at least one
21 nucleic acid sequence that identifies the second
22 location of the tissue sample"?

1 A Claim 1E as read.

2 Is that correct?

3 Q Yes.

4 A Yes, I see Claim 1E paragraph and steps.

5 Q Okay. What is your understanding of the
6 extension reaction in that step?

7 A I'm going to my original declaration.

8 Can you repeat your question?

9 Q What is your understanding of the
10 extension reaction step?

11 A Steps D and E, or just E?

12 Q I think for our purposes they're
13 essentially the same, so you can speak to either
14 one.

15 A Targets, analytes that are being
16 spatially detected have had nucleic acid probes
17 bound to them in Step A. Those nucleic acid
18 probes or portions thereof were collected in Step
19 B as claimed. The collected probes in Step C
20 are -- yeah. So Steps B and C are collecting the
21 probes at at least two locations. And then the
22 collected probes are extended, incorporates a

1 nucleic acid sequence identifying the locations.

2 So that's a spatial barcode in the language of

3 my -- of my declarations.

4 Q It is your opinion that So-456 discloses
5 this claimed extension reaction step.

6 Is that right?

7 A Paragraph 170 of my initial declaration,
8 in my opinion So-456 includes these extension
9 steps.

10 Q So that would be a yes?

11 A That is a yes.

12 Q Can you turn to Paragraph 47 of your
13 reply declaration, Exhibit 1055.

14 (Exhibit 1055, previously marked, not
15 attached.)

16 A Paragraph 47 or Page 47? Apologies.

17 Q Paragraph 47.

18 A Yes, Paragraph 47 of my reply, yes.

19 Q Okay. Do you see that you have included
20 an annotated figure in that paragraph?

21 A I reference an annotated version of
22 Figure 9, yes, on the next page, 23.

1 Q And that, the annotation you added to
2 Figure 9, is to add red arrows, one pointing
3 upwards and one pointing downwards.

4 Is that correct?

5 A That is correct.

6 Q Can you explain this figure?

7 A The So-486 application -- sorry, So-456
8 application, intends that the amplicons which
9 include the original ligated probe shall bind to a
10 capture array, 110. And using a DNA directed DNA
11 polymerize, copy information from either Molecule
12 950 or from the bound oligo on the array, such
13 that both the original Molecule 950 and the
14 extension product of the molecule bound on the
15 surface of the array, should each contain the
16 information of the other.

17 Q And if I can direct you to Paragraph 48
18 of your reply declaration. Let me know when
19 you're there.

20 A Yes.

21 Q Do you see that you specifically point
22 out the reaction that occurs in the downward

1 direction in your annotated figure?

2 A I note that in the reaction depicted by
3 the downward arrow. Yes, I explicitly call that
4 out in this first sentence.

5 Q Just to be clear, is it your opinion that
6 the reaction that occurs as depicted by the
7 downward arrow is the extension reaction that
8 satisfied the extension reaction claim step in the
9 '689 patent?

10 MS. KHANDURI: Objection. Form.

11 A Yes.

12 Q Does the reaction as depicted by the
13 upward red arrow satisfy the extension reaction
14 claim step in the '689 patent?

15 MS. KHANDURI: Objection. Form.

16 A As I understand it, and I believe I've
17 opined -- the -- in my reply declaration in
18 Paragraph 7, the Board interpreted the term
19 "nucleic acid probes" to mean an oligonucleotide
20 comprising a target binding domain that binds to
21 one or more target analytes, and is modified after
22 collection to comprise a location identifying

1 nucleic acid sequence for use in identifying the
2 location of the target analyte.

3 In that context I have made the opinion
4 that the downward extension product includes the
5 oligonucleotides with a target binding domain
6 binding to the target analyte, which is then
7 modified after collection by the downward
8 extension.

9 The upward arrow would not meet that
10 criteria because the captured product is not being
11 modified -- sorry, the capturing oligo is not --
12 is being modified in that case to -- to include
13 information from 950, but the captured molecule is
14 only being modified in the downward direction.

15 Q So to clarify, you are relying only on
16 the reaction as depicted by the downward red arrow
17 to satisfy the claimed extension reaction step in
18 the '689 patent?

19 MS. KHANDURI: Objection. Form. Scope.
20 Relevance.

21 A The requirement under the IPR's board
22 determining that the nucleic acid probes being

1 modified after collection only -- the only -- only
2 the 950 downward extension product meets that
3 requirement in Figure 9.

4 Q And the reaction depicted by the upward
5 red arrow, just to reiterate, does not meet that
6 criteria.

7 Is that right?

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

10 A That's correct.

11 Q If I can direct you to Paragraph 67 of
12 your reply declaration.

13 A Yes.

14 Q You state that Figure 9 and Figure 6 have
15 the same design.

16 Do you see that?

17 A I do.

18 Q Further down in that paragraph, do you
19 see where you state that both extension products
20 can be used for downstream library generation?

21 A Yes.

22 Q Is it your opinion that only one of the

1 two strands is sufficient for downstream library
2 generation?

3 MS. KHANDURI: Objection. Form.

4 A When we look at Figure 9, both strands
5 would encode all of the necessary elements to go
6 into the next steps. So both strands would be
7 capable of further manipulation after the cleavage
8 of the 120 sequence releasing the bound -- the
9 product formed by the bound molecule -- sorry, by
10 the covalently attached to the substrate molecule.

11 Q So as an example, if only the strand
12 resulting from the extension reaction depicted by
13 the downward red arrow in your annotated figure
14 was released, would that be sufficient to generate
15 a downstream library according to So-456?

16 A According to Paragraph 67, as we've just
17 looked at, both extension products can be used for
18 downstream library generation. So either --
19 either or both.

20 Q Why do you think So-456 disclosure about
21 Figure 6 applies to Figure 9?

22 A So the architecture of Step 520 and the

1 architecture of Step 825 are analogous. A
2 single-stranded DNA molecule is bound to a
3 molecule on the surface. The numbering of the
4 elements is similar, leading a POSA to believe
5 that they are related. And the biochemistry
6 described is, to the best of my knowledge,
7 identical or nearly so.

8 Q Is it stated anywhere in So-456
9 explicitly that Figure 6 disclosure applies to
10 Figure 9?

11 A In Figure -- in Paragraph '142 of So, for
12 example, there is a direct relationship where the
13 capture region that they're labeling 135 is -- is
14 used to capture cDNA in Figure 6 and DNA amplicons
15 in Figure 9. So the POSA would understand that
16 they are related.

17 Q Are you aware of any other disclosure in
18 So-456 that relates Figure 6 to Figure 9?

19 A They are both examples of capturing DNA
20 onto the array with similar structures. And a
21 POSA would look to the entire specification to
22 understand how the system works.

1 Q Is it your opinion that So-456 teaches
2 the bidirectional extension reactions in your
3 annotated figure with the upward and downward red
4 arrows?

5 A Yes.

6 Q Is it your opinion that So-456 explicitly
7 teaches that bidirectional extension reactions in
8 your annotated figure?

9 A In my original declaration I -- in
10 step -- on Page 53, which is part of a long
11 paragraph that starts on Page 51, Paragraph 104,
12 the Step 5 of that identifies that preparing the
13 barcoded sequencing libraries includes all these
14 steps, the captured amplicons are available, the
15 three prime ends are available for enzymatic
16 extension. And that based on the teachings of
17 Figure 6, both extension products can be used for
18 downstream library generation when one has a
19 single-stranded DNA molecule bound to the capture
20 array, and the goal is to make double-stranded DNA
21 from that.

22 Q So you agree that So-456 explicitly

1 teaches this bidirectional extension reaction.

2 Is that right?

3 A So-456 explicitly teaches that in the
4 configuration of Figure 9, bidirectional synthesis
5 can happen, and both extension products are
6 available for downstream.

7 Additionally, the behavior of the
8 DNA-directed DNA polymerases is entirely
9 consistent with an inherent ability for the
10 DNA-directed -- DNA-directed DNA polymerases to
11 copy in -- the DNA in both directions up and down.

12 Q So that would be a yes?

13 A I believe it's explicit, yes.

14 Q To clarify, it is your opinion that
15 So-456 explicitly teaches the claimed extension
16 reaction step in the '689 patent?

17 A Under a whole set of assumptions that are
18 in my declaration, the down -- the extension --
19 the captured oligonucleotides that are ligated and
20 bound to the array are extended incorporating a
21 spatial barcode to meet all of the limitations of
22 the extension step of the '689 claims.

1 Q If you can turn to Paragraph 56 of the
2 reply declaration.

3 A Yes.

4 Q Do you see in that first sentence you
5 state that, "It is clear from Figure 6 full
6 disclosure that segment 130's identification as an
7 SBS primer region is a typographical error."

8 Do you see that?

9 A I do.

10 Q Can you explain why it is clear that that
11 is a typographical error?

12 A The short version summary of what I think
13 is quite clear in Paragraphs 56 and 57 and 58, is
14 that the specification from So-456 is teaching a
15 POSA to spatially detect nucleic acids using DNA
16 sequencing as an output. And that can only be
17 achieved if the products that go into DNA
18 sequencing have been tagged with spatial
19 information.

20 So a POSA, reading the specification,
21 would look for instruction on how to achieve that.
22 And based on the logic in Paragraphs 56, 57 and

1 58, would come to the conclusion that there are
2 typographical errors in the annotation for Figure
3 8 and 9. And that they can entirely be solved
4 consistent with the rest of the declaration using
5 the umbrella modeled shown on how to achieve this
6 in Figure 1 and 2.

7 Q So is it your opinion that Segment 130 in
8 Figure 9 has to be a spatial barcode?

9 A The last sentence of Paragraph 56 is my
10 conclusion. A POSA would readily know that
11 Segment 130 in Figure 9 and Figure 6's capture
12 probe is a spatial barcode. In Figure 6, a
13 different typographical error has occurred, in
14 which Segment 130 has two different functions that
15 are incompatible with one another. And as a
16 consequence, a POSA would look to all the other
17 figures identified midway through Figures 1B, 1C,
18 3, 4, 6, 7, et cetera, for clarification as to the
19 function of the sequences, knowing that the
20 purpose is spatial identification, and that a
21 spatial barcode must be present on the products to
22 achieve that.

1 Q So your opinion is that a POSA would
2 recognize that Segment 130 in Figure 9 is a
3 typographical error because the POSA will look to
4 Figure 6, which has a different typographical
5 error, and thus will look at the other figures to
6 resolve that.

7 Is that right?

8 MS. KHANDURI: Objection. Form.

9 A That's not quite what I said. I said a
10 POSA would look to the other figures, principally
11 the umbrella figure, Figures 1 and other figures,
12 to understand how spatial encoding is being
13 achieved. And the fact that Figure 6 also has a
14 typographical error would give the POSA even more
15 confidence because the specific Element 130 is
16 being doubly identified in different ways in
17 Figure 6, it would give the POSA confidence that
18 there really is a typo.

19 Q So your opinion is because Figure 6 has a
20 typo when Segment 130 serves two functions, a POSA
21 would be confident that the Segment 130 in Figure
22 9 must also be a typo?

1 MS. KHANDURI: Objection. Form.

2 A Figure -- Paragraph 56 lays that out.
3 Paragraph 57 and 58, they continued arguments as
4 to why a POSA would understand that Element 130 is
5 the spatial barcode, that are consistent with the
6 goals and the entirety of the specification as a
7 POSA would read it.

8 Q Is your opinion that a POSA would
9 recognize that Figure 9 contains a typographical
10 error as it pertains to Segment 130 because of the
11 error in Figure 6?

12 A As I highlight in Paragraph 56, a POSA
13 would also readily recognize that Figure 9's
14 disclosure repeats Figure 6 disclosure,
15 identifying Segment 130 as an SBS primer.

16 So it is far from the only reason that a
17 POSA would know that 130 is the spatial barcode,
18 but it is clear to the POSA that more than a
19 single mistake has been made.

20 Q But you agree that as printed, Segment
21 130 in Figure 9 is identified as an SBS primer.

22 Correct?

1 A Figure 6 and Figure 8-9 identify 130 as
2 the SBS primer region. And Figure 6 describes it
3 as an SBS sequencing primer -- sorry. Sorry.
4 They both -- Figure 6 describes an SBS primer
5 region. Figure 8-9 is an SBS sequencing primer.
6 In addition, Figure 6 also identifies it as a
7 spatial address.

8 Q And your opinion is that these are all
9 typographical errors. Correct?

10 A Yes.

11 Q Okay. If you can bring up Exhibit 1009,
12 which is the '487 application, and turn to
13 Paragraph 107.

14 A Paragraph 107, yes.

15 Q Do you see the second sentence in that
16 paragraph that starts with, "In a nonlimiting
17 example"?

18 A Yes.

19 Q Do you agree that the '487 application
20 teaches a probe with a cleavable linker?

21 A The '487 teaches a probe with a cleavable
22 linker, yes.

1 Q If you can turn to Paragraph 131, also of
2 the '487 application.

3 A Paragraph 131.

4 Q Do you agree that the '487 application
5 teaches that a nucleic acid adapter can include a
6 cleavable moiety?

7 A In Paragraph 131, which happens after
8 collection, they collect the -- a further nucleic
9 acid separate from the one bound to the -- to the
10 target analyte, can -- can contain a cleavable
11 moiety.

12 Q If you can turn to Paragraph 246.

13 A Yes, Paragraph 246.

14 Q Do you agree that the '487 application
15 teaches a probe with a cleavable motif?

16 A Yes.

17 Q If you can turn to Paragraph 317 of the
18 same application.

19 A Yes, Paragraph 317.

20 Q Do you agree that the '487 application
21 teaches that a target binding domain can be linked
22 to an identifiable oligonucleotide by a cleavable

1 linker?

2 A That is what is stated in 317, yes.

3 Q Does the '487 application require a
4 cleavable linker between the target binding domain
5 and the identifier oligonucleotide?

6 A So starting at Page 128 of my initial
7 declaration, I highlight that the '689 patent
8 claims do not have written description support for
9 the full scope of the '689 patents. And that is
10 because, as extensively documented, starting on
11 Page 129, the priority applications to the '689
12 patent disclose methods that use cleavable probes
13 and involve steps that occur on the target
14 analyte. And I have a very lengthy set of
15 references that show that all of the examples
16 meet -- have cleavable probes and involve steps
17 that occur on the target analyte. So that starts
18 at Page 129 of my original declaration and
19 continues onto 133.

20 Q So is it your opinion that the '487
21 application requires a cleavable linker between
22 the target binding domain and the identifier

1 oligonucleotide?

2 A The '487 priority application lacks
3 written description of -- of probes that are not
4 cleavable.

5 Q So is the answer yes, that the '487
6 application does require a linker between the
7 target binding domain and the identifier
8 oligonucleotide?

9 A I think my statement was that it lacks
10 written description support for such an example.

11 Q My question is, in the '487 application,
12 does the target binding domain and the identifier
13 oligonucleotide, do these two portions have to
14 have a cleavable linker between them?

15 MS. KHANDURI: Objection. Form.

16 A And I believe what I've answered is that
17 '689 patent does not benefit, as I say -- explain
18 clearly in Section 270, the '689 patent does
19 not -- claims priority benefit to the following
20 applications. But the priority applications --
21 the priority applications of the '689 do not
22 provide written description support for the full

1 scope of '689 claims under NanoString's
2 interpretation. As a result, the '689 patent
3 claims are not entitled to the filing date of
4 September -- before the patent's filing date of
5 September 16, 2021.

6 So there's -- the lack of written
7 description is the crux.

8 Q So are you able to tell me one way or the
9 other, sitting here today, does the specification
10 in the '487 application require a cleavable linker
11 between the target binding domain and the
12 identifier oligonucleotide?

13 MS. KHANDURI: Objection. Form.

14 A In Paragraph 48 I say, "The '689 patent's
15 methods require a user to collect proxies cleaved
16 off identifier oligonucleotides for the target
17 analytes from within a particular user-defined
18 region of interest of this tissue sample while
19 maintaining the target analyte spatial
20 information."

21 Q So is it your opinion that a probe in the
22 '487 application is required to have a cleavable

1 linker?

2 MS. KHANDURI: Objection. Form.

3 A In my declaration I identify many places
4 where I note that the methods require cleavable
5 probes; for example, in Paragraph 51.

6 "Importantly, the identifier oligonucleotide" is
7 separable from -- "is separable or released from
8 the rest of the probe upon application of a force,
9 and the released identifier oligonucleotide is
10 collected and analyzed."

11 Q Dr. Spellman, my question is not whether
12 the '487 application contains examples of
13 cleavable probes but, rather, whether the use of
14 such cleavable probes are required.

15 MS. KHANDURI: Objection. Form.

16 A In my reply declaration under Paragraph
17 7, I note that the -- that the Board interpreted
18 the term "nucleic acid probes" to mean an
19 oligonucleotide comprising a target binding domain
20 that binds to one or more target analytes, and is
21 modified after collection to comprise a
22 location-identifying nucleic acid sequence for use

1 in identifying the location of the target analyte.

2 In that case the Board has not required
3 that it have a cleavable element.

4 Q Are you able to render an opinion today
5 on whether a cleavable element is required of a
6 probe of the '487 application?

7 MS. KHANDURI: Objection. Form.

8 A As I've stated, every method in the '487
9 is a cleavable form. So all of the teachings are
10 toward cleavable probes. That is what a POSA
11 would learn from the application.

12 Q So are you prepared to say whether a
13 POSA, in light of the teaching, would find that a
14 cleavable probe is required in the '487
15 application's methods?

16 A As I've said, the Board interpreted the
17 claim "nucleic acid probe" to mean an
18 oligonucleotide comprising a target binding domain
19 that binds to one or more target analytes, and is
20 modified after collection to comprise a
21 location-identifying nucleic acid.

22 The Board's construction does not require

1 a cleavable element, to the best of my ability to
2 understand.

3 Q If you can turn to Paragraph 5 of the
4 '487 application.

5 A Paragraph 5, yes.

6 Q Does the word "cleave" or "cleavable"
7 appear in this paragraph?

8 A So Paragraph 5 requires binding of the
9 probe. The probe must contain a target binding
10 domain and an identifier domain. The identifier
11 must include a unique nucleic acid sequence
12 identifying the target. A force must be applied
13 that releases the identifier. And the identifier
14 must be collected. And then a series of things
15 happen to the identifier afterward.

16 No requirements are made that the target
17 binding domain is collected. And every version of
18 the methods presented in the application
19 separate -- include a cleavable -- a cleavable
20 probe that allows the release of the identifier.

21 So from a written description
22 perspective, all of the examples that a POSA would

1 understand exist from this application are ones in
2 which cleavable probes are used, because those are
3 the only ones provided where the application
4 teaches a POSA how to provide a force to a
5 location to release the identifier.

6 The crux of this disagreement lies on
7 providing a force to a location of the tissue
8 sample to release the identifier, which is the
9 entire basis of the -- perhaps being a little too
10 strong, but how one releases the identifier in a
11 specific location is critical. And all of the
12 examples of the '487 do so with a cleavable
13 linker.

14 You are correct that "cleave" or
15 "cleavable" does not appear in Paragraph 5.

16 Q Does the word "cleave" or "cleavable"
17 appear in Paragraph 6?

18 A Paragraph 6 mirrors nearly all of the
19 constraints of Paragraph 5 and adds some
20 additional ones. It requires a force to a
21 location to release the identifier. All of the
22 examples that meet this involve cleavable probes

1 and teach a POSA to use cleavable probes to
2 achieve this objective.

3 It does not explicitly require that the
4 probes are cleaved, nor does it say "cleave" or
5 "cleaved."

6 Q Does the word "cleave" or "cleavable"
7 appear in Paragraph 7?

8 A Paragraph 7 mirrors Paragraphs 5 and 6
9 with slight differences in downstream detection,
10 again requiring providing force to a location to
11 release the identifier, and all the examples use
12 cleavable probes to do so.

13 Q In Paragraph 7 there is no explicit
14 mention of "cleave" or "cleavable."

15 Is that right?

16 A That is correct.

17 Q If you can turn to Paragraph 18.

18 Do you see that a cleavable moiety is
19 mentioned in Paragraph 18?

20 A Yes, I do.

21 Q Is the cleavable moiety described here
22 between a target binding domain and an identifier

1 oligonucleotide?

2 MS. KHANDURI: Objection. Form.

3 A The enzymatically cleavable moiety here,
4 which is in contrast to the preferred
5 photocleavable moieties presented in the other
6 steps of the application, is post ligation and
7 handled, and is not used for spatial detection.
8 Or it's not used in the same way for spatial
9 detection.

10 Q So the cleavable moiety described here
11 is -- does not exist on a probe.

12 Is that right?

13 A Correct. It is -- it is added later on,
14 as I understand it.

15 Q If you can bring up your reply
16 declaration and turn to Paragraphs 72 to 74.

17 A I'm going to need a break pretty soon.
18 We're well past 1:00 p.m.

19 Q I expect we'll be done in the next few
20 minutes, so just bear with me.

21 A Yes, Paragraph 72.

22 Q Okay. In your reply declaration you

1 opine that treating a tissue sample to facilitate
2 probe binding would have been obvious.

3 Is that correct?

4 A That is the title of the legend above
5 Paragraph 72, "Treating a tissue sample to
6 facilitate probe binding would have been obvious."

7 Q Did you provide this opinion in your
8 first declaration?

9 A So in my initial declaration in Paragraph
10 125, which is on Page 65, under Anticipation, I
11 point out that treatment is provided. And that
12 continues on in Paragraph 126 and 127.

13 The logic behind those paragraphs extends
14 into my obviousness argument. And I believe I
15 port the arguments from -- from the anticipation
16 argument into the obviousness argument.

17 Q If I can direct you to Paragraph 75 in
18 your reply declaration.

19 A Yes.

20 Q You opine that ligating nucleic acids
21 would have been obvious. Correct?

22 A In which section of Paragraph 75 do I say

1 that?

2 Q I believe it's the title.

3 A I don't think that's my opinion. I think
4 that's just the title of the section.

5 Q Is your opinion that ligating nucleic
6 acids would not have been obvious?

7 A My apologies. If you look at -- if you
8 look on Page 38 midway through. Second, given
9 that ligation was a routine skill possessed by a
10 POSA, the POSA would easily have interpreted
11 So-456 method as teaching a ligation step between
12 the two probes in Figure 9.

13 Yes, I agree that ligation in the context
14 of Figure 9, the extension ligation reaction is
15 obvious.

16 Q Did you provide the opinions here in your
17 reply declaration, Paragraphs 75 to 76, in your
18 first declaration?

19 A So throughout my section on obviousness
20 based on So, I refer to the ligated -- the ligated
21 products I believe is how I refer to them. Let me
22 get you the exact -- ligated probes perhaps. Hold

1 on.

2 So again, Paragraph 230 I say that So-456
3 suggests the enzymatic extension of the 3 prime
4 end of the captured probes and the 3 prime end of
5 the ligated probe to be -- to incorporate a
6 spatial barcode. So from that it is clear that I
7 consider it obvious that the Figure 8 and 9
8 includes a ligation step.

9 I think my section here in Paragraph 75
10 is refuting the position from Dr. Sherman that
11 there is no ligation step, or there is no
12 ligation, which is nonsense. And I could not
13 reply to Sherman in my initial declaration because
14 I obviously didn't have his declaration.

15 The first time I replied to the assertion
16 there is no ligation is in this section. To my
17 mind, the fact that I identify ligated probes and
18 extension ligation reactions is more than enough
19 to overcome any assertion that I did not refer to
20 ligation as being obvious.

21 Q And can I direct you to Paragraph 77 in
22 your reply declaration.

1 A Yes.

2 Q You opined that adding a spatial barcode
3 by extension would have been obvious.

4 Is that correct?

5 A Yes.

6 Q In your reply declaration do you opine on
7 whether it would have been obvious to collect
8 ligated probes?

9 A In my reply do I collect ligated probes?

10 In the So-456?

11 Q Correct.

12 A I mean, it -- in this particular case
13 it's both explicit and inherent in the So-456
14 declaration -- specification. There's no reason
15 that it wouldn't happen. It essentially has to
16 happen, given the architecture of the system
17 shown. And in Figure 6 they explicitly say that
18 it should happen, there's benefit to it.

19 So I covered that in my initial
20 declaration. I believe it's also in my reply
21 declaration. I'd have to check.

22 Q Are you able to point to any specific

1 paragraph in your reply declaration where you
2 opine that it would have been obvious to collect
3 ligated probes and not their copies?

4 A Again, I think this is an issue of
5 inherency. Given the architecture of Figures 8
6 and 9, there's -- and the teaching, and explicit
7 in Figure 6 of So, that collection of the ligated
8 probes will happen in the architecture of Figure 9
9 where the ligated probes are captured -- sorry,
10 Figure 6 is irrelevant. That the architecture of
11 the system means that it's inherent, and the
12 labeling of the Molecules 950 indicates that all
13 of them are available. And that's in my reply
14 declaration and in my original declaration.

15 MS. KHANDURI: Counsel, can we take a
16 break? Dr. Spellman asked for a break about 20
17 minutes ago. It's been one-and-a-half hours or so
18 since we've been going.

19 MR. CHEUNG: Yeah, that's all for me, I'm
20 done.

21 MS. KHANDURI: So let's take a break,
22 half an hour break. Dr. Spellman can get lunch,

1 and we're going to do what we need to do.

2 (A recess was taken.)

3 EXAMINATION BY COUNSEL FOR PETITIONER

4 BY MS. KHANDURI:

5 Q Dr. Spellman, do you recall discussing
6 earlier today Paragraphs 56 through 58 of your
7 reply declaration in the context of typographical
8 errors in So-456's description of Figures 6 and 9?

9 A Yes.

10 Q Have you changed any of your opinions set
11 forth in Paragraphs 56 through 58 of your reply
12 declaration?

13 A No.

14 MS. KHANDURI: Thank you. We'll pass the
15 witness.

16 MR. CHEUNG: Yeah, I don't have anything.

17 MS. KHANDURI: Okay. Great. Thank you.

18 (Off the record at 5:09 p.m. EST.)
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ACKNOWLEDGMENT OF DEPONENT

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

(DATE)

(SIGNATURE)

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C E R T I F I C A T E

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

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

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

I further certify that the deposition of
PAUL T. SPELLMAN, Ph.D., occurred virtually, on
Thursday, December 19, 2024, from 12:05 p.m. to 5:09
p.m. EST.

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

7
8 IN WITNESS WHEREOF, I have hereunto set my
9 hand this 21st day of December, 2024.

10
11 My commission expires:

12 October 31, 2027

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14  

15 -----
16 E-NOTARY PUBLIC IN AND FOR THE
17 COMMONWEALTH OF VIRGINIA

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