UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.,
Petitioner

v.

BRUKER SPATIAL BIOLOGY, INC.,
Patent Owner

Case IPR2023-01300
U.S. Patent No. 11,473,142

REPLY DECLARATION OF PAUL T. SPELLMAN, PH.D.

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10x EX1055
10x v. Bruker
IPR2023-01300

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I, Paul T. Spellman, hereby declare as follows.

I. INTRODUCTION

1. I am over the age of 18 and competent to make this declaration.

2. I have previously provided a declaration dated September 25, 2023—my first declaration (EX1044)—in this proceeding in support of 10x Genomics, Inc.'s ("10x") Petition for the above-captioned *inter partes* review (IPR). The opinions I expressed in my first declaration remain unchanged. My professional background and qualifications discussed in ¶¶12-23 of my first declaration also remain unchanged. I am being compensated for my time in connection with this IPR.

3. I understand that this declaration accompanies 10x's Reply to Bruker Spatial Biology's ("Bruker") Patent Owner Response.[1] In preparing this declaration, I have reviewed Dr. Sherman's declaration (EX2008) and each of the documents cited therein, along with each of the documents cited in this declaration and in my first declaration in light of general knowledge in the art before February 12, 2018. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I have

[1] I understand that Bruker acquired NanoString, and Bruker is now the owner of the 142 patent.

also considered the viewpoint of a person of ordinary skill in the art ("POSA"), which I defined in my first declaration (EX1044, ¶¶25-26), prior to February 12, 2018.

II. LIST OF DOCUMENTS I CONSIDERED IN FORMULATING MY OPINIONS

4. In formulating my opinions, I have considered all the references and documents noted above, including those listed below.

Paper/Exhibit No.	Description
25	Decision on Institution ("DOI")
1005	International Patent Application Publication No. WO 2017/019456 A2 to So et al., published February 2, 2017 ("So456")
1015	"Visium Spatial Gene Expression Reagent Kits," 10x Genomics, Inc., Document No. CG000239, Rev. F, 2021
1016	Stahl *et al*., "Visualization and analysis of gene expression in tissue selections by spatial transcriptomics," *Science* 353(6294):78-82 (July 1, 2016), with attached Supplementary Materials
1017	International Patent Application Publication No. WO 2012/140224 A1 to Frisen *et al.*, published October 18, 2012
1022	NanoString Technologies, Inc.'s Initial Infringement Contentions with Attachment A and Exhibit 1, *10x Genomics, Inc. et al. v. NanoString Technologies, Inc.*, Case No. 1:22-cv-01375 (D. Del.), filed November 23, 2022
1042	U.S. Patent No. 10,329,600 to Fu *et al*., issued June 25, 2019

Paper/Exhibit No.	Description
1043	U.S. Patent No. 11,473,142 to Beechem *et al.*, issued October 18, 2022 ("142 patent")
1044	Declaration of Paul Spellman, Ph.D.
1048	Khodakov *et al.*, "Recent developments in nucleic acid identification using solid-phase enzymatic assays," *Microchem Acta,* 181(13-14):1633-1646 (2014)
1049	European Patent Application Publication No. EP 1114859 A1 to Ota *et al.*, published July 11, 2001
1056	Deposition Transcript of David Sherman, Ph.D. (January 30, 2025)
1057	Asp *et al*., "Spatial detection of fetal marker genes expressed at low level in adult human heart tissue," *Nature Scientific Reports*, 7:12941 (2017)
1058	Lieben, L., "Spatial transcriptomics in plants," *Nature Reviews Genetics* (2017)
2008	Declaration of Dr. David H. Sherman, Ph.D., in Support of Patent Owner's Response
2009	Transcript from the deposition of Paul T. Spellman, Ph.D., taken on Nov. 7, 2024
2013	Mercier, J., et al., "Solid Phase DNA Amplification: A Brownian Dynamics Study of Crowding Effects," Biophysical Journal, Vol. 89, No. 1, pp. 32-42 (2005)

III. CLAIM CONSTRUCTION

5. I understand that in a parallel district court litigation Bruker alleged that 10x's Visium FF infringes the 142 patent claims. In my first declaration, I

applied Bruker's interpretations according to its infringement positions. EX1044, ¶97; EX1022.

6. I further understand that in its decision granting institution of this IPR, the Board construed certain terms of the 142 patent claims. Dr. Sherman also provides constructions for these claim terms. I discuss these interpretations below.

A. "synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction"

7. Steps (c) and (d) of claim 1 recite the following:

> *[S]ynthesizing a first [and second] plurality of DNA products* by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) [and step (b)] as templates and incorporates at least one [spatial barcode] into each of the first [and second] plurality of DNA products.

EX1043, 147:42-53 (emphasis added).

8. I understand that, after 10x filed the Petition with my first declaration, Bruker argued that Visium FF's step 1 (first-strand cDNA synthesis) and step 2 (second-strand cDNA synthesis) *together* perform the claimed synthesis reaction ("Bruker's previous IPR position" or "Bruker's previous IPR interpretation"). EX1022, 18-20.

9. I understand that in its decision granting institution of this IPR, the

Board interpreted "synthesizing DNA products" as follows:

> We interpret "synthesizing DNA products" consistent with its usage in claim 1 as amplifying the collected plurality of oligonucleotides released after application of a force from the location of the sample using primers that 1) have binding sites on the collected oligonucleotide and 2) contain location-identifying nucleic acid sequences that are incorporated into the DNA product upon synthesis.
>
> …
>
> [W]e apply this construction, and interpret "synthesizing DNA products" *not* to require direct replication of the first cDNA strand – and only this strand – to create the end product, as Patent Owner urges.

DOI, 21-22, 40.

10. I understand that the Board found its interpretation consistent with the 142 patent specification's disclosure and with Bruker's previous IPR position. DOI, 22.

11. Thus, I understand that the Board interpreted "synthesizing DNA products" in steps (c) and (d) as encompassing multi-step synthesis resulting in DNA products containing location-identifying nucleic acid sequences. I further

understand that the Board interpreted the "DNA products" of steps (c) and (d) as not limited to the first cDNA strand – and only this strand. Instead, I understand that the Board interpreted "DNA products" of steps (c) and (d) to encompass the second-strand cDNAs (e.g., of Stahl and So-456).

12. Dr. Sherman disagrees with the Board, arguing that the Board's construction improperly equated "synthesizing" and "amplifying." EX2008, ¶31. Dr. Sherman is wrong. It is clear from the specification, claims, and Bruker's infringement interpretations that "synthesizing" in claim 1 includes "amplifying." For example, the specification repeatedly and consistently refers to amplification reactions as part of synthesizing DNA products. *See e.g.,* EX1043, 1:44-67, 2:1-25, 2:26-54, 3:24-47, 3:48-4:9, 4:34-5:2, 5:3-37, 5:44-6:8, 6:9-43, 6:44-7:9, 7:10-44, 8:18-52, 8:53-9:23, 9:24-58, 9:59-10:29, 11:1-25, 11:26-52, 12:29-57, 12:58-13:8, Examples 1-6. Claim 5 specifies that "synthesizing" in each of steps (c) and (d) comprises a specific type of amplification (solid-phase). EX1043, 148:37-41. And, Bruker's infringement contentions for claim 5 cite to second-strand cDNA synthesis in Visium FF for solid-phase amplification. EX1022, 32-34.

13. Moreover, the Board accurately understands that a synthesis reaction that uses an oligonucleotide as a template (as required in steps (c) and (d) of claim 1), is a copying reaction, where the first round of a copying reaction produces more molecules of the original molecule and is thus reasonably viewed as an

amplification reaction.

14. Dr. Sherman misapplies my deposition testimony (which was made in the general context of synthesis and amplification reactions) to a templated synthesis of steps (c) and (d). EX2008, ¶31. As I emphasized even in Dr. Sherman's quoted portions of my testimony, the difference between a DNA synthesis reaction and a DNA amplification reaction "would depend on context quite often." EX2008, ¶31 (citing EX2009, 28:3-29:22). And, as mentioned above, in the context of templated synthesis, a synthesis reaction is also an amplification reaction.

15. Dr. Sherman also misapplies the phosphoramidite synthesis example I provided during deposition. I identified phosphoramidite synthesis as one of the "examples of a synthesis reaction," which I explained encompassed a "far from limiting set of DNA synthesis reactions [that] include a nucleic acid polymerases … to synthesize templated polymers [i.e., templated synthesis]… [and] in vitro synthesis of molecules by, for example, phorphoramidite chemistry." EX2009, 28:11-29:5. As Dr. Sherman admits, phosphoramidite synthesis does not use a template, and thus, is irrelevant to the templated synthesis required in steps (c) and (d) of claim 1. EX1056, 31:3-5.

16. Without agreeing to its merits, I note that Dr. Sherman proposes the following meaning for "synthesizing a first plurality [and second plurality] of DNA

products by performing a synthesis reaction":

> A POSA would have understood this claim limitation to require a synthesis reaction that generates DNA products. As part of the synthesis reaction that results in DNA products, the remainder of claim 1(c) and 1(d) require the collected oligonucleotides to be used as templates and require the location-identifying sequences to be incorporated into the DNA products.

EX2008, ¶35.

17. I consider these interpretations in my opinions below.

B. "identifying a first [and second] plurality of DNA products by sequencing"

18. Step (e) of claim 1 recites the following:

> [I]dentifying the first plurality of DNA products and the second plurality of DNA products synthesized in step (c) and step (d) by sequencing the first plurality of DNA products and the second plurality of DNA products, thereby spatially detecting the plurality of oligonucleotides collected from the first location of the tissue sample and the plurality of oligonucleotides collected from the second location of the tissue sample.

EX1043, 147:54-61.

19. I understand that the Board interpreted the term "identifying a first plurality [and second plurality] of DNA products by sequencing" as follows:

> [L]ocating the specific target analyte within the tissue sample by correlating the DNA product using the location-identifying nucleic acid sequences.

DOI, 28, 37.

20. I understand that the Board found its interpretation consistent with the 142 patent specification's disclosure and with Bruker's previous IPR position. DOI, 28.

21. Dr. Sherman disagrees with the Board's interpretation because it allows "any method of determining the identity of DNA products that does not involve sequencing." EX2008, ¶29. Dr. Sherman is wrong. The Board's interpretation requires that the target analytes (i.e., collected oligonucleotides of claim 1) are located "*using* the location-identifying *nucleic acid sequences*," which are of course determined *by sequencing*.

22. Without agreeing to its merits, I note that Dr. Sherman proposes the following interpretation:

> "[L]ocating the specific target analyte within the tissue sample by correlating the DNA product using the location-

> identifying nucleic acid sequences, wherein the sequence of the DNA product and the sequence of the location-identifying nucleic acid sequences are determined via sequencing" is more aligned with how a POSA would understand the claim term[.]

EX2008, ¶29.

23. Thus, both the Board's and Bruker's previous IPR position encompass sequencing molecules that are different from the first-strand (and second-strand) cDNAs due to, e.g., addition of adapters and index sequences.

24. I consider these interpretations in my opinions below.

IV. TECHNICAL TERMINOLOGY

25. I am using the same terms as in the manner set forth in my first declaration. EX1044, ¶¶45-48.

26. Further, I use "location-identifying sequence(s)," "location-identifying nucleic acid sequence(s)," and "spatial barcode(s) interchangeably in this declaration.

V. GROUND 1: STAHL ANTICIPATES CLAIMS 1-4 AND 6-13

27. In my first declaration, I opined that, under Bruker's infringement interpretation, Stahl anticipates claims 1-4 and 6-13 of the 142 patent because Stahl teaches every element of the claims, arranged as claimed. EX1044, ¶¶98-159. I

offer the following additional comments in response to Dr. Sherman's declaration.

28. Dr. Sherman argues that Stahl does not "meet[] claim elements involving (1) sequencing DNA products; (2) synthesizing DNA products that incorporate a nucleic acid sequence that identifies location; and (3) amplifying a library using DNA products as templates." EX2008, ¶40. As I explain below, I disagree with Dr. Sherman's opinions.

A. As explained in my first declaration, Stahl teaches a method that includes steps (c) and (d) of claim 1 under Bruker's infringement interpretation

29. Claim 1's steps (c) and (d) (the "synthesizing steps" of claim 1) recite:

> [S]ynthesizing a first [and second] plurality of DNA products by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) [and (b)] as templates and incorporates at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample into each of the first [and second] plurality of DNA products.

EX1043, 147:42-53.

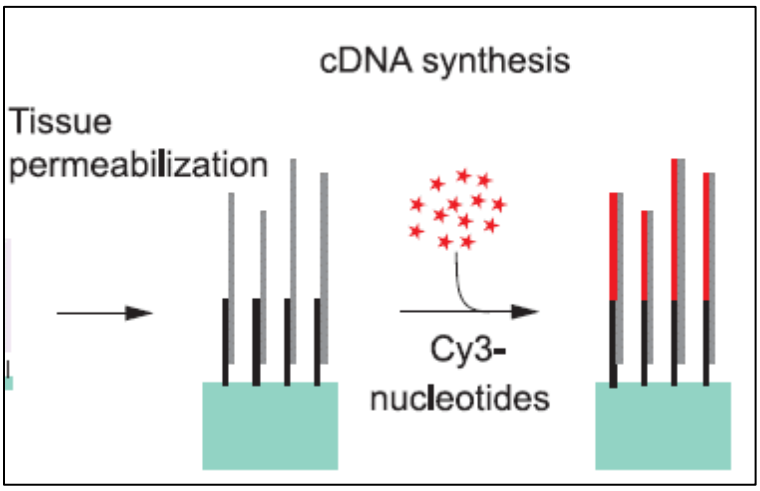
30. The synthesizing steps 1(c) and 1(d) impose two requirements on "a synthesis reaction" for "synthesizing DNA products." *First*, the synthesis reaction uses the collected oligonucleotides as templates to synthesize DNA products

(template requirement). *Second*, at least one sequence that identifies the location of the tissue sample (i.e., spatial barcode or location-identifying sequence) is incorporated into the DNA products (incorporation requirement). EX1044, ¶¶62-63.

31. Dr. Sherman agrees with this interpretation, stating that a POSA would have understood that steps 1(c) and 1(d) "require a synthesis reaction that generates DNA products" and the synthesis reaction requires "the collected oligonucleotides to be used as templates" and "the location-identifying sequences to be incorporated into the DNA products." EX2008, ¶35; *see also* EX1056, 26:8-27:7. Dr. Sherman also agrees that a *single* synthesis reaction meets both the template requirement and incorporation requirement of steps 1(c) and 1(d) of claim 1. EX2008, ¶35; EX1056, 28:6-24 (stating that "[*a*] *single event* provides that synthesis of that product" and "there's *a reaction* and it synthesizes the product in *a single event*").

32. As explained in my first declaration, under Bruker's infringement interpretation, Stahl teaches the synthesizing steps (c) and (d) of claim 1 because Stahl's method includes synthesizing first-strand cDNAs via reverse transcription using the captured poly-adenylated mRNAs as templates, with the resulting first-strand cDNAs incorporating spatial barcodes. EX1044, ¶¶107-115; EX1016, FIGs 1-2, S2, 78-79, Suppl. Materials 4-5. Stahl's Figure 1A reproduced below provides

an example of this first-strand cDNA synthesis, depicted in red bars:



EX1016, FIG 1A.

33. As explained in my first declaration, the "red bars" in the above Figure are a representative depiction of first-strand cDNA synthesis, not a depiction of the first-strand cDNAs (i.e., "DNA products" of claim 1's steps (c) and (d)). *See* EX1044, ¶107 ("Stahl 2016's Figure 1A *depicts cDNA synthesis* as red bars." (emphasis added)); *id*. ("Stahl 2016 discloses the synthesis steps (c) and (d) because its method includes a reverse transcription reaction to *'synthesize' cDNA* products using the captured mRNAs as templates." (emphasis added)); *id*. ("Stahl 2016 teaches '[sp]atially localized *cDNA synthesis*' and '*cDNA synthesis* with Cy3-labeled nucleotides.'"); *id*. ("'[w]e used fluorescently labeled nucleotides to visualize the *synthesized cDNA*.'" (emphasis added)). During deposition, I confirmed my opinion that the red bars were merely a visualization of Stahl's

methods of cDNA synthesis. EX2009, 58:15-22[2].

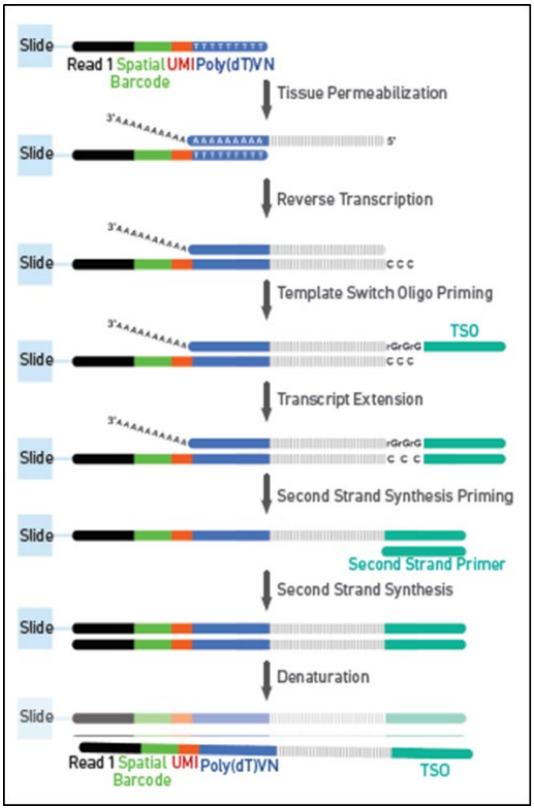
34. Further, as explained in my first declaration, the first-strand cDNAs (the "DNA products" of claim 1's steps (c) and (d)) are the entire molecules comprising the sequence of the capture probe and the sequence of the synthesized DNA. *See, e.g.,* EX1044, ¶¶107-114, 153. Dr. Sherman mischaracterizes my testimony when he argues that 10x identified only the synthesized DNA, and not the entire molecule, as the first-strand cDNA. *See, e.g.*, EX2008, ¶61 ("Petitioner's identified 'DNA products' in Stahl is the *first-strand cDNA* synthesized with Cy3-nucleotides, *as depicted in red* in Stahl's Figure 1A." (emphasis added)).

35. Indeed, a POSA would know that Stahl's Figure 1A depicts results from a proof-of-principle experiment showing by visualization that the cDNA synthesis using the capture probes bound on an array works. EX1016, FIG. 1, 78, Suppl. Materials 4-6; EX1044, ¶¶7-9, 107-108. A POSA would understand that Stahl applies the synthesis design confirmed in Figure 1's experiment in Figure 2's experiment, wherein Figure 2's experiment involves further steps of synthesizing second-strand cDNAs, generating a sequencing library, and sequencing the library to determine the spatial location of the target mRNAs in the tissue sample.

[2] The page numbers for EX2009 are based on the native page numbers (and not the stamped page numbers).

EX1016, FIG. 1, 78, 81, Suppl. Materials 3-5; EX1044, ¶¶7-9, 107-115 (citing EX1016, Suppl. Materials 4-5).

36. Stahl's first-strand cDNA synthesis meeting each of claim 1's steps (c) and (d) is consistent with Bruker's infringement contentions. EX1044, ¶¶107-115. Bruker's infringement contentions cite Visium FF's "Step 1 Permeabilization & Reverse Transcription" for claim 1's steps (c) and (d) and includes the following portions of Visium FF's workflow depiction.



EX1022, 18-20, 22; EX1015, 17; EX1044, ¶¶107-115. Bruker's infringement contentions also note that Visium FF's Step 1 involves adding a "RT Master Mix containing reverse transcription reagents" which "produces spatially barcoded,

full-length cDNA from poly-adenylated mRNA." EX1022, 18-19. Thus, for steps (c) and (d) of claim 1, Bruker's infringement contentions rely on Visium FF's first-strand cDNA synthesis, which is similar to Stahl's first-strand cDNA synthesis.

37. Although Bruker's infringement contentions for claim 1's steps (c) and (d) also cite Visium FF's "Step 2 Second Strand Synthesis & Denaturation," a POSA would understand that Visium FF's Step 2 does not meet claims 1's steps (c) and (d). EX1022, 18-20, 22; EX1022, 17. This is because Visium FF's Step 2 does not meet the template requirement of steps (c) and (d): the second-strand synthesis in Visium FF's Step 2 uses the first-strand cDNAs as templates rather than the collected oligonucleotides (mRNAs), as necessary under claim 1's template requirement. *Id*. And because a *single* synthesis reaction must meet both the template requirement and incorporation requirement of claim 1's steps (c) and (d), Bruker's infringement contentions for claim 1's steps (c) and (d) must be based on Visium FF's Step 1 (Reverse Transcription Step). EX1015, 17; EX1022, 18-20; EX1044, ¶¶62-63, 107-115; EX1056, 28:6-24.

38. Dr. Sherman now argues that Stahl does not disclose steps (c) and (d) of claim 1 because Stahl's method "does not incorporate the location-identifying sequence insofar as the location-identifying sequence is not synthesized." EX2008, ¶¶55; *see also id*. ("Petitioner fails to show that the location-identifying sequence is synthesized during synthesis of the first-strand cDNA."), 56 ("Stahl does not

disclose incorporating the location-identifying sequence into the DNA products … during the DNA products' synthesis."). According to Dr. Sherman, "a POSA would have understood 'incorporate' [in steps (c) and (d) of claim 1] to refer to addition of a sequence as each nucleotide is sequentially added during synthesis." EX2008, ¶52. And, according to Dr. Sherman, steps (c) and (d) of claim 1 "require a synthesis reaction that incorporates a location-identifying sequence into 'DNA product' that are synthesized." EX2008, ¶52.

39. I disagree with Dr. Sherman. A POSA would *not* have understood that incorporation of the location-identifying sequences must be by the synthesis of the sequences, but rather that the products of the synthesis reactions include location-identifying sequences. EX1044, ¶¶111-115. A POSA would have understood that including non-templated sequences (e.g., primers) into a DNA product was a standard method, and in fact, the normal method for introducing new sequences into a copy of a DNA sequence.

40. Furthermore, Dr. Sherman's construction of "incorporates" requiring location-identifying sequence to be incorporated *during* synthesis does not align with Bruker's infringement contention for claim 1's steps (c) and (d), which relies on Visium FF's first-strand synthesis (Step 1) for meeting both the template requirement and the incorporation requirement and where the location-identifying sequence incorporated into the first-strand cDNA is present in the capture probe

(and not added during synthesis). EX1022, 18-19.

41. Dr. Sherman points to Figure 7 to support his flawed interpretation of "incorporate" as requiring incorporation of the location-identifying sequences during synthesis. EX2008, ¶54 (citing EX1043, FIG. 7). However, Figure 7 does not support Dr. Sherman's interpretation. The method depicted in Figure 7 does not use the collected oligonucleotides (i.e., identifier oligonucleotides) as templates for a synthesis reaction, as required in steps (c) and (d) of claim 1. EX1043, FIG. 7, 25:19-33. Instead, as Dr. Sherman also admits, the synthesis reaction in the method of Figure 7 is an amplification reaction, wherein the ligated probes generated by ligating a pair of nucleic acid probes ("First Nucleic Acid Probe" and "Second Nucleic Acid Probe") are used as a templates, and not the collected oligonucleotides. EX1043, FIG. 7, 25:19-33; EX2008, ¶54. In Figure 7's method, the collected "identifier oligonucleotides" are only used to bring the two nucleic acid probes together for ligation, rather than being used as a template for a synthesis reaction. EX1043, FIG. 7, 25:19-33. Thus, the method of Figure 7 does not meet the template requirement of claim 1. EX1044, ¶¶62, 107, 109, 114.

42. Dr. Sherman also cites to various instances of where the 142 patent's specification uses "incorporate," noting that "[e]ach of these usages … refers to the successive addition of nucleotides onto a polynucleotide strand." EX2008, ¶53. Dr. Sherman is incorrect. The specification does not provide a controlling definition of

"incorporate" and thus a POSA would understand the term in the full use of the word. A POSA would be well aware that incorporation of functional sequences without successive addition of nucleotides onto a polynucleotide strand was routine in art, e.g., by ligation, in a primer (e.g. the p5/p7 sequences), or any other number of methods. In fact, a POSA would not have understood "incorporate" to be limited to incorporation of nucleotides during synthesis, as Dr. Sherman proposes.

43. Moreover, the instances of "incorporate" that Dr. Sherman cites are in the context of DNA sequencing, and a POSA would reject such a heavily constrained use of the term as irrelevant to the incorporation required in the claim. In the context of DNA sequencing, as in each of Dr. Sherman's identified instances, single bases are incorporated rather than an entire location-identifying sequence. Thus, a POSA would reject Dr. Sherman's proposed limitation of the term. Rather, a POSA would understand that a location-identifying sequence, which is at a specific place in the capture probe and has a specific length, would not be constrained by the use of incorporation based on the sequencing instances that Dr. Sherman cites.

44. Thus, I maintain my opinion that, under Bruker's infringement interpretation, Stahl teaches steps (c) and (d) of claim 1. EX1044, ¶¶107-115.

B. Stahl teaches a method that includes steps (c) and (d) of claim 1 under the Board's construction

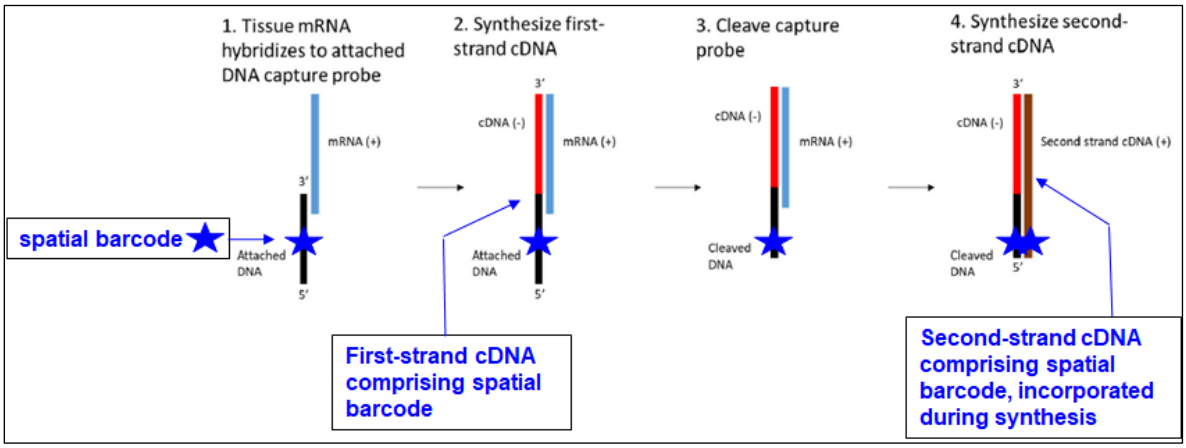
45. In my opinion, Stahl teaches a method that includes steps (c) and (d) of claim 1 under the Board's interpretation of "synthesizing DNA products." *See* Section III.A.

46. As discussed above, I understand that the Board interpreted "synthesizing DNA products" as encompassing a two-step synthesis of the DNA products. *Id*.; DOI, 21-22. I further understand that the Board interpreted the "DNA products" of steps (c) and (d) of claim 1 as not limited to "the first cDNA strand – and only this strand." *Id*. I also understand that, after 10x filed the Petition with my first declaration, Bruker argued Visium FF's step 1 (first-strand cDNA synthesis) and step 2 (second-strand cDNA synthesis) *together* perform the claimed synthesis reaction. *Id*.

47. As I explained in my first declaration, Stahl's method includes using the collected oligonucleotides (mRNAs) as a template to synthesize first-strand cDNAs comprising a spatial barcode. EX1044, ¶¶72, 107-115; EX1016, FIGs. 1-2, S2, 78-79, Suppl. Materials, 4-5. This step in Stahl's method meets the template requirement of steps (c) and (d) of claim 1. EX1044, ¶109. Next, second-strand cDNA synthesis uses the first-strand cDNAs as templates to generate the second-strand cDNAs, whereupon the spatial barcode present in the first-strand cDNAs is incorporated into the second-strand cDNAs during synthesis. EX1044, ¶¶149-154;

EX1016, Suppl. Materials 6. This step in Stahl's method meets the incorporation requirement of steps (c) and (d) of claim 1, under the interpretation of "incorporate" that Dr. Sherman proposes in ¶52 of his declaration. EX2008, ¶52.

48. Dr. Sherman's schematic of Stahl's workflow also depicts this two-step process for "synthesizing DNA products" that meets the Board's construction of "synthesizing DNA products":



EX2008, ¶¶46, 55 (annotated in blue).

49. In the above schematic, a collected oligonucleotide (mRNA) first hybridizes with a DNA capture probe ("Attached DNA") containing a spatial barcode (step 1). *Id*. The collected mRNA is used as a template to synthesize a first-strand cDNA comprising the spatial barcode (step 2). *Id*. Next after cleavage and release of the capture probe from the array (step 3), a second-strand cDNA, shown in brown, is synthesized using the first-strand cDNA comprising the spatial barcode as a template, wherein the spatial barcode is incorporated into the second-

strand cDNA during synthesis (step 4). *Id*.; EX1016, 78-79, Suppl. Materials 4-6; EX1044, ¶¶107-115.

50. Thus, Stahl's first-strand cDNA synthesis meets the template requirement of steps (c) and (d) of claim 1. And, Stahl's second-strand cDNA synthesis meets the incorporation requirement of steps (c) and (d) of claim 1, under the interpretation of "incorporate" that Dr. Sherman proposes in ¶52 of his declaration. EX2008, ¶52. Accordingly, Stahl's first-strand cDNA synthesis and second-strand cDNA synthesis *together* meet the template and incorporation requirements of steps (c) and (d) of claim 1 and perform these synthesizing steps under the Board's interpretation. EX1016, Suppl. Materials 4-6; *See* Section III.A, DOI, 21-22. And, Stahl's second-strand cDNAs are the "DNA products" of steps (c) and (d) of claim 1 under the Board's and Bruker's IPR constructions. *See* Section III.A, DOI, 21-22.

51. Stahl's first- and second-strand cDNA synthesis steps shown in Dr. Sherman's schematic also mirror Visium FF's steps 1 and 2, wherein Visium FF's step 1 meets the claim's template requirement and step 2 meets claim's the incorporation requirement under Dr. Sherman's construction of "incorporate." EX1022, 18-20; EX1015, 17.

52. Accordingly, Stahl teaches a method that includes first- and second-strand synthesis of DNA products that together meet each of steps (c) and (d) of

claim 1 under the Board's construction.

C. As explained in my first declaration, Stahl teaches the claimed sequencing step according to Bruker's infringement contentions

53. Step (e) of claim 1 (the "sequencing step" of claim 1) of the 142 patent recites the following:

> [I]dentifying the first plurality of DNA products and the second plurality of DNA products synthesized in step (c) and step (d) by sequencing the first plurality of DNA products and the second plurality of DNA products, thereby spatially detecting the plurality of oligonucleotides collected from the first location of the tissue sample and the plurality of oligonucleotides collected from the second location of the tissue sample.

EX1043, 147:54-61.

54. As explained in my first declaration, Stahl teaches the sequencing step of claim because Stahl's method sequences a library of molecules and the molecules in this library comprise spatial barcodes that identify the first and second locations of the tissue sample by using "paired-end sequencing" on the "Illumina NextSeq platform," and wherein the sequencing library was constructed from the amplified copies of second-strand cDNAs, which themselves were generated downstream from the first-strand cDNAs reverse transcribed from the

collected target mRNAs. EX1044, ¶¶116-121; EX1016, 78, Suppl. Materials, 6-8. Stahl further discloses spatially detecting the mRNAs collected from the tissue sample (i.e. the "collected oligonucleotides" of the claim) by using the spatial barcodes to identify the spatial origins of the corresponding mRNAs in the tissue sample. EX1044, ¶¶116-121; EX1016, 78, 81, FIGs. 2, 3, S4, S10A-10C.

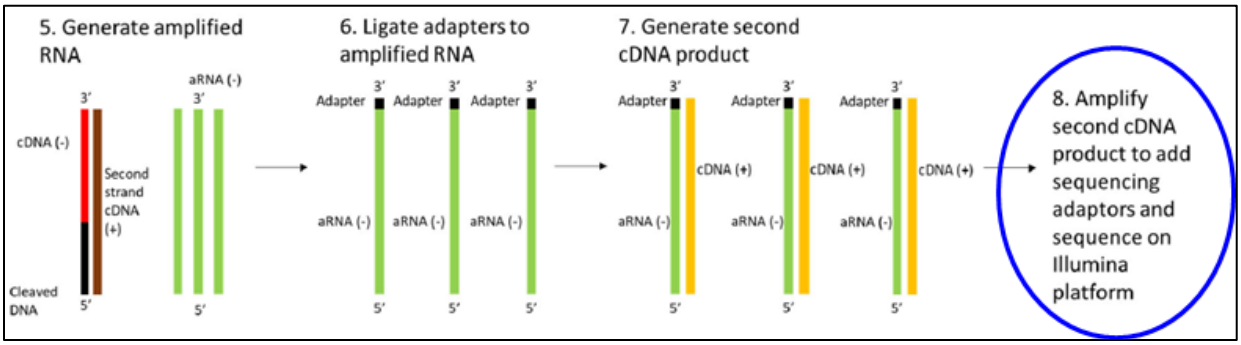
55. This is consistent with Bruker's infringement contentions for step (e) of claim 1, which states that in Visium FF, "*[l]ibraries* are … generated from the cDNA and sequenced" and cites Visium FF's Step 4 ("Visium Spatial Gene Expression *Library Construction*") and Step 5 ("Sequencing"). EX1022, 22-23; EX1044, ¶¶116-121. Visium FF's Steps 4 and 5 involve sequencing via Illumina paired-end sequencing (in Step 5) an amplified library constructed (in Step 4) from the amplified copies of second-strand cDNAs, which themselves were generated *downstream* from the first-strand cDNAs. EX1015, 17-18. Thus, under Bruker's litigation interpretation, step (e) of claim 1 encompasses sequencing molecules that are not the first- or second-strand cDNAs and do not possess their exact sequence, at least because of the added sequences such as adapters and index sequences. EX1044, ¶¶116-121.

56. My opinion in the first declaration is also consistent with the Board's interpretation of claim 1's step (e), which I understand is the following: "locating the specific target analyte within the tissue sample by correlating the DNA product

using the location-identifying nucleic acid sequences." *See* Section III.B; DOI, 28; EX1044, ¶¶97, 116-121. The Board's interpretation encompasses sequencing molecules that are different from the first-strand (and second-strand) cDNAs due to, e.g., addition of adapters and index sequences. In Stahl's method, the sequences of the DNA products and their spatial barcodes are determined via sequencing the library, and the spatial barcodes are used to correlate the DNA product with its spatial location. EX1044, ¶¶116-121; EX1016, 78, 81, FIGs. 2, 3, S4, S10A-10C.

57. My opinion in the first declaration is also consistent with Dr. Sherman's interpretation of claim 1's step (e), which is the following: "locating the specific target analyte within the tissue sample by correlating the DNA product using the location-identifying nucleic acid sequences, wherein the sequence of the DNA product using the location-identifying nucleic acid sequences are determined via sequencing." *See* Section III.B; EX2008, ¶29. Dr. Sherman's interpretation encompasses sequencing molecules that are different from the first-strand (and second-strand) cDNAs due to, e.g., addition of adapters and index sequences, to locate the target mRNAs within the tissue sample. EX2008, ¶29. Stahl's method determines the sequences of DNA products—and their accompanying spatial barcodes—through sequencing of a library before correlating the DNA products with their spatial location in the original tissue sample. EX1044, ¶¶116-121; EX1016, 78, 81, Suppl. Mat. 6-8, FIGs 2, 3, S4, S10A-10C.

58. Dr. Sherman argues that "a POSA would have understood sequencing a nucleic acid to refer to the nucleic acid being directly sequenced." EX2008, ¶48. And, based on this premise, Dr. Sherman argues that Stahl's method does not meet step (e) of claim 1, because "Stahl does not disclose sequencing the DNA products identified by Petitioner" when Stahl's method sequences a "second cDNA product (depicted in orange)" that is "different from to the first-strand cDNA (depicted in red)." EX2008, ¶¶47-49; *see also id.*, ¶¶45 ("[I]t is my opinion that the first-strand cDNA in Stahl is not sequenced. Rather, as explained below, Stahl sequences a second cDNA product."), 46-48.



EX2008, ¶46 (annotated in blue).

59. In particular, Dr. Sherman argues that "second cDNA product" (depicted in orange) and the first-strand cDNA (depicted in red) are "*different molecules* and only the second cDNA product (depicted in orange) is sequenced (step 8)." EX2008, ¶47 (emphasis added). Dr. Sherman further argues that the sequenced second cDNA product has a *different sequence* from the first-strand cDNA for the following reasons: (1) "the *directionality* of the second cDNA

product and the first-strand cDNA is different"; and sequencing Illumina *adaptors are appended* to the second cDNA product that are not on the first-strand cDNA. EX2008, ¶¶47-48 (emphasis added).

60. Dr. Sherman mischaracterizes Stahl's method when he states that "Stahl's workflow implements … stranded RNA sequencing or strand-specific RNA sequencing" to "ensure that the strand specificity of the target mRNA is maintained as the sequence of the RNA is determined so that information on strand origin is not loss [sic] during sequencing." EX2008, ¶47. For one, strand preservation is an inherent feature of Stahl's method due to its capture of RNAs via their oligoA tails using capture probes containing an oligo dT sequence. EX1016, Suppl. Materials 2-5; EX1044, ¶70. Strand orientation in Stahl is not maintained by which strand is sequenced but rather by knowing the orientation of sequencing that occurs. Put another way, either the +, -, or both strands are sequenced as long as additional information is attached that allows orientation. In the case of Stahl and its derivatives this orientation is encoded in which end of the + (or -) end strand has the polyA tail and which end has the p5/p7 Illumina sequencing adapters. As Dr. Sherman also admits, Stahl's method amplifies the orange "cDNA products" of the schematic while adding sequencing adapters to generate a sequencing library for Illumina "paired-end sequencing." EX2008, ¶46; EX1056, 52:5-16; EX1016, Suppl. Materials 6-7.

61. Furthermore, Stahl's method sequences both the molecules comprising the sequence of the captured mRNAs (sense (+) strand) and the molecules comprising the complementary sequence (antisense (-) strand). EX1016, Suppl. Materials 6-7. As I explained in my first declaration, Stahl discloses generating "sequencing libraries" for use in Illumina paired-end sequencing. EX1044, ¶¶139-142; EX1016, Supp. Materials 6-8. Stahl's method in particular performs an initial in vitro transcription reaction to produce amplified RNA molecules. EX1044, ¶117; EX1016, Supp. Materials 6-8. Stahl's method then adds DNA adapters to the ends of the amplified RNA, reverse transcribes this amplified RNA into cDNA, and then performs PCR to amplify the cDNA to create an Illumina paired-end sequencing library. EX1044, ¶117; EX1016, Suppl. Materials, 7. By design, the library generated for Illumina paired-end sequencing in Stahl includes both the molecules containing sequences of the captured mRNAs (sense (+) strand) and the molecules containing sequences of the complementary sequence (antisense (-) strand). EX1016, 6-8. Dr. Sherman's step 8 in its schematic is disingenuous at best in that it omits paired-end sequencing from the figure (circled above). EX2008, ¶46. Dr. Sherman also mischaracterizes Stahl's method when he argues that "only the second cDNA product (depicted in orange) is sequenced (step 8)." EX2008, ¶47. As Dr. Sherman's own schematic in step 8 notes, the second cDNA products (depicted in orange) are amplified "to add

sequencing adaptors" and the resulting molecules are sequenced. EX2008, ¶46; EX1044, ¶¶139-142; EX1016, Supp. Materials 6-8. Thus, Stahl's method sequences molecules with different sequence from the second cDNA product (depicted in orange).

62. Dr. Sherman's arguments are also inconsistent with the 142 patent's specification. The specification of the 142 patent repeatedly discloses sequencing molecules in libraries that are amplified downstream of the DNA products synthesized using the collected oligonucleotides as templates, and not the original DNA products. *See, e.g.*, EX1043, 42:26-40, 43:56-44:19; 1:44-67, 2:1-25, 2:26-54, 3:24-47, 3:48-4:9, 4:34-5:2, 5:3-37, 5:44-6:8, 6:9-43, 6:44-7:9, 7:10-44, 8:18-52, 8:53-9:23, 9:24-58, 9:59-10:29, 11:1-25, 11:26-52, 12:29-57, 12:58-13:8, 57:6-58:20, 61:40-62:6.

63. For example, the 142 patent discloses that "the products produced by the methods of the present disclosure can be used for nucleic acid amplification," including for "preparing a library of template polynucleotide molecules" through "solid-phase nucleic acid amplification." EX1043, 42:26-40. Likewise, the 142 patent notes that the invention "provides a method of nucleic acid sequencing comprising amplifying a library of nucleic acid templates." EX1043, 43:47-49.

64. Furthermore, the 142 patent discloses that the sequenced library molecules incorporate sequencing adapters not located in the first-strand cDNA

molecules. EX1043, 43:65-44:2 ("[O]ne or both of the *adapters added during formation of the template library* may include a nucleotide sequence which permits annealing of a sequencing primer to amplified products derived by … solid-phase amplification of the template library." (emphasis added)); *see also* id. 1:44-67, 2:1-25, 2:26-54, 3:24-47, 3:48-4:9, 4:34-5:2, 5:3-37, 5:44-6:8, 6:9-43, 6:44-7:9, 7:10-44, 8:18-52, 8:53-9:23, 9:24-58, 9:59-10:29, 11:1-25, 11:26-52, 12:29-57, 12:58-13:8, 13:50-67, 57:6-58:20, 61:40-62:6.

65. Dr. Sherman's arguments are also inconsistent with Bruker's infringement contentions for step (e) of claim, which also identified sequencing molecules that are *different* from the first-strand cDNAs in Visium FF (which Bruker identified as the "DNA products" of steps (c) and (d) of claim 1, *see* Section V.A above). This is at least because the sequence molecules in Visium FF include additional sequences, such as adapters, that were not in the first-strand cDNAs. EX1044, ¶¶118-120; EX1022, 23; EX1015, 17-18.

66. As explained above, Bruker's infringement contentions for step (e) of claim 1 state that in Visium FF, "*[l]ibraries* are … generated from the cDNA and sequenced" and cites Visium FF's Step 4 ("Visium Spatial Gene Expression *Library Construction*") and Step 5 ("Sequencing"). EX1022, 23; EX1015, 17-18. Visium FF's Steps 4 and 5 involve generating an amplified library (in Step 4) from the amplified copies of second-strand cDNAs (which themselves were generated

downstream from the first-strand cDNAs) and sequencing via Illumina paired-end sequencing (in Step 5) the library. EX1015, 17-18. During Visium FF's Step 4, additional sequence elements such as adapter or index sequences and primer sequences are added to amplification products "via End Repair, A-tailing, Adaptor Ligation, and PCR." EX1022, 23; EX1015, 17-18. The molecules produced by PCR (that are sequenced) include the reverse complement DNA sequence (which is distinct and predictable) and also include additional sequence, such as adapters, not present in the first-strand cDNAs due to additional adapters. EX1044, ¶¶118-120; EX1022, 23; EX1015, 17-18.

67. Finally, Dr. Sherman argues that 10x did not satisfy step (e) of claim 1 because 10x states that "it is the cDNA synthesis in Stahl utilizing Cy3-nucleotides that meets the 'DNA products' in the claims" and these Cy3-labeled cDNAs are not sequenced. EX2008, ¶44. Dr. Sherman misrepresents the statements in my first declaration.

68. First, I highlighted the "red bars" as a representative depiction of first-strand cDNA synthesis, not a depiction of the first-strand cDNAs (i.e., "DNA products" of claim 1's steps (c) and (d)). *See* EX1044, ¶107 ("Stahl 2016's Figure 1A *depicts cDNA synthesis* as red bars." (emphasis added)); *id*. ("Stahl 2016 discloses the synthesis steps (c) and (d) because its method includes a reverse transcription reaction to *'synthesize' cDNA* products using the captured mRNAs as

templates." (emphasis added)); *id*. ("Stahl 2016 teaches '[sp]atially localized *cDNA synthesis*' and '*cDNA synthesis* with Cy3-labeled nucleotides.'"); *id*. ("'[w]e used fluorescently labeled nucleotides to visualize the *synthesized cDNA*.'" (emphasis added)). I also cited to Stahl's Supplemental Materials section that described first-strand cDNA synthesis by reverse transcription for "samples intended for sequencing." EX1044, ¶¶107-108 (citing EX1016, Suppl. Materials 4-5). During deposition, I confirmed my opinion that the red bars were merely a visualization of Stahl's methods of cDNA synthesis. EX2009, 58:15-22. And, as explained in my first declaration, the first-strand cDNAs (the "DNA products" of claim 1's steps (c) and (d)) are the entire molecules comprising the sequence of the capture probe and the sequence of the synthesized DNA. *See, e.g.,* EX1044, ¶¶107-114, 153.

69. Moreover, when discussing claim 1's step (e), I pointed to Stahl's Figure 2B (which depicts the results of Stahl's methods obtained from sequencing the molecules generated downstream of the first-strand cDNAs without Cy3-nucleotides) and Supplemental Materials section on pages 6-7 (which discloses methods and results for *sequencing* the cDNAs without Cy3-nucleotides). EX1044, ¶¶119-120, (citing EX1016, FIG. 2B).

70. Therefore, I maintain my position that Stahl teaches a method that includes the claimed sequencing step under Bruker's infringement contentions. EX1044, ¶¶116-121.

D. Stahl teaches a method that includes the claimed sequencing step under the Board's constructions

71. As I discuss above, under the Board's interpretation of "synthesizing DNA products," Stahl's first-strand synthesis and second-strand synthesis *together* generate the claimed DNA products, i.e., the second-strand cDNAs. *See* Sections III.A, V.B. Also as I discuss above, the Board's and Bruker's interpretations encompass sequencing molecules that are different from the first- or second-strand cDNAs and allow the identification of the DNA products but need not be limited to their exact sequence. *See* Section V.C.

72. In my opinion, Stahl teaches claim 1's step (e) under the Board's interpretation because Stahl teaches a method that includes sequencing a library of molecules generated from the amplified copies of the second-strand cDNAs (DNA products), and determining the sequences of the DNA products and their spatial barcodes. *See* Section V.C. Furthermore, Stahl teaches correlating the spatial barcodes in the DNA products to identify the spatial location of the collected mRNAs in the tissue sample. EX1044, ¶¶117-120; EX1016, 78, 81, Suppl. Materials, 6-7, FIGs 2, 3, S4, S10A-10C.

73. Thus, Stahl teaches a method that includes step (e) of claim 1 under the Board's constructions.

E. Stahl teaches amplifying a library using the DNA products as templates (claim 7)

74. Claim 7 of the 142 patent recites that the method of claim 1 "further comprises amplifying a library using the first plurality of DNA products and the second plurality of DNA products as templates." EX1043, 148:44-46; EX1044, ¶141. As I explained in my first declaration, Stahl teaches amplifying a library by using DNA products as a template under Bruker's infringement interpretation. EX1044, ¶¶141-142; EX1016, Suppl. Materials, 6-7. Bruker asserts that Visium FF's steps 3 and 4 practice claim 7 of the 142 patent. EX1022, 35-36; EX1015, 17-18. Visium FF's step 3 "cDNA Amplification & QC" constitutes amplifying the "spatially barcoded" second-strand cDNAs "after transfer of [the second-strand] cDNA from the slide" via denaturation (in step 2). EX1015, 17. The second-strand cDNAs are synthesized (in step 2) using the first-strand cDNAs with the incorporated spatial barcode (Bruker's identified DNA products in Visium FF) as templates. *Id.* Because the first-strand cDNAs remain attached to the slide in step 2, only the second-strand cDNAs are transferred "to a corresponding tube for amplification and library construction." *Id*. Thus, only second-strand cDNAs are used as templates for cDNA amplification and library preparation in Visium FF's steps 3 and 4. *Id*., 17-18.

75. As I explained in my first declaration, similar to Bruker's identified Visium FF's steps 3 and 4, Stahl's method includes multi-step amplification of

second-strand cDNAs (synthesized from the first-strand cDNAs as templates) and generation of a "cDNA library … for sequencing," with only the second-strand cDNAs being used as templates. EX1044, ¶¶141-142; EX1016, Suppl. Materials, 5-7.

76. As Dr. Sherman also agrees, Stahl's method includes an initial transcription/amplification to produce amplified RNA ("aRNA") molecules from the second-strand cDNAs (step 5 of Dr. Sherman's schematic on page 20 of his declaration). EX2008, ¶46; EX1044, ¶¶141-142; EX1016, Suppl. Materials, 5-7. Next, Stahl's method adds DNA adapters to the ends of the aRNA and reverse-transcribes the aRNA to generate molecules comprising the sequence of the second-strand cDNAs (Steps 6 and 7 of Dr. Sherman's schematic). EX2008, ¶46; EX1044, ¶¶141-142; EX1016, Suppl. Materials, 5-7. Stahl's method then performs PCR using the molecules comprising the sequence of the second-strand cDNAs as templates to generate a library of molecules with added adapters for Illumina NextSeq paired-end sequencing (step 8 of Dr. Sherman's schematic). EX2008, ¶46; EX1044, ¶¶141-142; EX1016, Suppl. Materials, 5-7. Therefore, a POSA would have understood Stahl's method comprises amplifying a library using the second-strand cDNAs as templates, similar to Visium FF steps 3 and 4 cited in Bruker's contentions. EX1044, ¶¶141-142.

77. Dr. Sherman argues that "Petitioner fails to show that Petitioner's

identified 'DNA products' in Stahl act as templates in an amplification reaction" because the "template is the second cDNA product" rather than first-strand cDNA. EX2008, ¶¶60-64. Dr. Sherman's position is however inconsistent with Bruker's infringement contentions for claim 7, which as explained above, rely on Visium FF's second-strand cDNA amplification (step 3) and subsequent library preparation (step 4)—neither of which use the first-strand cDNAs as templates for amplification. EX1022, 35-36.

78. Moreover, in my opinion Stahl's multi-step amplification and library cDNA generation also meets the requirements of claim 7 under the Board's interpretation of "synthesizing DNA products." I understand that the Board interpreted "DNA products" of steps (c) and (d) of claim 1 as not limited to "the first cDNA strand – and only this strand." *See* Section III.A. Thus, a POSA would have understood that "DNA products" under the Board's interpretation include Stahl's second-strand cDNAs, which Stahl's method uses as templates in a multistep amplification to generate cDNA sequencing libraries as explained above. EX1044, ¶¶141-142; EX1016, Suppl. Materials, 6-7.

79. Thus, Stahl teaches a method that includes amplifying a library using DNA products as templates, as required in claim 7. EX1044, ¶¶141-142.

VI. GROUNDS 2 AND 3: CLAIMS 1-13 ARE OBVIOUS OVER STAHL, AND CLAIM 5 IS OBVIOUS OVER STAHL AND FRISEN

A. Claims 1-4 and 6-13 are obvious over Stahl

80. As explained in my first declaration, because Stahl teaches all the limitations of claims 1-4 and 6-13, no modification is needed for a POSA to practice these claims. EX1044, ¶¶160-164. And assuming for argument's sake that Stahl does not anticipate claims 1-4 and 6-13, it would have rendered the claims obvious under Bruker's infringement interpretations. EX1044, ¶¶160-164.

81. My first declaration explained that a POSA would have been motivated to practice the methods in claims 1-4 and 6-13 in view of Stahl. EX1044, ¶¶160-164. I noted that a POSA would have understood that Stahl discloses a method for "spatial transcriptomics" that "provides quantitative gene expression data and visualization of the distribution of mRNAs within tissues sections," and "enables novel types of bioinformatics analyses." EX1044, ¶162; EX1016, Abstract, 82.

82. Dr. Sherman argues this only shows that Stahl is directed to a similar field of endeavor as the 142 patent and that "nothing suggests that a POSA would be motivated to modify Stahl to arrive at the claimed methods." EX2008, ¶68. Dr. Sherman also argues that a POSA would not have had reason to modify Stahl due to the straightforward methods used and the demonstrated success of Stahl's procedure. EX2008, ¶69. I disagree with Dr. Sherman.

83. As Dr. Sherman agrees, "the skill level of a POSA relevant to the '142 patent is high" and that a POSA would have "at least two years of experience in the use and development of approaches for spatial detection of proteins and nucleic acids of interest in a biological sample." EX2008, ¶21; *see also* EX1044, ¶25 ("A POSA would typically have a Ph.D. in a relevant field … with two years of experience in the use and development of genetics and genomics approaches for detecting and monitoring human diseases, such as spatial detection of a target analyte (e.g., mRNA or DNA) in a tissue section"). In view of such high skill level, Stahl teaches all of the elements of the claims (as explained in my first declaration and also under the Board's constructions as explained above in Section V) and, for the reasons explained in my first declaration, a POSA would have been motivated to perform the methods of claims 1-4 and 6-13 with a reasonable expectation of success. EX1044, ¶¶25, 160-164.

84. Accordingly, I maintain my opinion set forth in my first declaration that claims 1-4 and 6-13 would have been obvious over Stahl. EX1044, ¶¶160-164. Further, claims 1-4 and 6-13 would have been obvious over Stahl under the Board's constructions.

B. Claim 5 is obvious over Stahl

85. Claim 5 depends from claim 4 and further requires that each synthesis step (c) and (d) "comprises performing a solid-phase amplification reaction,

wherein the solid-phase amplification reaction is carried out on the microscope slide using the plurality of primers immobilized on the microscope slide." EX1043, 148:37-41; EX1044, ¶165.

86. As explained in my first declaration, claim 5 would have been obvious over Stahl. EX1044, ¶¶165-178. My first declaration explained why a POSA would have been motivated to modify Stahl's method to include the solid-phase amplification reaction of claim 5 under Bruker's infringement contentions by synthesizing the second-strand cDNAs on Stahl's array, for several reasons, including improved "sensitivity, selectivity, and scalability," reduced "undesirable primer interactions," and improved parallelization for high-throughput systems. EX1044, ¶¶165-196. My first declaration also explained why a POSA would have had a reasonable expectation of successfully performing solid-phase second-strand synthesis in Stahl's modified method. EX1044, ¶¶175-177.

87. Dr. Sherman argues that modifying Stahl to perform solid-phase second-strand cDNA synthesis would not meet claim 5's limitations as it does not synthesize 10x's "identified DNA products," the first-strand cDNAs. EX2008, ¶73. I disagree with Dr. Sherman.

88. As explained in my first declaration, I understand that because claim 5 recites "comprises," it only requires that solid-phase amplification take place as part of claim 1's steps (c) and (d), before sequencing in claim 1's step (e). EX1043,

148:37-41; EX1044, ¶166. In Stahl, solid-phase second-strand cDNA synthesis takes place after the first-strand cDNA synthesis but *before* sequencing. EX1016, 78-79, FIGs. 1-2, Suppl. Materials, 4-5; EX1044, ¶¶169-170. Therefore, solid-phase second-strand synthesis in Stahl would satisfy claim 5

89. As explained in my first declaration, Bruker's infringement contentions for claim 5 are based on Visium FF's second-strand cDNA synthesis, while Bruker's infringement contentions for claim 1 are based on Visium FF's first-strand cDNA synthesis and first-strand cDNAs as DNA products of claim 1's steps (c) and (d). EX1044, ¶¶165-178; EX1022, 18-22, 32-33; *see* Section V.A. Thus, Dr. Sherman's position is inconsistent with Bruker's own infringement contentions. Further, as discussed above, Stahl's second-strand cDNAs are "DNA products" of claim 1's steps (c) and (d) under Bruker's IPR and the Board's constructions for "synthesizing DNA products." *See* Sections V.B; III.A; DOI, 21-22. Thus, Dr. Sherman's position is moot under Bruker's IPR and the Board's constructions.

90. Dr. Sherman also argues that my first declaration does not "provide sufficient details on ***how*** a POSA could have modified Stahl to practice claim 5." EX2008, ¶74. Dr. Sherman ignores the full context of my first declaration and the knowledge and capabilities of a POSA. My first declaration explained in detail that the solid-phase synthesis reactions, including for amplification, were well-known

and routinely performed in the art before February 12, 2018. EX1044, ¶¶175-177. This was particularly the case for high-throughput molecular bioanalytical methods like Stahl's. EX1044, ¶175. I also provided several notable examples of solid-phase amplification approaches that would have guided a POSA's routine modifications to Stahl's workflow. EX1044, ¶¶175-177 (citing EX1005, EX1017, EX1042, EX1049).

91. For example, I discussed So-456 disclosing several solid-phase synthesis reactions for amplification performed on an array, including those illustrated in step 2425 of Figures 24 and 25 reproduced below:

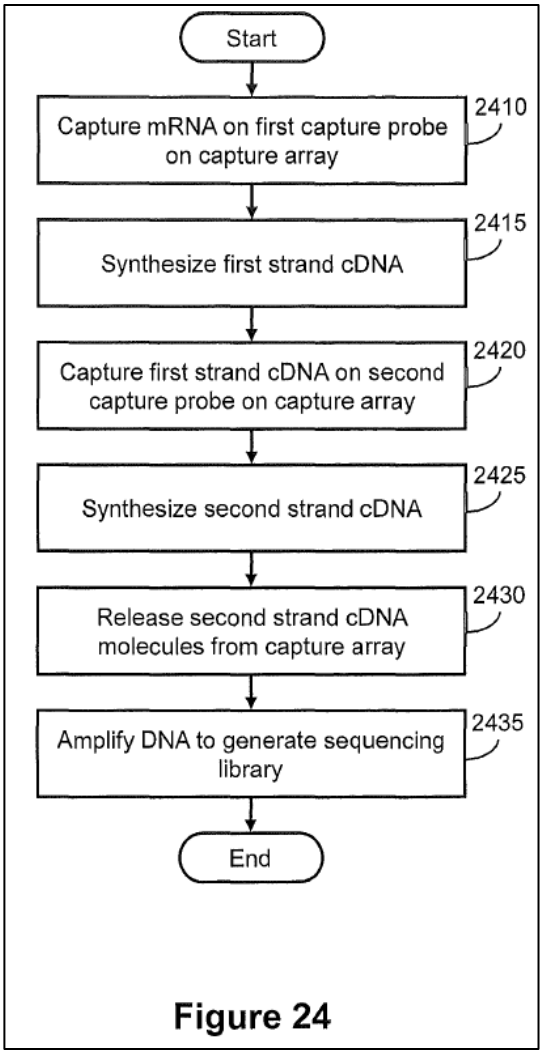
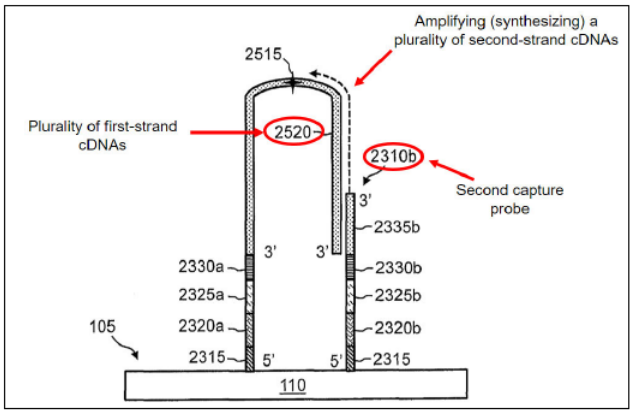


Figure 24



EX1005, FIGs 24, 25B (annotated), ¶¶[0034]-[0035],] [00307]-[00320]; EX1044, ¶175.

92. Likewise, I discussed Frisen providing exemplary methods for DNA synthesis, including second-strand cDNA synthesis, on an array. EX1044, ¶¶175-176; *see also* EX1017, 12:9-11 ("second strand cDNA synthesis may optionally take place on the array, or it may take place in a separate step, after release of first strand cDNA from the array"); EX1017, 38:20-23 ("The step of second strand

DNA, e.g. cDNA, synthesis may take place *in situ* on the array"), 38:27-39:16 ("Where second strand synthesis takes place on the array …. The second strand synthesis reaction may be performed on the array directly …"), 42:28-43:7 ("[A] single amplification reaction, e.g. PCR, may be sufficient to amplify all of the DNA, e.g. cDNA molecules …. [I]n other embodiments, amplification may be performed on the array …"). In fact, Dr. Sherman agrees that Frisen teaches both second-strand cDNA synthesis and library amplification as optional steps and that Frisen teaches that second-strand cDNA synthesis "may be achieved by any means known in the art," including "whilst the cDNA is immobilized on the array" EX2008, ¶¶88-89; EX1017, 39:1-8; EX1044, ¶¶175-176.

93. These examples demonstrate that Stahl's modification to include solid-phase second-strand synthesis would be routine because it is a minor modification and predictable to the POSA with the high skill level Dr. Sherman acknowledges for this patent. EX2008, ¶21 ("I agree with Dr. Spellman that the skill level of a POSA relevant to the '142 patent is high."); EX1044, ¶25. Furthermore, Stahl's method already showed how to perform first-strand cDNAs on the microscope slide—something a POSA would have understood to be solid-phase synthesis and therefore a POSA would not consider it a stretch to perform a second reaction on the same microscope slide. EX1044, ¶175; EX1016, 78, FIGs. 1A, 2B. Modifying the second-strand cDNA synthesis of Stahl to remain on the

array would simply represent an extension of the well-known and well-applied DNA synthesis techniques described above.

94. Dr. Sherman's additional arguments for lack of reasonable expectation of success also fail. EX2008, ¶¶74-78, 85. As a preliminary note, Dr. Sherman provides little to no supporting references for his arguments. *See, e.g.,* EX2008, ¶¶74-78, 85. Further, I disagree with Dr. Sherman for the reasons explained below.

95. Dr. Sherman argues that the modification of Stahl's method to perform solid-phase, second-strand synthesis would have led to the following "issues that cannot easily be resolved": (i) DNA polymerases for solid-phase and solution-phase amplification are different (¶74); (ii) solid-phase amplification is less efficient than solution-phase (¶76); and (iii) solid-phase amplification creates spatial constraints on RNA polymerase used in Stahl for generating amplified RNAs (¶77). EX2008, ¶¶74-77. However, none of Dr. Sherman's issues alone or together is a concern.

96. Dr. Sherman's argument that there were different polymerases optimized for solid-phase and solution-phase amplification ignores the high skill level of a POSA. EX2008, ¶¶74, 21; EX1044, ¶25. A variety of polymerase enzymes were well known in the art and selection of optimal enzymes for a particular use (e.g., solid-phase amplification) was routine for a POSA. *See, e.g.*,

EX1017, 39:28-40:4 (citing Klenow polymerase as a preferable polymerase for second-strand synthesis, including under solid-phase conditions); *see also* EX1017, 43:8-18, 51:1-26, 84:20-26; EX1042, 27:36-39, 15:24-46; EX1044, ¶194.

97. Further, Dr. Sherman argues that polymerases for solid-phase and solution-phase synthesis are optimized for their particular function, with polymerases for solid-phase synthesis being "optimized for surface-bound templates," "specifically engineered [] for robust performance," and "typically optimized for high processivity." EX2008, ¶74. However, these arguments are geared towards alleged higher efficiency of an optimized polymerase over a non-optimized polymerase. As Dr. Sherman also agrees, claim 5 does not require any particular efficiency for the solid-phase amplification. EX1056, 36:11-20; EX1043, 148:37-41. Instead, claim 5 simply requires "performing a solid-phase amplification reaction, wherein the solid-phase amplification reaction is carried out on the microscope slide using the plurality of primers immobilized on the microscope slide." EX1043, 148:37-41; EX1044, ¶¶165-166.

98. A POSA would have known that a non-optimized polymerase would still perform solid-phase synthesis, albeit less efficiently, so long as conditions sufficient for templated DNA synthesis were maintained. *See, e.g.*, EX1017, 39:28-34 (describing how "second strand synthesis *may be achieved by any suitable means* … the first-strand cDNA, preferably, but not necessarily, released from the

array substrate, may be incubated … *under conditions sufficient for templated DNA synthesis to occur*" (emphasis added)). Further, processivity (which is a polymerase's tendency to stay attached to the replicating DNA) is irrelevant here, and there is no evidence that the polymerases here benefit from high processivity. Therefore, even if polymerases optimized for solution-phase synthesis were not optimized for solid-phase reactions, they would still perform solid-phase synthesis to meet claim 5.

99. Dr. Sherman's argument that "any reaction performed in solid-phase would be less efficient [than] its counterpart in Stahl where it is performed in solution" also fails. EX2008, ¶76. Again, as noted above, claim 5 does not require any particular efficiency for the solid-phase amplification. EX1043, 148:37-41; EX1056, 36:11-20; EX1044, ¶¶165-166. And, as discussed above, a POSA would have had a thorough understanding of solid-phase synthesis, which were commonly and successfully performed in the art before February 12, 2018. EX1044, ¶¶175-177; *see, e.g.*, EX1005; EX1017; EX1042; EX1049.

100. Dr. Sherman's argument that "generating amplified RNA is unlikely to succeed" if "second-strand cDNA synthesis occurs in solid phase" due to spatial constraints on the RNA polymerase also fails. EX2008, ¶77. First, Dr. Sherman erroneously assumes that Stahl's *RNA amplification* must occur in solid phase. EX2008, ¶77. In a simple modification of Stahl's method, the cleavage step would

be deferred and the first-strand cDNAs would remain bound to the array surface rather than being released into solution. The second-strand cDNAs would then be synthesized on the array using the first strand cDNA as templates (and bound or unbound primers). EX1044, ¶¶167-168. This second-strand cDNA synthesis on the array satisfies claim 5's solid-phase amplification requirement under Bruker's infringement contentions. EX1044, ¶¶167-168; EX1022, 32-33.

101. The double stranded cDNAs (resulting after second-strand synthesis) in Stahl's modified method could be released from the array to perform RNA amplification in solution (using Stahl's method). Alternatively, the double stranded cDNAs could be maintained on the array to perform RNA amplification on the array for library preparation. EX1017, 84:20-31; EX1005, ¶¶[00327]-[00330].

102. A POSA would have known to increase the length of Stahl's capture probe (containing RNA polymerase promoter) if the RNA polymerase required more physical space for solid-phase RNA amplification. Such modifications to probe length were well within the basic capabilities of a POSA and would represent routine procedures for a POSA to perform, and not "significant modifications" as Dr. Sherman alleges. EX2008, ¶78; EX1056, 20:11-21:10; EX1044, ¶¶194. A POSA would have known that the solid-phase first-strand synthesis (reverse transcription) reaction and solid-phase RNA amplification steps in Stahl's modified method would occur in the same direction and thus by having a

linker long enough the in vitro transcription RNA amplification reaction would proceed. The linker in Stahl is

5'UUUUUGACTCGTAATACGACTCAC**TATA**GGGACACGACGCTCTTCCG ATCT[18bp]WSNNWS 3' followed by the capture primer. The bold TATA represents the start site of in vitro transcription, and therefore, if needed, a POSA would have lengthen the sequence between the 5 uracils (U's) and the TATA.

103. Dr. Sherman arguments for lack of motivation also fail. EX2008, ¶¶79-85. As a preliminary note, Dr. Sherman provides little to no supporting references for his arguments. *Id*. Instead, Dr. Sherman simply assumes that because the authors of Frisen published one method (Stahl) that the other possibilities do not work ("The natural inference is that Petitioner's proposed modifications do not work") completely unsupported by fact, or reason. Numerous reasons can lead to a single method being published (for example, better intellectual property, modest improvements in performance, or decrease in cost).

104. Dr. Sherman first argues against motivation because Stahl's authors "while in possession of everything disclosed in Frisen, published the most optimized workflow for the purpose they sought at the time of publication" and did not publish a method with Frisen's solid-phase synthesis. EX2008, ¶79. Dr. Sherman also points to Spatial Transcriptomics's commercial workflow using solution-phase second-strand synthesis as some sort of indication for lack of

motivation to modify Stahl's method to perform solid-phase second-strand synthesis. EX2008, ¶80. I disagree with Dr. Sherman. As I explained at deposition, a POSA would have had "a large number of reasons" to modify Stahl's workflow, e.g., "spacially restrict individual … molecules" or "as simple as wanting to skip the user enzyme [i.e., cleavage] step, for example." EX2009, 92:18-19, 92:14-20, 98:5-6. Dr. Sherman ignores this testimony that comes before my testimony that Dr. Sherman cites out of context. EX2008, ¶79 (citing EX2009, 101:3-101:10). In fact, my testimony that Dr. Sherman cites stating that Stahl's authors published "something that worked" is consistent with my remaining testimony. EX2009, 100:3-11.

105. Dr. Sherman next argues against motivation to modify Stahl because sensitivity and selectivity offered by solid-phase amplification are "highly dependent on the workflow and require significant experimentation to modify Stahl's existing workflow." EX2008, ¶82. To support this assertion, Dr. Sherman cites to a statement indicating that "the emergence of 'active' arrays ***may*** provide the sensitivity and selectivity for nucleic acid identification and genotyping," emphasizing that the reference's use of "may" would inform a POSA that the potential benefits were uncertain. EX2008, ¶82 (quoting EX1048, 11). I disagree with Dr. Sherman.

106. The teaching that solid-phase amplification "may" improve sensitivity

and selectivity would have highlighted the *possibility* that the technique could provide such benefits rather than teaching a POSA that the benefits were unlikely. EX1048, 11. Moreover, Dr. Sherman's cited reference explicitly teaches that "[a] large variety of enzymatic reactions have been *shown to be successfully performed on microarrays*" and "*progress has been made* in the implementation of these techniques on classic planar surfaces." EX1048, 11; EX1044, ¶¶172-174. Far from discouraging a POSA, this teaching would have encouraged a POSA to consider them and would have given the POSA a reasonable expectation of success in adapting the techniques for a "large variety of enzymatic reactions," including the synthesis reactions in Stahl. EX1048, 11; EX1044, ¶¶172-174.

107. Dr. Sherman further argues lack of motivation to modify Stahl due to concern with "the many drawbacks of solid-phase amplification." EX2008, ¶83. According to Dr. Sherman, the "many drawbacks" of solid-phase amplification included "electrostatic forces, the finite number of primers, polymerase and nucleotide availability, sterile molecules, and DNA rigidity." EX2008, ¶83 (citing EX2013 at 40-41). I disagree with Dr. Sherman.

108. EX2013 that Dr. Sherman cites never refers to these qualities as "drawbacks." *See* EX2013. Instead, the reference merely characterizes these aspects as "effect[s]" that can "play a role in the [solid-phase amplification] process and should be considered for a complete understanding of [solid phase

amplification].” EX2013, 41. In fact, EX2013 published more than 10 years before Stahl and the 142 patent—in 2005—and introduced solid-phase amplification as a “*new method* to amplify DNA.” EX2013, Abstract (emphasis added). Over the 10-year period after EX2013’s publication, there were developments in the art providing solutions by 2018, as evidenced by the numerous examples and methods for performing solid-phase amplification in the art, including Stahl (providing solid-phase first-strand cDNA synthesis. *See, e.g.*, EX1044, ¶175 (citing EX1005; EX1017; EX1042; EX1049); EX1016. Thus, by 2018, solid-phase synthesis for amplification was a well-tested, useful technique such that a POSA would not have been dissuaded by any purported drawbacks published that EX2013 noted in 2005. EX1044, ¶175.

109. Further, EX2013’s method that “attach[es] the primers (via their 5’ end) to a solid surface” has all primers in the reaction bound to the surface. EX2013, 32. But, under the specification, the Board’s construction, and Bruker’s infringement interpretation, claim 5 requires that only one of the primers is bound to the solid surface. EX1022, 32-33; Section III.A; EX1043, 42:41-45. Dr. Sherman’s interpretation based on EX2013 is thus flawed. The major concerns that Dr. Sherman points to from EX2013 are essentially irrelevant as EX2013 focused on multiple rounds of PCR amplification, and not second strand synthesis or in vitro transcription.

110. Dr. Sherman's criticisms of solid-phase amplification based on EX1050's also fail as those criticisms are based on discussion of *colony* amplification, and not second-strand cDNA synthesis or *in vitro* transcription

111. Dr. Sherman finally argues against motivation because "Stahl already benefits from employing a solid-phase reaction, such as being able to easily wash away unbound sample" and therefore a POSA "would not have further modified Stahl to implement solid-phase amplification for additional steps." EX2008, ¶84. I disagree with Dr. Sherman.

112. While, Dr. Sherman agrees that Stahl performs a solid-phase synthesis (in first-strand cDNA synthesis) and that solid-phase synthesis has advantages, he then argues that the solid-phase synthesis is no longer needed. EX2008, ¶84. The benefits from solid-phase synthesis of Stahl's first-strand cDNAs (retaining spatial information of the target mRNAs) as in the Stahl method and second-strand cDNAs (e.g., scalability) as in the modified Stahl method are different and non-interchangeable. Moreover, solid-phase synthesis for second-strand cDNA synthesis in the modified Stahl method would avoid the use of RNAse to degrade the mRNA used to make first strand and instead would use washes prior to the second strand, something that Sherman acknowledges is a benefit of solid phase. EX2008, ¶84 ("such as being able to easily wash away unbound sample").

113. Accordingly, I maintain my opinion set forth in my first declaration

that claim 5 would have been obvious over Stahl. EX1044, ¶¶165-178. Further, claim 5 would have been obvious over Stahl under the Board's constructions.

C. Claim 5 is obvious over Stahl and Frisen

114. As explained in my first declaration, claim 5 would have been obvious over Stahl and Frisen. EX1044, ¶¶179-196. Dr. Sherman makes the same arguments against obviousness over Stahl and Frisen as he did against obviousness over Stahl. EX2008, ¶¶86-87, 91-93, 95. I disagree with Dr. Sherman for the reasons explained above in Section VI.B.

115. Additionally, Dr. Sherman argues against a POSA being motivated to combine Stahl and Frisen because Frisen disclosed that solid-phase second-strand cDNA synthesis was "optional" and that the "'synthesis may be achieved by any means known in the art' and is preferably in solution." EX2008, ¶¶88-89. In my opinion, however, these Frisen disclosures would not have detracted a POSA from modifying Stahl's method in view of Frisen's solid-phase second-strand synthesis. As discussed above, a POSA would have had a substantial understanding of the potential benefits, advantages, and use-cases of solid-phase amplification from their knowledge of the prior art. *See* Section VI.B; EX1044, ¶¶175, 188-194. A POSA with this knowledge would have been sufficiently motivated to combine Stahl with Frisen to arrive at claim 5, regardless of Frisen's disclosure that Dr. Sherman cites. EX1044, ¶¶179-196.

116. Dr. Sherman also argues against motivation because Frisen's second-strand cDNA is synthesized "so that the double-stranded cDNA 'may be sequenced directly,'" whereas Stahl's method purposefully "amplified RNA so as to maintain strand preservation" "completely contrary to Frisen's teaching." EX2008, ¶89 (citing EX1017, 39:1-8). There are two problems with this argument; first, the second strand synthesis done directly from the first strand template meets the claim limitations of the solid phase synthesis itself, thus admitting that Frisen discloses solid phase synthesis. Second, Dr. Sherman mischaracterizes Frisen's cited paragraph—which is just one "instance" disclosed in Frisen where large amounts of RNA in the sample allow direct sequencing of second-strand cDNAs without amplification; no teaching in Frisen should be viewed as exclusionary to other teachings. EX1017, 39:1-8.

117. As Dr. Sherman acknowledges, the "other embodiment[]" disclosed immediately after Dr. Sherman's cited paragraph states that "it will be necessary to enhance, i.e. *amplify*, the amount of secured nucleic acid, e.g. *synthesized [second-strand] cDNA* to yield quantities that are sufficient for DNA sequencing…. [S]econd strand of DNA, e.g., cDNA, which itself will act as a template for further cycles of the amplification reaction." EX1017, 39:9-16 (emphasis added); EX2008, ¶90. Dr. Sherman however mischaracterizes this paragraph of Frisen as well when he states that it "does not discuss solid-phase amplification." EX2008, ¶90. Both of

Dr. Sherman's cited Frisen paragraphs appear as part of a discussion on solid-phase synthesis, e.g., stating: "The step of second strand DNA, e.g. cDNA, synthesis may take place *in situ* on *the array*, either as a discrete step of second strand synthesis, for example using random primers as described in more detail below, or in the initial step of an *amplification reaction*." EX1017, 38:9-34 (emphasis added).

118. Moreover, as explained above, strand preservation is an inherent feature of Stahl's method due to its design to capture RNAs with oligoA tails using capture probes containing oligo dT sequence and is not dependent on Stahl's RNA amplification step. See Section V.C; EX1056, 71:4-7, 81:22-82:6; EX1044, ¶70. And, a POSA would still have been able to include RNA amplification and subsequent Stahl steps after synthesizing second-strand cDNA on the array. *See* Section VI.B.

119. Dr. Sherman argues that parallelization does not provide motivation for solid-phase synthesis because "[m]odifying Stahl's method so that there is additional parallelization of DNA amplification is unnecessary as each capture probe already contains a location-identifying sequence so that the sequenced result can be traced back to the location of the array where the mRNA was captured." EX2008, ¶94. I disagree with Dr. Sherman.

120. Sherman again applies an inappropriate narrow construction to the

terms amplification and solid phase, which as construed in this litigation mean "the synthesis of a nucleic acid from a template using a primer" and "where one product is bound to a solid substrate", and not "clonal amplification with linked primers" or any such more specific term as Sherman continues to imply. In this context, there are multiple valid reasons for parallelization, for example, gaskets that created multiple reaction chambers were routinely used to segment different parts of an arrays in parallel to perform downstream reactions (e.g. second strand synthesis) rather than extracting material from the array.

121. Finally, Dr. Sherman argues against reasonable expectation of success in modifying Stahl with Frisen. EX2008, ¶95. I disagree with Dr. Sherman for the reasons explained above in this section and in Section VI.B. Accordingly, I maintain my opinion set forth in my first declaration that claim 5 would have been obvious over Stahl and Frisen. EX1044, ¶¶179-196. Further, claim 5 would have been obvious over Stahl and Frisen under the Board's constructions.

VII. GROUND 4: SO-456 ANTICIPATES CLAIMS 1-13

A. As explained in my first declaration, So-456 teaches the claimed synthesis steps according to Bruker's infringement contentions

122. Claim 1 steps (c) and (d) (the "synthesizing steps" of claim 1) recite:

> [S]ynthesizing a first [and second] plurality of DNA products by performing a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) [and (b)]

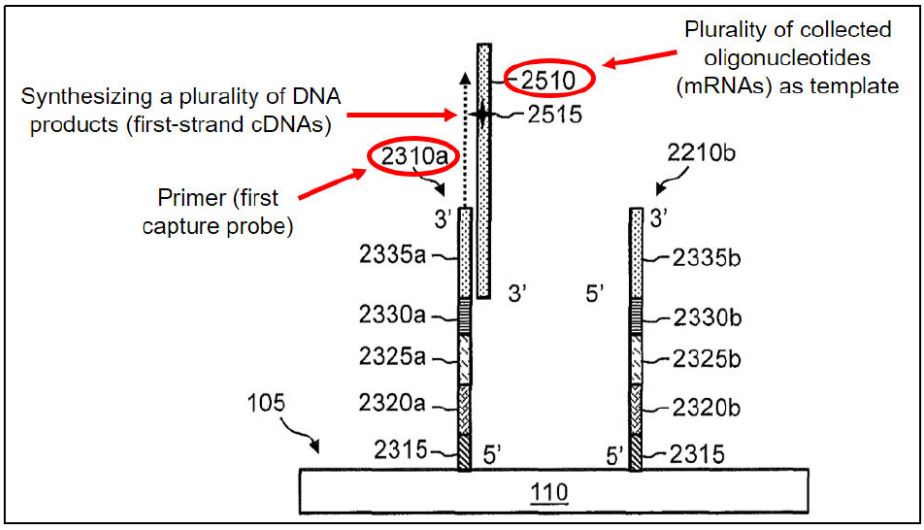
> as templates and incorporates at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample into each of the first [and second] plurality of DNA products.

EX1043, 147:42-53.

123. As discussed in Sections III.A and V.A above, the synthesizing steps 1(c) and 1(d) impose two requirements on "a synthesis reaction" for "synthesizing DNA products." *First*, the synthesis reaction uses the collected oligonucleotides as templates to synthesize DNA products (template requirement). *Second*, at least one sequence that identifies the location of the tissue sample (i.e., spatial barcode or location-identifying sequence) is incorporated into the DNA products (incorporation requirement). EX1044, ¶¶62-63.

124. Dr. Sherman agrees with this interpretation, stating that a POSA would have understood that steps 1(c) and 1(d) "require a synthesis reaction that generates DNA products" and the synthesis reaction requires "the collected oligonucleotides to be used as templates" and "the location-identifying sequences to be incorporated into the DNA products." EX2008, ¶35; EX1056, 26:8-27:7. Dr. Sherman agrees that a *single* synthesis reaction meets both the template requirement and incorporation requirement of steps 1(c) and 1(d) of claim 1. EX2008, ¶35; EX1056, 28:6-24.

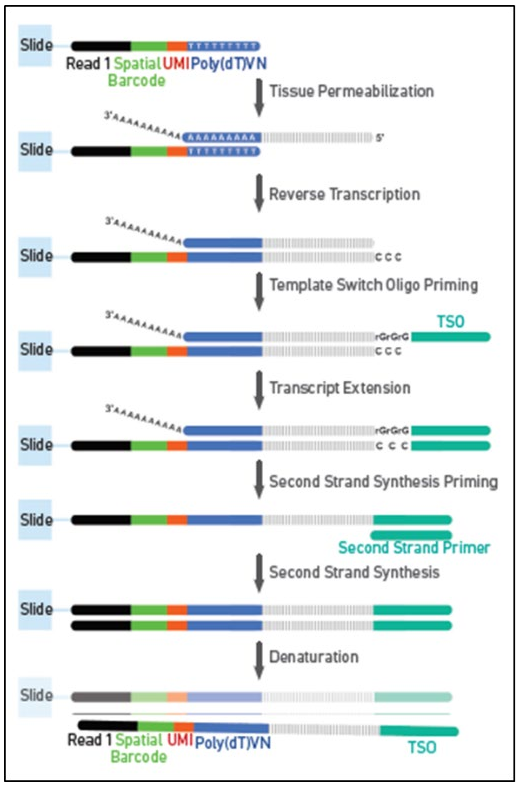
125. As explained in my first declaration, under Bruker's infringement contentions, So-456 teaches claim 1's steps (c) and (d) because So-456's method includes synthesizing first-strand cDNAs by reverse transcription using "captured mRNA molecules" (i.e., captured oligonucleotides) as templates, with the resulting first-strand cDNAs (DNA products of steps (c) and (d) of claim 1) incorporating spatial barcodes. EX1044, ¶¶209-215; EX1022, 18-22; EX1005, ¶¶[00309], [00316], FIGs 24, 25A. This first-strand cDNA synthesis is depicted as a dotted arrow in the annotated version of So-456's Figure 25A from my first declaration reproduced below:



EX1044, ¶209; EX1005, FIG. 25A (annotated).

126. So-456's first-strand cDNA synthesis is consistent with Bruker's contentions, which cite Visium FF's "Step 1 Permeabilization and Reverse Transcription" for claim 1's steps (c) and (d) and includes the following portions of

Visium FF's workflow depiction.



EX1022, 18-20, 22; EX1015, 17. Bruker's infringement contentions note that Visium FF's Step 1 involves adding a "RT Master Mix containing reverse transcription reagents" which "produces spatially barcoded, full-length cDNA from poly-adenylated mRNA." EX1022, 18-19.

127. As also explained in Section V.A., although Bruker's infringement contentions for claim 1's steps (c) and (d) also cite Visium FF's "Step 2 Second Strand Synthesis & Denaturation," a POSA would understand that Bruker's contentions are not based on Visium FF's Step 2. *See* Section V.A; EX1022, 17-20, 22. This is because Visium FF's Step 2 does not meet the template requirement of claim 1's steps (c) and (d): the second-strand synthesis in Visium FF's Step 2

uses the first-strand cDNAs as templates rather than the collected mRNAs, as necessary under claim 1's template requirement. *Id*. And because a *single* synthesis reaction must meet both the template requirement and incorporation requirement of claim 1's steps (c) and (d), Bruker's infringement contentions for claim 1's steps (c) and (d) must be based on Visium FF's Step 1 (Reverse Transcription Step). EX1044, ¶¶62-63, 209-215.

128. Dr. Sherman now argues that So-456's first-strand cDNA synthesis does not meet claim 1's steps (c) and (d) for two reasons. *First*, as he also argued for Stahl, Dr. Sherman argues that So-456 "does not disclose that the nucleic acid sequence used for location identification is incorporated *during the synthesis reaction*." EX2008, ¶103 (emphasis added); *see also id*., ¶¶104-106. *Second*, Dr. Sherman argues that So-456's "first-strand cDNA … only incorporates ***half*** the information necessary to identify the location." EX2008, ¶101; *see also id.*, ¶¶99-100. I disagree with each of Dr. Sherman's arguments and discuss them in turn below. In this case the primer used to initiate the synthesis reaction (a required element in the template directed reaction) carries the location identifying sequence and that primer is incorporated into the molecule during the synthesis reaction using the mRNA as template EX2008, ¶¶103-106; see Section V.A.

129. Dr. Sherman's first argument fails for the same reasons discussed above for Stahl. *See* Section V.A. As explained above in Section V.A, Dr. Sherman

is wrong to interpret "incorporate" in steps (c) and (d) of claim 1 to refer to "addition of a sequence as each nucleotide is sequentially added during synthesis." EX2008, ¶52; *see* Section V.A. Instead, as Dr. Sherman also notes as part of his interpretation of steps (c) and (d) of claim 1, all that is required is that "the location-identifying sequences to be incorporated into the DNA products." EX2008, ¶35; *see* Section V.A.

130. Dr. Sherman's argument is inconsistent with Bruker's infringement contentions that Visium FF's first-strand cDNA synthesis meets steps (c) and (d) of claim 1, when Visium FF's first-strand cDNA synthesis similar to So-456's first-strand cDNA synthesis does not incorporate the spatial barcode into the first-strand cDNA *during* the synthesis. EX1022, 18-19; EX1015, 17; *see* Section V.A. In Visium FF, "the spatial address region [i.e., spatial barcode] is already found in the capture probe that is extended" similar to So-456's method. EX2008, ¶105; EX1022, 18-19; EX1015, 17.

131. Dr. Sherman's second argument likewise is wrong as it ignores the plain language of claim 1, which only requires that "*at least one* nucleic acid sequence that identifies the first [and second] location of the tissue sample" be incorporated into the DNA products. EX1044, ¶¶212-215; EX1043, 147:42-53. As Dr. Sherman acknowledges, "sequence 2325a (encoding the X-coordinate) is part of the [first-strand] cDNA." EX2008, ¶101; EX1044, ¶88. As Dr. Sherman also

acknowledges, "'spatial address region 2325a' is 'a unique spatial address sequence for the X dimension.'" EX2008, ¶99; EX1043, 147:42-53; EX1044, ¶¶214-215. Thus, the spatial barcode (2325a) incorporated into the first-strand cDNAs in So-456's method identifies the location of a stripe along the X-dimension of the tissue sample and satisfies the requirements of steps (c) and (d) of claim 1. No requirements of the claim limit the spatial location to be a grid coordinate, or any other constraint as to the shape of the location is required. In the 142 patent, the illustrative examples all encode an arbitrary user defined area, which are typically drawn as a region of interest but could just as easily be a stripe.

132. Thus, I maintain my opinion that So-456 teaches steps (c) and (d) of claim 1 under Bruker's infringement contentions. EX1044, ¶¶209-215.

B. So-456 teaches a method that includes steps (c) and (d) of claim 1 under the Board's construction

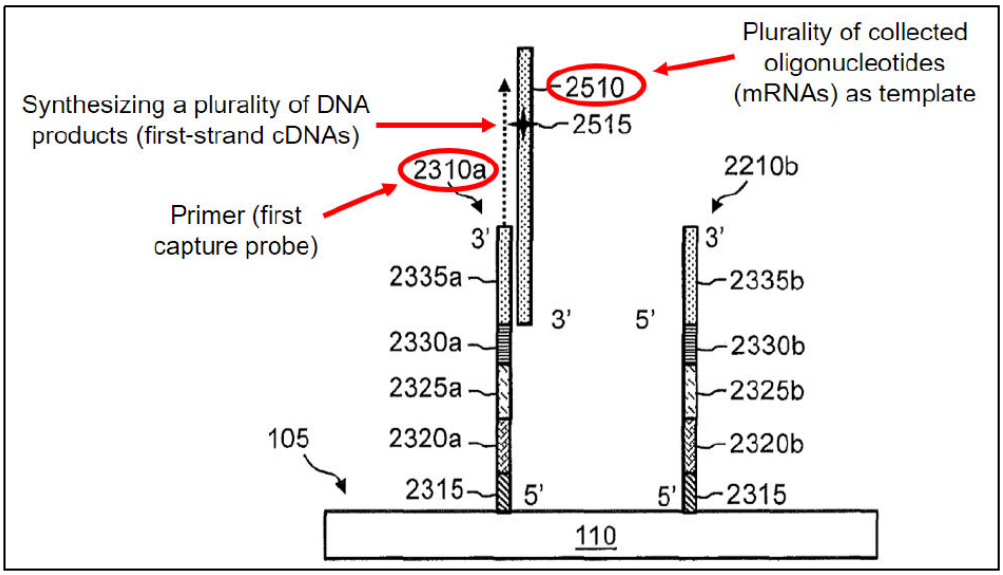
133. In my opinion, So-456 teaches a method that includes steps (c) and (d) of claim 1 under the Board's interpretation of "synthesizing DNA products." *See* Section III.A.

134. As discussed above, I understand that the Board interpreted "synthesizing DNA products" as encompassing a two-step synthesis of the DNA products. *See* Section III.A. I understand that the Board interpreted the "DNA products" of steps (c) and (d) of claim 1 as not limited to "the first cDNA strand – and only this strand." *See* Section III.A. I also understand that, after 10x filed the

Petition with my first declaration, Bruker argued that Visium FF's step 1 (first-strand cDNA synthesis) and step 2 (second-strand cDNA synthesis) *together* perform the claimed synthesis reaction. EX1022, 18-20.

135. As explained in my first declaration, So-456's method includes synthesizing first-strand cDNAs comprising a spatial barcode by using the collected mRNAs as templates (e.g., FIG. 25A, step 2415) and synthesizing second-strand cDNAs using the first-strand cDNAs as templates, wherein the spatial barcode present in the first-strand cDNAs is incorporated into the second-strand cDNA during synthesis (e.g., FIG. 25B, step 2425). EX1005, FIG. 25-A-B, ¶¶[00314]-[00318]; EX1044, ¶¶209-215. So-456's second-strand cDNAs are the "DNA products" of steps (c) and (d) of claim 1 under the Board's and Bruker's IPR constructions. EX1044, ¶¶209-215.

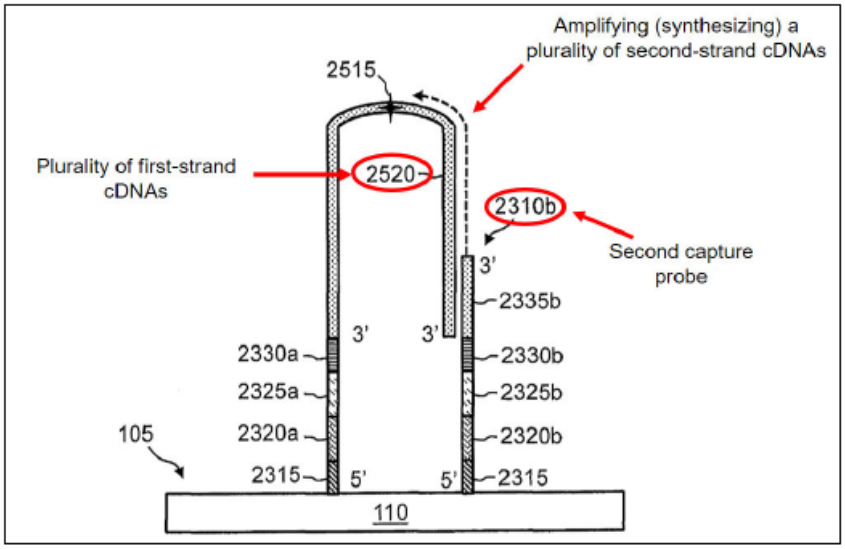
136. So-456's method includes a first step of synthesizing first-strand cDNAs comprising a spatial barcode using the collected mRNAs as templates. EX1044, ¶¶209-215; EX1005, FIG. 25A, ¶¶[00314]-[00317]. This first step is depicted in So-456's annotated Figure 25A from my first declaration:



EX1044, ¶209; EX1005, FIG. 25A, step 2415 (annotated).

137. As shown in the Figure above, So-456's method collects mRNAs (2510) using capture probes (2310a) attached to an array (110). EX1005, FIG. 25A; EX1044, ¶¶213-215. The collected mRNAs are then used as templates for synthesizing first-strand cDNAs (in step 2415), with the synthesis shown by the dotted arrow. *Id*. The capture probes include a spatial barcode (2325a), which is incorporated into the first-strand cDNAs. *Id.*

138. Next, So-456's method includes synthesizing second-strand cDNAs using the first-strand cDNAs as templates, wherein the spatial barcode present in the first-strand cDNA is incorporated into the second-strand cDNA during synthesis. EX1044, ¶¶209-215; EX1005, FIG. 25B, ¶¶[00317]-[00318]. This second step is illustrated in So-456's annotated Figure 25B from my first declaration:



EX1044, ¶¶88, 209-215, 233; EX1005, FIG. 25B (annotated).

139. As shown in the figure above, the second step (Step 2425) of So-456's method uses the first-strand cDNAs (2520) as templates to synthesize second-strand cDNAs ("DNA products" of steps (c) and (d) of claim 1), with the synthesis shown by the dotted arrow. EX1005, Figure 25B. This synthesis copies and incorporates the spatial barcode in the first-strand cDNAs (2325a) into the second-strand cDNAs. *Id*.

140. Thus, So-456's first-strand cDNA synthesis meets the template requirement of steps (c) and (d) of claim 1. EX1044, ¶¶62-63, 209-215. And, So-456's second-strand cDNA synthesis meets the incorporation requirement of steps (c) and (d) of claim 1, under the interpretation of "incorporate" that Dr. Sherman proposes in ¶52 of his declaration and under the interpretation of "incorporate" applied in my first declaration (and above in Section V.A). EX1044, ¶¶111-115.

Accordingly, So-456's first-strand cDNA synthesis and second-strand cDNA synthesis (steps 2415 and 2425) *together* satisfy the template and incorporation requires of each of steps (c) and (d) of claim 1 and perform these steps. EX1044, ¶¶88, 209-215; EX1005, FIG. 25-A-B, ¶¶[00314]-[00318]. And So-456's second-strand cDNAs are the "DNA products" of steps (c) and (d) of claim 1 under the Board's and Bruker's IPR constructions.

141. So-456's first- and second-strand cDNA synthesis are equivalent to Visium FF's steps 1 and 2. EX1022, 18-19; EX1015, 17. These Visium FF steps present a two-step process of synthesizing spatially barcoded first-strand cDNAs using collected mRNAs as templates (step 1), and synthesizing spatially barcoded second-strand cDNAs ("DNA products" of steps (c) and (d) of claim 1) using the first strand cDNAs as templates, wherein the spatial barcode in the second-strand cDNAs is incorporated during synthesis. *See* Sections V.A-B.

142. Thus, So-456 teaches a method that includes steps (c) and (d) of claim 1 under the Board's construction of "synthesizing DNA products."

C. As explained in my first declaration, So-456 teaches conditions that release oligonucleotides

143. Claim 1 steps (a) and (b) recite:

> Collecting a plurality of oligonucleotides from a first location [and second location] of a tissue sample under conditions that release the plurality of oligonucleotides

from the first location [and second location] of the tissue sample.

EX1043, 147:34-41.

144. As explained in my first declaration, So-456 teaches claim 1's recited "conditions that release the plurality of oligonucleotides from the first location [and second location] of the tissue sample" under Bruker's infringement contentions. EX1044, ¶¶207-208; EX1005, ¶¶[00152], [00154]-[00155], [00308], [00315]. Dr. Sherman argues that the So-456 disclosures I relied upon "do[] not disclose treating a tissue sample so that the oligonucleotides are released." EX2008, ¶116; *see also id.*, ¶¶109-115. I disagree with Dr. Sherman.

145. As explained in my first declaration, So-456 expressly teaches that the "tissue sample is prepared for analysis" (in step 210) *before* "the target nucleic acid … in the tissue section *is transferred onto an array*" (in step 220) in So-456's methods. EX1044, ¶¶207-208; EX1005, ¶¶[00152], [00154]; *see also id.*, ¶¶[00308] ("mRNA molecules are *captured* onto the array" (emphasis added)), [00315] ("mRNA molecule 2510 in a tissue sample is *captured* on capture probe" (emphasis added)).

146. Moreover, the conditions that release the target oligonucleotides in the tissue sample depend on the type of tissue sample, sample's prior treatments, and the objective of the experiment. EX2009, 109:13-121:11. Appropriate treatments

include, for example, thawing, sectioning, immobilization, de-paraffinization, de-crosslinking, and/or permeabilization. And, such treatments were routine in the art. EX1016, 78, Supp. 4-6 (teaching a method for "permeabilization and reverse transcription"); EX1057, 2, 7, FIG. 1; EX1058, 1. Dr. Sherman acknowledges that permeabilization meets the claimed conditions. EX2008, ¶¶109-111. For example, as I testified in my deposition, thawing of a frozen tissue sample is one such condition that would, at least partially, release the target mRNAs from the tissue sample. EX2009, 114:22-115:11, 117:12-18, 119:22-120:21.

147. Dr. Sherman wrongly argues that So-456 disclosure in paragraph 152 "refer[s] to the sectioning, as the paragraph does not disclose any steps of treatment to facilitate nucleic acid release." EX2008, ¶112. Dr. Sherman misses that paragraph 152 teaches the tissue sample is "sectioned onto a slide" in only "some embodiments" of So-456's methods. EX1005, ¶[00152].

148. Dr. Sherman is also wrong to argue that So-456's paragraphs 154, 308, and 315 are "focused on the step of contacting a tissue sample with a probe, and not creating conditions that release the nucleic acids." EX2008, ¶113. As explained in my first declaration, these paragraphs expressly teach that the target nucleic acids are "transferred onto an array," "captured onto the array," and "captured on capture probe" from the tissue sample. EX1044, ¶¶207-208; EX1005, ¶¶[00154], [00308], [00315]. Thus, these paragraphs teach release of the target

mRNAs from the tissue sample and transfer to the array (or capture probe on the array), rather than merely contacting the tissue sample with a probe as Dr. Sherman alleges. EX1044, ¶¶207-208; EX2008, ¶115.

149. Dr. Sherman ignores So-456's paragraph 155 I cited in my first declaration. EX1044, ¶207; EX1005, ¶[00155]. So-456's paragraph 155 discloses multiple methods involving target nucleic acids "diffuse" from the tissue sample. *See e.g.* EX1005, ¶[00155] ("probes may be contacted with target nucleic acid by … placing the tissue on a substance such as a filter or a gel or a thin buffer layer separating the tissue from the probes such that the target nucleic acid may *diffuse from the tissue*" (emphasis added)). Thus, as explained in my first declaration, So-456's paragraph 155 teaches that the conditions that release the target nucleic acids from the tissue sample were *necessarily* included in So-456's method:

> So-456 [in paragraph 155] discloses that the "target nucleic acid" (mRNA) "diffuse[s] from the tissue" onto the array. In my opinion, this further confirms that the tissue sample was treated to create a condition to "release" the mRNA from the tissue onto the array.

EX1044, ¶207.

150. I confirmed my opinion during deposition. EX2009, 119:7-12 ("[R]elease of mRNA from the tissue sample] would be required so that it can be

captured on the array"), 119:13-21 ("It [So-456] says that it happens. It literally says it. It says the array elements collect the mRNA."). In fact, Dr. Sherman agrees with me, stating that "it would be impossible to perform the analysis" of the target nucleic acids in a tissue sample "without first treating the sample in a manner to create the conditions for release." EX2008, ¶110. Dr. Sherman mischaracterizes my deposition testimony when he alleges that I "did not find [inherency argument] present in [my first] declaration." EX2008, ¶115 (citing EX2009, 18:21-19:2, 19:22-26:7). Dr. Sherman however ignores my testimony, where I noted that by asking me to identify inherency arguments in my first declaration, Bruker's counsel was "asking me to memorize specific sections" in an "almost 150 pages long" declaration (which I denied to do); that the "specific words 'inherent' or 'inherency' do not appear to be present anywhere other than in [paragraphs] 36, 36, 37" of my first declaration; and that my first declaration is my testimony. EX2009, 22:6-26:7.

151. Dr. Sherman also argues that "the claimed 'conditions' would have been different from those in prior methods, such as in situ hybridization, which did not collect and identify nucleic acids from the tissue sample." EX2008, ¶109. However, Dr. Sherman's reliance on "in situ hybridization" for the conditions required in steps (a) and (b) of claim 1 is misleading. In particular, Dr. Sherman points to "in situ hybridization" methods that may not release target nucleic acids

from the tissue sample (as the hybridization may be performed on the tissue sample), while ignoring several prior spatial genomics and transcriptomics references that taught treatments for conditions that release oligonucleotides from tissue samples. EX1044, ¶¶105-106, 207-208. For example, EX1016, 78, Supp. 4-6 (teaching a method for "permeabilization and reverse transcription"); EX1057, 2, 7, FIG. 1; EX1058, 1. Thus, Dr. Sherman does not address prior art methods that a POSA would have known were applicable to the release of oligonucleotides from a tissue sample in spatial genomics and spatial transcriptomics.

152. Finally, Dr. Sherman points to the 142 patent's disclosure in Figure 22B allegedly showing the "FFPE block [is] sectioned" and the "sections are processed 'with multiplexed cocktails'" as a "'processing' step [that] creates that claimed 'condition' for release." EX2008, ¶¶109-110. However, Dr. Sherman is again wrong. Even assuming for argument sake that Figure 22B of the 142 patent discloses conditions that are "different from those in prior methods" (which it does not), the 142 patent claims are not limited to an FFPE tissue sample. *See* EX1043, 41:26-41 ("The sample can be cultured cells or dissociated cells (fixed or unfixed) that have been immobilized onto a slide. A sample can be a formalin-fixed paraffin-embedded (FFPE) tissue sample"); EX2008, ¶109. And as I explained above, the conditions to release target nucleic acids from the tissue samples both FFPE and other types (e.g. frozen) were known in the prior art.

153. Thus, I maintain my opinion that So-456 teaches a method that includes conditions that release oligonucleotides, as required in claim 1. EX1044, ¶¶207-208.

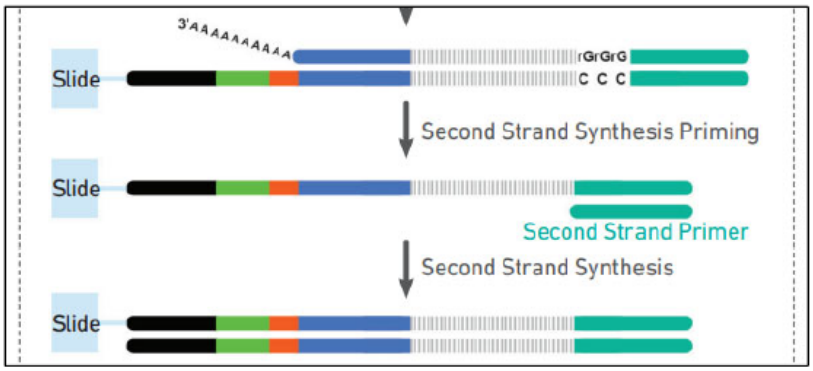
D. So-456 teaches solid-phase amplification to synthesize DNA products (claim 5)

154. Claim 5 depends from claim 4, and requires that each of step (c) and (d) "comprises performing a solid-phase amplification reaction, wherein the solid-phase amplification reaction is carried out on the microscope slide using the plurality of primers immobilized on the microscope slide." EX1043, 148:37-41. As explained in my first declaration, So-456 anticipates claim 5 because it teaches a method that includes solid-phase second-strand cDNA synthesis using the first-strand cDNA products as templates. EX1044, ¶¶230-235; EX1005, FIG. 25B, ¶[00318].

155. Dr. Sherman argues that 10x "must show that synthesis of the *first-strand cDNA* is performed using a solid-phase amplification reaction." EX2008, ¶118 (emphasis added). I disagree with Dr. Sherman. As explained in my first declaration, I understand that because claim 5 recites "comprises," it only requires that solid-phase amplification take place as part of claim 1's steps (c) and (d), before sequencing in claim 1's step (e). EX1043, 148:37-41; EX1044, ¶230. In So-456, solid-phase second-strand cDNA synthesis takes place after the first-strand cDNA synthesis but *before* sequencing. EX1005, ¶¶[308]-[313]; EX1044, ¶¶231-

235. Therefore, solid-phase second-strand synthesis in So-456 would satisfy claim 5.

156. Furthermore, Dr. Sherman's argument is inconsistent with Bruker's own infringement contentions for claim 5. As I explained in my first declaration, Bruker's infringement contentions also rely on Visium FF's second-strand cDNA synthesis to meet the solid-phase amplification of claim 5, while relying on Visium FF's first-strand cDNA synthesis for "synthesizing DNA products" and first-strand cDNAs for "DNA products" of claim 1's steps (c) and (d). EX1044, ¶231; EX1022, 32-33, 18-22. For example, Bruker cites for claim 5 the following excerpts of Visium FF's workflow showing the second-strand cDNAs synthesis from the first-strand cDNAs attached to a slide—*i.e. solid-phase second-strand synthesis*:



EX1022, 33; EX1015, 17.

157. So-456 also anticipates claim 5 under the Board's construction of "synthesizing DNA products." As discussed above, I understand that the Board

interpreted "DNA products" as *not* limited to "the first cDNA strand – and only this strand." *See* Sections III.A, V.A, VI; DOI, 22. Thus, the synthesized "DNA products" under the Board's construction include So-456's second-strand cDNAs generated by solid-phase amplification—just like Visium FF's "second strand synthesis" in Step 2 identified in Bruker's infringement contentions. EX1022, 32-33; EX1017, 17; EX1005, ¶¶[308]-[313]; EX1044, ¶¶231-235.

158. Thus, So-456 teaches a method that includes solid-phase amplification to synthesize DNA products, as required in claim 5. EX1044, ¶¶230-235.

E. So-456 teaches amplifying a library using DNA products as templates (claim 7)

159. Claim 7 of the 142 patent recites that the method of claim 1 "further comprises amplifying a library using the first plurality of DNA products and the second plurality of DNA products as templates." EX1043, 148:44-46.

160. As explained in my first declaration, So-456 teaches amplifying a library by using the first-strand cDNAs (DNA products of steps (c) and (d) of claim 1) as templates under Bruker's infringement interpretation. EX1044, ¶¶238-239; EX1005, [00310], [00317]-[00318], FIGs. 24, 25B.

161. Bruker's infringement contention asserts that Visium FF's steps 3 and 4 practice claim 7 of the 142 patent. EX1022, 35-36; EX1015, 17-18. Visium FF's step 3 "cDNA Amplification & QC" constitutes amplifying the "spatially barcoded" second-strand cDNAs "after transfer of [the second-strand] cDNA from

the slide" via denaturation (in step 2). EX1015, 17. The second-strand cDNAs were synthesized (in step 2) using the first-strand cDNAs with incorporated spatial barcode (Bruker's identified DNA products in Visium FF) as templates. *Id.* Because the first-strand cDNAs remain attached to the slide in step 2, only the second-strand cDNAs are transferred "to a corresponding tube for amplification and library construction." *Id*. Thus, only second-strand cDNAs are used as templates for cDNA amplification and library preparation in Visium FF's steps 3 and 4. *Id*., 17-18.

162. As explained in my first declaration, similar to Bruker's identified Visium FF's steps 3 and 4, So-456's method includes multi-step amplification of the second-strand cDNAs (synthesized from the first-strand cDNAs as templates) released from the array to "generate a sequencing library," with only the second-strand cDNAs being used as templates. EX1005, ¶¶[00312]-[00318], FIG. 24; EX1044, ¶¶238-239. So-456's Figure 24 depicts this process:

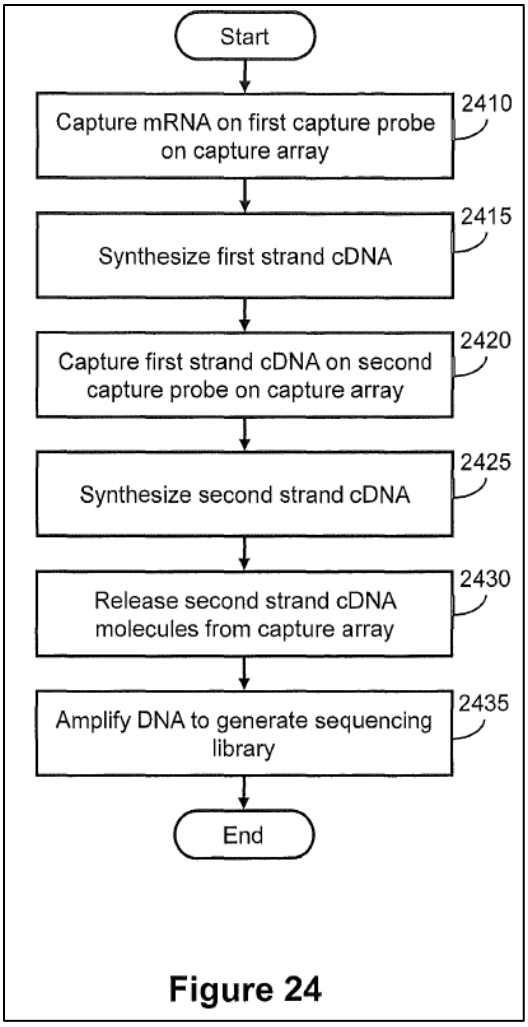


Figure 24

EX1005, FIG. 24.

163. As shown in the Figure, first-strand cDNAs are initially synthesized on the array using captured mRNAs as a template (step 2415). *Id.* These first-strand cDNAs are copied into second-strand cDNAs using the first-strand cDNAs as templates (step 225). *Id.* Next, the second-strand cDNAs are released from the array and amplified to generate a sequencing library (steps 2430 and 2435). *Id.*

164. Dr. Sherman argues that So-456's amplification reactions for library preparation do not satisfy claim 7 because they do not use the first-strand cDNAs

as templates. EX2008, ¶¶121-123. Dr. Sherman's position is however inconsistent with Bruker's infringement contentions for claim 7, which as explained above, rely on Visium FF's second-strand cDNA amplification (step 3) and subsequent library preparation (step 4)—neither of which use the first-strand cDNAs as templates for amplification. EX1022, 35-36.

165. Dr. Sherman also argues that the first-strand cDNA is "different from the second-strand cDNA" that is used as a template in So-456's amplification steps. EX2008, ¶¶121-123. Dr. Sherman specifically notes that "[t]o permit amplification, the second-strand cDNA includes additional sequences that are not part of the first-strand cDNA." EX2008, ¶123. Once again, Dr. Sherman's argument conflicts with Bruker's infringement contentions. As discussed above, Bruker's infringement contentions for claim 7 are based on Visium FF's amplification steps that use the second-strand cDNAs as templates. EX1022, 35-36. Thus, the additional sequences Dr. Sherman highlights in So-456 are similar to those in the allegedly infringing Visium FF. *See* Section V.A, (discussing how second-strand cDNAs in Visium FF are not the exact same molecule as the first-strand cDNAs and that they possess a *different sequence* from the first-strand cDNA due to different directionality and additional adapters and index sequences); EX1022, 23; EX1015, 17-18. Dr. Sherman's argument once again runs counter to Bruker's infringement contentions.

166. Finally, in my opinion, So-456's second-strand cDNA amplification to generate sequencing library also meets the requirements of claim 7 under the Board's interpretation of "synthesizing DNA products." I understand that the Board interpreted "DNA products" of steps (c) and (d) of claim 1 as not limited to "the first cDNA strand – and only this strand." *See* Section III.A. Thus, a POSA would have understood that "DNA products" under the Board's interpretation include So-456's second-strand cDNAs, as So-456's method includes 1) generating first-strand cDNAs using collected oligonucleotides as a template before 2) generating second-strand cDNAs using the first-strand cDNAs as templates. EX1044, ¶¶238-239; EX1005, ¶¶[00311]-[00313], FIGs. 25A-B. So-456's method then uses the second-strand cDNAs as templates for amplification to generate cDNA sequencing libraries as explained above. EX1044, ¶¶238-239; EX1005, ¶¶[00312]-[00318], FIG. 24.

167. Thus, So-456 teaches a method that includes amplifying a library using DNA products as templates, as required in claim 7. EX1044, ¶¶238-239.

VIII. GROUND 5: CLAIMS 1-13 ARE OBVIOUS OVER SO-456

168. I opined in my first declaration that claims 1-13 would have been obvious over So-456. EX1044, ¶¶253-256.

169. Dr. Sherman argues that 10x "merely shows that So-456 and the '142 patent are directed to similar fields." EX2008, ¶¶125-126. I disagree with Dr.

Sherman. Dr. Sherman agrees that "the skill level of a POSA relevant to the '142 patent is high" and that a POSA would have "at least two years of experience in the use and development of approaches for spatial detection of proteins and nucleic acids of interest in a biological sample." EX2008, ¶21; *see also* EX1044, ¶25 ("A POSA would typically have a Ph.D. in a relevant field … with two years of experience in the use and development of genetics and genomics approaches for detecting and monitoring human diseases, such as spatial detection of a target analyte (e.g., mRNA or DNA) in a tissue section"). In view of high skill level, So-456 teaches all of the elements of the claims (as explained in my first declaration and also under the Board's constructions as explained above in Section VII) and, for the reasons explained in my first declaration, a POSA would have been motivated to arrive at the claims with a reasonable expectation of success. EX1044, ¶¶253-256.

170. Accordingly, I maintain my opinion set forth in my first declaration that claims 1-13 would have been obvious over So-456. EX1044, ¶¶253-256. Further, claims 1-13 would have been obvious over So-456 under the Board's constructions.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the U.S. Code.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Respectfully submitted,

_____
Paul T. Spellman, Ph.D.

Date: February 12, 2025

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