IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.,
Petitioner

v.

NANOSTRING TECHNOLOGIES, INC.,
Patent Owner

Case IPR2023-01298
U.S. Patent No. 11,377,689

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,377,689

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1032	U.S. Patent No. 9,567,645 to Fan *et al.*, issued February 14, 2017 ("Fan 645")
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I. INTRODUCTION

Petitioner 10x Genomics, Inc. requests review of claims 1-30 of U.S. Patent No. 11,377,689, which is assigned to NanoString Technologies, Inc.

The challenged claims of the 689 patent relate to spatially detecting target analytes (*e.g.*, nucleic acids) in biological samples using spatial barcode arrays.

NanoString has accused 10x's spatial gene expression products (Visium) of infringing the 689 patent in related litigation. However, the broad claims of the 689 patent—*which were written after the accused Visium products were already on the market*—run afoul of significant prior art describing the array-based "spatial barcoding" paradigm that long predate the 689 patent's claimed February 2018 priority date. By this time, numerous publications of spatially detecting target analytes with arrays of spatial barcodes existed, including the "So-456" reference relied on herein.

A further consequence of the litigation-driven origins of the 689 patent claims is that they lack 35 U.S.C. § 112 support in the corresponding specification, which does not describe arrays of spatial barcodes. Instead, it describes NanoString's GeoMx product, which has probes and workflows distinct from the array-based Visium technology. GeoMx requires a user to select a region of interest in a tissue sample and extract spatial information about the analytes in that region by releasing an oligonucleotide fragment from the tissue sample. EX1001,

FIG. 20. The 689 patent describes extension and ligation chemistries only to the extent that they occur *after* the oligonucleotide fragment is already released from the analyte in the sample. In contrast, 10x's Visium products use, and the 689 claims allegedly cover, extension and ligation steps that occur in the tissue sample, *before* any nucleic acid is "released" or "collected" from it (even under NanoString's broad interpretation of its claims).

This Petition demonstrates that claims 1-30 of the 689 patent should be cancelled for at least the following reasons:

First, claims 1-30 of the 689 patent as interpreted by NanoString are anticipated and/or rendered obvious by So *et al.* ("So-456"), a patent publication by Illumina. So-456 describes a spatial analysis technique that uses arrays of immobilized oligonucleotide probes that each occupy a distinct position on the array. EX1005, ¶[0085]. Each probe includes a nucleic acid sequence, called a "spatial address," that corresponds to the two-dimensional position of the probe on the array. After overlaying a tissue sample onto the array, target analytes in the tissue sample are captured on the array and labeled with the spatial address using various chemistries, including the same ligation and extension chemistries claimed in the 689 patent. This process generates nucleic acid molecules comprising the target analyte sequence and the spatial address sequence. These spatially addressed nucleic acid molecules are then sequenced and distinguished based on their spatial

address, so that they can be mapped onto their original location in the tissue sample. *Id*. ¶[0089]. So-456 describes all of the steps of the 689 patent's claimed methods. Additionally, Stahl—a 2016 publication—successfully demonstrated the well-known technique of including a unique molecular identifier ("UMI") in probes on spatially barcoded arrays. So-456's teachings in view of Stahl further render obvious certain 689 patent claims.

Second, claims 1-30 as interpreted by NanoString are anticipated by Chell *et al.*, a 10x PCT publication. Chell discloses methods of spatial analysis comprising contacting a tissue sample with pairs of primary probes that bind to target mRNAs in the tissue, ligating the primary probe pairs while bound to the target mRNAs, releasing the ligated probes from the target mRNAs, capturing the ligated probes on an array of immobilized capture probes, and performing an extension reaction on the captured products to tag them with a spatial barcode. EX1006, 80:14-82:2. Chell is intervening prior art that anticipates the challenged claims because none of the 689 patent claims are entitled to their claimed February 2018 priority date.

Accordingly, the Board should cancel claims 1-30 of the 689 patent.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

10x certifies that the 689 patent (EX1001) is IPR-eligible and 10x is not barred or estopped from requesting IPR of any 689 patent claim.

III. PRECISE RELIEF REQUESTED (37 C.F.R. § 42.22(a))

10x petitions for IPR, requesting cancelation of claims 1-30 of the 689 patent, because each claim is unpatentable under 35 U.S.C. §§ 102 and 103. The Petition is supported by the declaration of Paul Spellman, Ph.D. (EX1002), Professor of Medicine and Human Genetics and an expert in genetics and genomics approaches for detecting and monitoring human diseases. *Id.*, ¶¶11-17.

IV. IDENTIFICATION OF THE CHALLENGE (37 C.F.R § 42.104(B))

10x requests IPR based on the grounds below.

Ground	35 U.S.C. Section (AIA)	Claims	References
1	§ 102	1-8, 11-23, and 26-30	So-456
2	§ 103	1-30	So-456
3	§ 103	9, 10, 24, 25	So-456 and Stahl
4	§ 102	1-30	Chell

The asserted references are prior art for at least the following reasons. WO 2017/019456 ("So-456") was filed on July 21, 2016, and published on February 2, 2017, which are before the 689 patent's February 12, 2018, earliest claimed priority date. So-456 is prior art under AIA 35 U.S.C. §§ 102(a)(1) and 102(a)(2).

Stahl *et al.*, *Science* 353(6294):78-82 (2016) ("Stahl") (EX1016) published on July 1, 2016, which is before the 689 patent's February 12, 2018, earliest

claimed priority date. Stahl is prior art under AIA 35 U.S.C. § 102(a)(1).

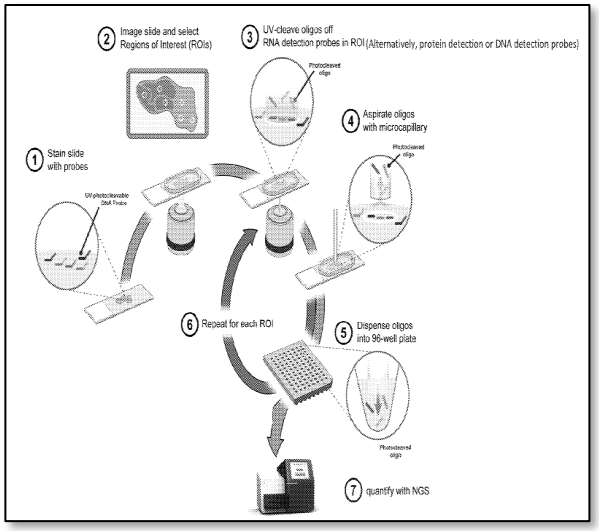
WO 2021/133849 ("Chell") is prior art because the 689 patent is not entitled to a filing date any earlier than September 16, 2021. *See infra*, Section XII.A. Chell was filed on December 22, 2020, and published on July 1, 2021, which are before September 16, 2021. Thus, Chell is prior art under AIA 35 U.S.C. §§ 102(a)(1) and 102(a)(2).

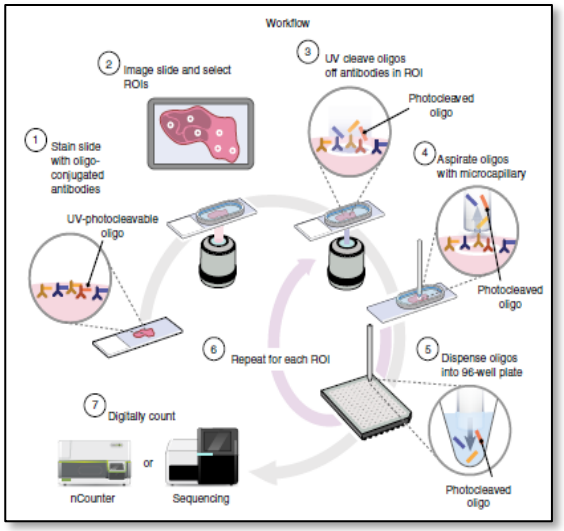
All four Grounds are presented under NanoString's interpretation of the challenged claims in district court.

V. THE 689 PATENT

The 689 patent issued on July 5, 2022, from U.S. Appl. No. 17/476,707 ("707 application"), filed September 16, 2021. The 707 application is a continuation of 16/272,487 ("487 application"; EX1009), filed on February 11, 2019, which claims priority to U.S. Appl. Nos. 62/771,212 (EX1010), filed November 26, 2018, and 62/629,180 (EX1011), filed February 12, 2018. EX1001, 1-2.

The 689 patent relates to spatially detecting and quantifying proteins or nucleic acids in tissues and cells. EX1001, Abstract; EX1002, ¶39-65. As evident from its disclosures throughout, the 689 patent specification is tailored towards NanoString's product, "GeoMx":





Compare EX1001, FIG. 20 *with* EX1013 (GeoMx publication), FIG. 1A; EX1002, ¶¶59-75.

The 689 patent discloses methods using probes comprising: (a) a "target binding domain" that binds to the analyte, and (b) an "identifier oligonucleotide" region that is cleaved off, collected, and analyzed. EX1001, 37:14-16, FIGs. 20, 11; EX1002, ¶¶44-52.

Independent claims 1 and 16 of the 689 patent each recites a "method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample," and requires contacting, collecting, extension, and sequencing steps. Claim 16 also requires that the "nucleic acid probes" be *primary probe pairs* (a "first" and "second" plurality of "nucleic acid probes") and adds a ligation step in which the probe pairs are ligated to form "*ligated probes*," which are then collected. EX1001, 145:51-147:11, 147:54-148:47; EX1002, ¶¶76-79.

Claims 2-15 and 17-30 depend from claims 1 and 16, respectively, and further narrow the independent claims with, *e.g.*, the tissue sample type, sequencing method, and library amplification steps. EX1001, 147:12-53, 148:48-150:17; EX1002, ¶79.

During prosecution, the examiner issued a single Office action, rejecting the pending claims for indefiniteness and lacking enablement. EX1004, 224-235. No prior art rejections were raised. *Id.* NanoString subsequently amended the claims, interviewed the examiner, and the Office issued a Notice of Allowance. *Id.*, 253-257, 266-272, 469-476, 484-485, 493-504. The examiner neither considered So-456, Stahl, and Chell, nor the 689 patent's defective priority claim.

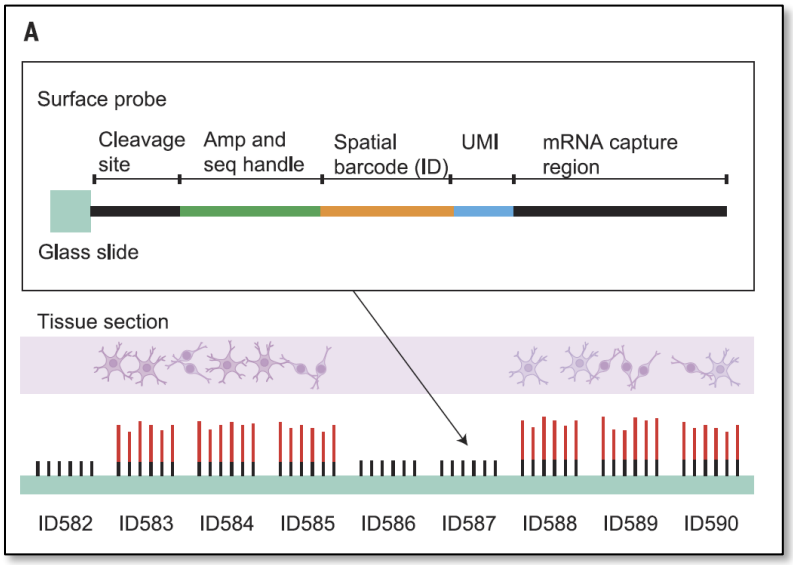
VI. STATE OF THE ART PRE-DATING THE 689 PATENT

Spatial array barcoding originated from Spatial Transcriptomics (ST) in 2011. EX1017; EX1002, ¶¶81-82. Subsequently, numerous publications, including So-456 and Chell, incorporated ligation chemistries into the ST technology. EX1005; EX1006; *See also* EX1025; EX1026; EX1027; EX1028; EX1002, ¶82.

A. Stahl disclosed spatially barcoded arrays

Stahl, ST's *Science* publication, disclosed methods of achieving spatial resolution in tissue sections using DNA sequences called "positional barcodes" or "spatial barcodes" to identify the locations of molecules. EX1016, Abstract; EX1002, ¶¶83-94; *see also* EX1017, Abstract. Stahl's methods incorporated these

spatial barcodes into arrays of oligonucleotide "surface probes" immobilized in clusters ("spots") on a solid substrate. EX1016, 78, FIG. 2A; EX1002, ¶¶83-94. Stahl's barcoded array approach is shown below:



EX1016, FIG. 2A.

Each spot on the array (ID583, ID584, etc.) contained a cluster of surface probes having a unique spatial barcode, as well as a unique molecule identifier ("UMI") sequence to identify duplicate post-amplification molecules. EX1016, Abstract, 78, FIG. 2A; EX1018, 3; EX1002, ¶¶85-94. The surface probes within one spot on the array (*e.g.*, ID583) have a different spatial barcode than the probes within other spots (*e.g.*, ID584). *Id.*

The spatial barcodes served as tags for locations of their corresponding surface probes on the solid substrate. *Id*. This allowed differentiation of biological

molecules based on their spatial location within the sample. EX1016, Abstract, 78, FIG. 2A; EX1002, ¶¶85-94.

B. So-456 taught spatially barcoded arrays using ligation chemistries

In July 2016, So *et al.* filed a PCT application entitled "Spatial Mapping Of Nucleic Acid Sequence Information," which published on February 2, 2017 as WO 2017/019456 ("So-456"). EX1005, Face.

Figure 2 of So-456 highlighted the steps of preparing a tissue sample, performing *in situ* biochemistry steps (including a probe ligation step), capturing nucleic acids onto an array, and preparing a sequencing library for analysis:

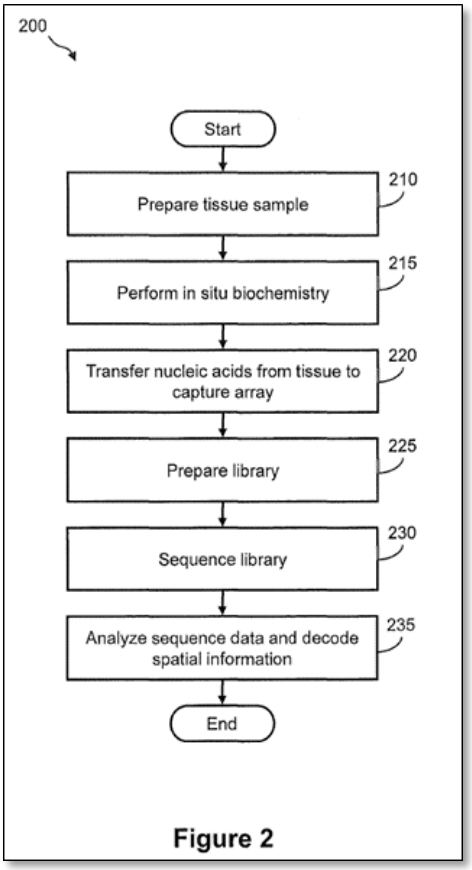
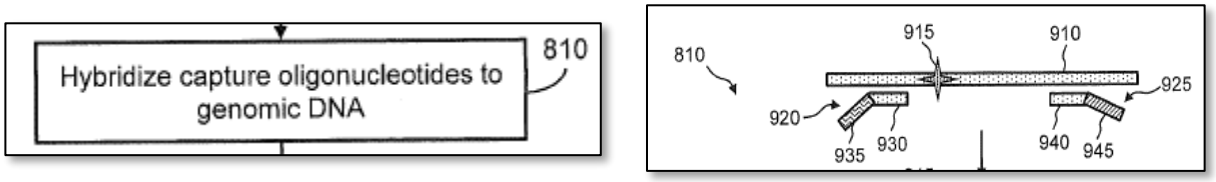


Figure 2

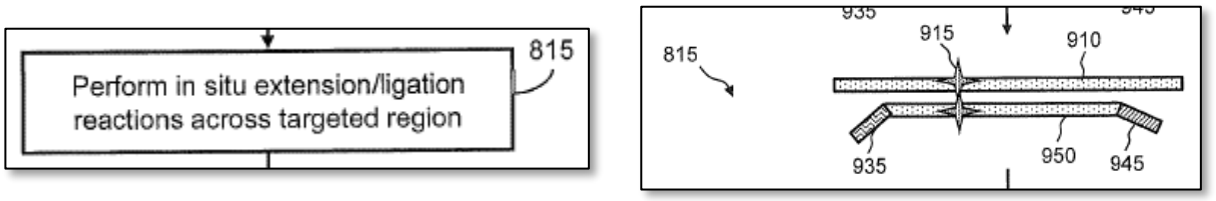
EX1005, FIG. 2, ¶[00151]; EX1002, ¶¶95-104.

So-456 taught a primary probe-ligation approach, in which a tissue sample is mounted on a slide and contacted with pairs of primary probes (referred to as "capture oligonucleotides" 920 and 925 in Figures 8-9) that bind to a target genomic DNA within the tissue sample, as depicted in step 810 of Figures 8-9:



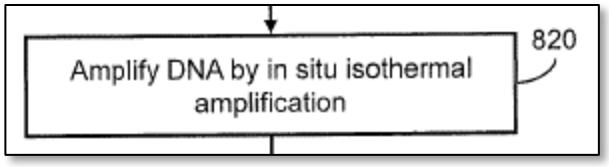
EX1005, FIGs. 8-9, ¶¶[0018]-[0019], [00182]-[00183]; EX1002, ¶¶102-104.

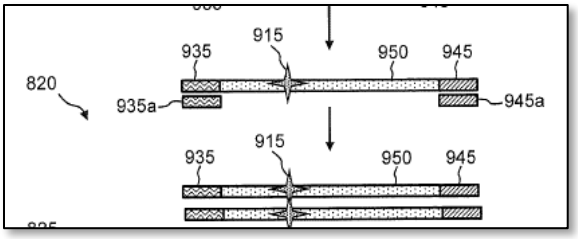
Next, the bound pairs of primary probes 920 and 925 are ligated to produce a ligation product, referred to as "DNA molecule 950" in Figure 9. See step 815 in Figures 8 and 9:



EX1005, FIGs. 8-9, ¶¶[0018]-[0019], [00182]-[00183]; EX1002, ¶¶102-104.

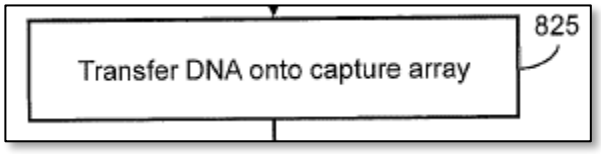
After ligation, So-456's method amplified (copied) the ligation product (step 820 in Figures 8-9), releasing the ligation product from the target genomic DNA:

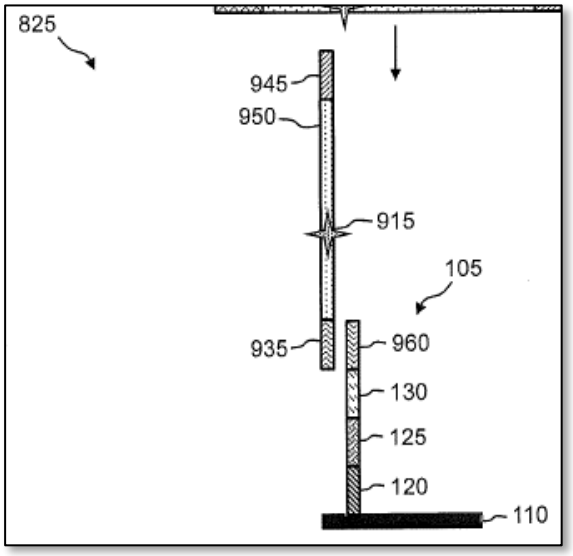




EX1005, FIGs. 8-9, ¶¶[0018]-[0019], [00182]-[00183]; EX1002, ¶¶102-104.

So-456's method then captured the released amplified ligation products (950) by hybridization (step 825) on an array of immobilized, spatially-barcoded array probes:

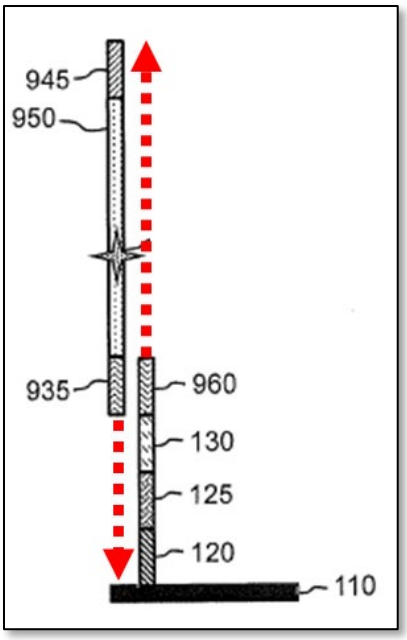




EX1005, FIGs. 8-9, ¶¶[0018]-[0019], [00182]-[00183]; EX1002, ¶¶102-104.

After capture, So-456 taught performing an extension reaction to tag the captured ligation products with spatial barcodes. EX1005, ¶¶[0089], [00109], [0173]; EX1002, ¶94. This extension reaction incorporated the spatial barcode sequence and a pair of sequencing primer binding sites into the captured ligation products to prepare them for sequencing and analysis. EX1005, ¶¶[00182],

[00141]; EX1002, ¶94. So-456 taught immobilizing the "*capture primers* … such that a 3'-end is available for *enzymatic extension*…." EX1005, ¶[00109][1]; EX1002, ¶94. So-456 also explained that the extension reactions extend both the capture probe and the captured ligation product, and that "[b]oth extension products can be used for downstream library generation." EX1005, ¶[00173], Fig. 6; EX1002, ¶104. So-456's extension process is depicted in Dr. Spellman's annotation of So-456's Figure 9:



EX1005, FIG. 9, ¶¶[00182]-[00183]; EX1002, ¶104. The resulting extension products are DNA molecules comprising sequences of the captured ligation product and the spatial barcode sequence. *Id.*

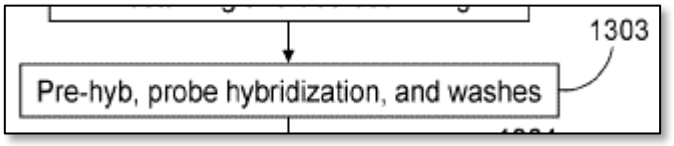
[1] Emphasis has been added throughout, unless otherwise noted.

C. Chell taught spatially barcoded arrays using ligation chemistries

10x's PCT application was filed on December 22, 2020, and published as WO 2021/133849 ("Chell") on July 1, 2021. EX1006, Face; EX1002, ¶¶105-115. Chell disclosed "methods of detecting an analyte of interest to interrogate spatial gene expression in a sample using RNA-templated ligation." EX1006, Abstract.

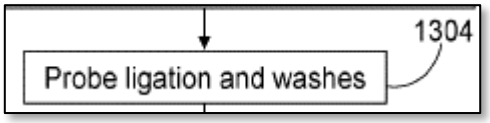
Figure 13 of Chell generally entailed the following steps:

- Contacting a tissue sample with primary probe pairs that hybridize to target mRNAs (1303):



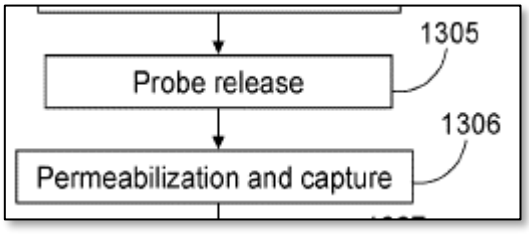
;

- Ligating the primary probe pairs bound to the target mRNA (1304):



;

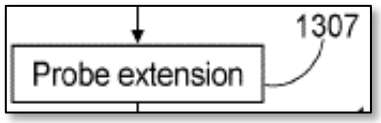
- Releasing (1305) and capturing (1306) the ligated probes onto an array of immobilized, spatially barcoded array probes:



;

- Performing an extension reaction with the captured ligated probes to

add a spatial barcode (1307):



;

and sequencing the extension products to determine the spatial location in the tissue. EX1006, 7:29, 8:5-8, 8:22, 23:30-24:13, 80:14-85:4, FIGs. 1, 6-7, 13-20; EX1008, 19-21; EX1002, ¶¶105-115.

VII. PERSON OF ORDINARY SKILL IN THE ART

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, equipped with conventional wisdom and ordinary creativity. Here, a POSA would have possessed a strong understanding in the use and development of genetics and genomics approaches for detecting or monitoring human diseases, such as spatial detection of a target analyte (*e.g.*, mRNA or DNA) in a tissue, and would typically have a Ph.D. in a relevant field (*e.g.*, molecular biology, genetics, and bioinformatics) with two years of experience. EX1002, ¶¶24-25. *See also* EX1004, 268 (NanoString admitting during prosecution that "the skill level of a [POSA] in the context of the instant application is high, at least that of a PhD in biology, if not higher.").

VIII. CLAIM CONSTRUCTION

Solely for the purposes of this IPR, 10x applies NanoString's interpretations of the 689 patent claims from the concurrent litigation. *See* EX1020 (infringement

contentions); EX1021 (pleading). NanoString's statements before a Federal court in which it "took a position on the scope" of its patent claims are properly cited here under 35 U.S.C. §§ 301(a)(2) and §301(d) and appropriate for consideration by the Board. *See e.g., 10x Genomics, Inc. v. Bio-Rad Lab'ys, Inc*., IPR2020-00086, Paper 8 (P.T.A.B. Apr. 27, 2020), at 9-17 (adopting claim constructions that the Board deemed "consistent with Patent Owner's infringement contentions.").

Relevant for the Board's decision here is NanoString's interpretation of the "collecting" steps in claims 1 and 16. EX1001, 145:61-146:52, 148:11-22. According to NanoString, the claimed collecting steps are broad enough to encompass diffusion and capture of *whole* probes or *whole* oligonucleotides across the *whole* tissue sample. EX1020, 22-27, 53-54; EX1002, ¶116.

IX. GROUND 1: SO-456 ANTICIPATES CLAIMS 1-8, 11-23, AND 26-30

So-456 anticipates claims 1-8, 11-23, and 26-30 under NanoString's interpretation of these claims. EX1002, ¶¶117-216.

A. Claim 16

1. Preamble: "A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising"

So-456 teaches methods for spatially detecting at least one target analyte in a tissue sample under NanoString's interpretation. For example, So-456's Figure 2

provides an overview of a workflow for its "*method* … of *spatial detection* and analysis of a *nucleic acid* [*i.e.*, at least one target analyte] *in a tissue sample*" using spatially barcoded arrays. EX1005, ¶¶[00151], [00150], FIG. 2; EX1002, ¶¶119-120. So-456 provides specific embodiments of Figure 2's method, including a primary probe-ligation approach depicted in Figures 8 and 9 comprising each of the contacting, collecting, extension, and sequencing steps of claim 16. EX1005, ¶¶[00177]-[00183], FIGs. 8-9; EX1002, ¶¶119-120.

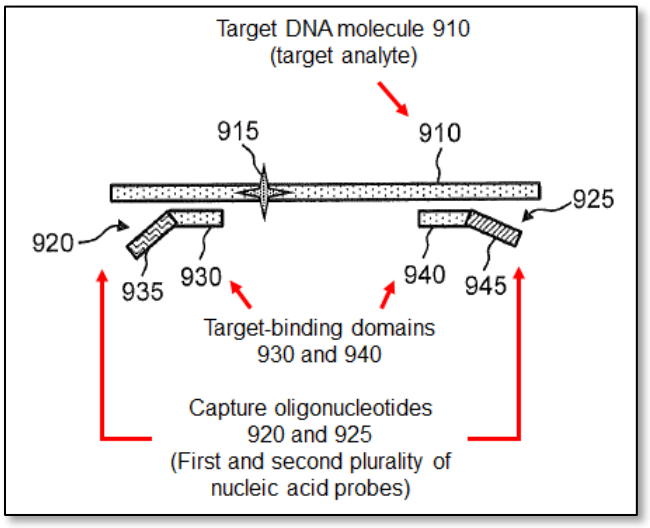
2. "a) contacting the tissue sample with a first plurality of nucleic acid probes and a second plurality of nucleic acid probes,

wherein each of the nucleic acid probes in the first plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte,

wherein each of the nucleic acid probes in the second plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte

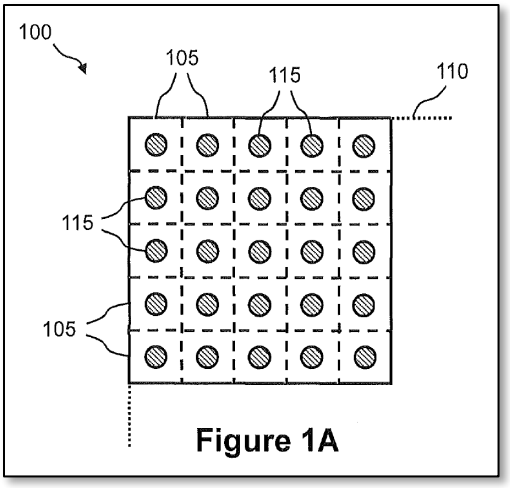
So-456 discloses the contacting step. So-456's method contacts "a tissue section … compris[ing] a *target genomic DNA molecule 910*" (*i.e.*, at least one target analyte) with primary probe pairs "first [and second] *gene-specific capture oligonucleotide 920 [and 925]*" (*i.e.*, a first plurality and second plurality of nucleic acid probes), such that the probes flanking a region of interest are "*hybridized* in situ to [the] DNA molecule" in the tissue. EX1005, ¶[00182], FIG. 9; EX1002, ¶¶121-124. So-456's primary probes comprise a "gene-specific region 930 [and 940]" (*i.e.*, target binding domain) that hybridizes to the target DNA

molecule (*i.e.*, target analyte), as claimed. EX1005, ¶¶[00141], [00182], FIGs. 1B, 2, 8, 9; EX1002, ¶¶123-124. These aspects are shown in Dr. Spellman's annotations of So-456's Figure 9:



EX1002, ¶123; EX1005, FIG. 9.

So-456 further discloses that its methods utilize a "first plurality" and "second plurality" of nucleic acid probes, as claimed, because So-456 discloses performing its methods across an array of multiple "capture sites" (labeled as "105" in Figure 1A:



EX1005, FIG. 1A, ¶¶[0002], [0003], [0085], [00154]; EX1002, ¶124. Thus, So-456 teaches contacting a plurality of primary probe pairs at multiple locations in a tissue sample. *Id*.

"wherein the tissue sample is treated to facilitate binding of the first plurality of nucleic acid probes and the second plurality of nucleic acid probes to the at least one target analyte"

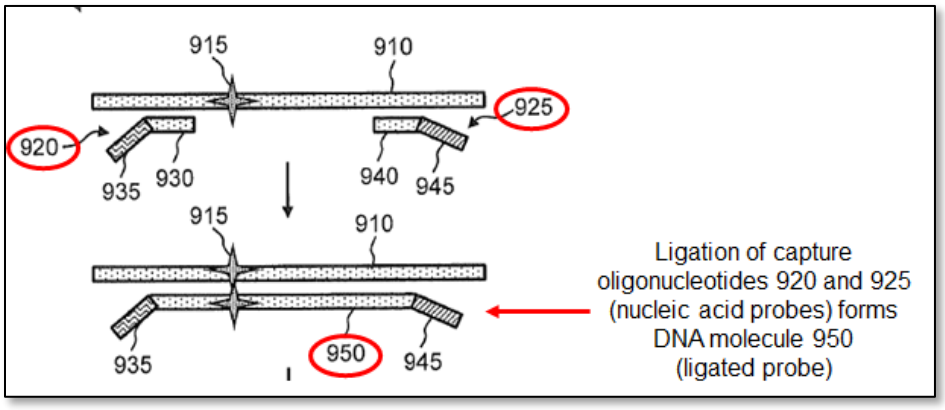
So-456 also teaches treating the tissue sample to facilitate probe binding, as claimed, because So-456 discloses that the "*tissue sample is prepared* for analysis" and that "in situ *biochemistry is performed* on the tissue section to *facilitate subsequent manipulation* of a nucleic acid in the sample." EX1005, ¶¶[00152]-[00153]; EX1002, ¶¶125-127. Further, So-456's Figure 2 depicts performing "in situ biochemistry" on the tissue sample, which facilitates probe binding because Figure 8 depicts "[h]ybridiz[ing] capture oligonucleotides to genomic DNA" (*i.e.*,

binding). EX1005, FIGs. 2, 8, 9, ¶¶[00153], [00178], [00182]; EX1002, ¶¶125-127. Thus, So-456's tissue was treated to facilitate probe binding, as claimed. *Id*.

Accordingly, So-456 teaches claim 16's contacting step.

3. "b) forming ligated probes by ligating each of nucleic acid probes from the first plurality of nucleic acid probes and each of nucleic acid probes from the second plurality of nucleic acid probes that are bound to each of identical molecules from the at least one target analyte"

So-456 teaches claim's 16 ligation steps because So teaches that "an extension/*ligation* reaction is performed in situ between the flanking capture oligonucleotides 920 and 925 [*i.e.*, the primary nucleic acid probe pairs] across the region of interest," which forms ligated probes ("DNA molecule 950"), as claimed. EX1005, ¶[00182], FIGs. 8, 9; EX1002, ¶¶128-130. The 689 patent confirms that "ligating" probe pairs includes ligating pairs that are "not adjacent and are not overlapping" (like So-456's probe pairs) by "performing a gap extension reaction and a nick repair reaction." *See e.g.,* EX1001, 25:66-26:6; EX1002, ¶128. Dr. Spellman's annotation of So-456's ligation step is shown below:



EX1002, ¶129; EX1005, FIG. 9.

Accordingly, So-456 teaches claim 16's ligation step.

4. "c) [and (d)] collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte in a first location [and second location] of the tissue sample under conditions that release the ligated probes, or portions thereof, from the first location [and second location] of the tissue sample"

So-456 discloses claim 16's collecting steps (c) and (d) under NanoString's interpretation. EX1002, ¶¶131-137. In concurrent litigation, NanoString alleged that these collecting steps encompass diffusion and capture of *whole* ligation products generated from ligating the primary probe pairs across the *whole* tissue sample, all at the same time. EX1020, 53-54; EX1008, 19-20; EX1002, ¶132. This is taught in So-456.

After ligating the primary probe pairs, So-456's method amplifies the ligated probes (950) "to generate multiple copies … of the targeted region of interest" by "isothermal amplification," generating unbound amplified ligated probes ("amplicons"). EX1005, ¶[00182]; EX1002, ¶¶134-135. The amplified ligated probes (950) free from the target DNA molecules are "transferred from a sample . . . onto a capture array by passive diffusion" and "*captured* onto the capture site 105" of the array. EX1005, ¶¶[00182], [00215]; FIGs. 2, 8, 9; EX1002, ¶¶134-135.

The capture site comprises immobilized array probes ("capture probes" 115) containing a spatial barcode ("spatial address region" 130) and a "capture region"

(135 or 960) that hybridizes a complementary region on the ligated probes ("universal capture region" 935). EX1005, ¶¶[00141], [00182]-[00183]; EX1002, ¶¶135-137. These details are depicted in Dr. Spellman's annotations of So-456's Figures 9 and 1A:

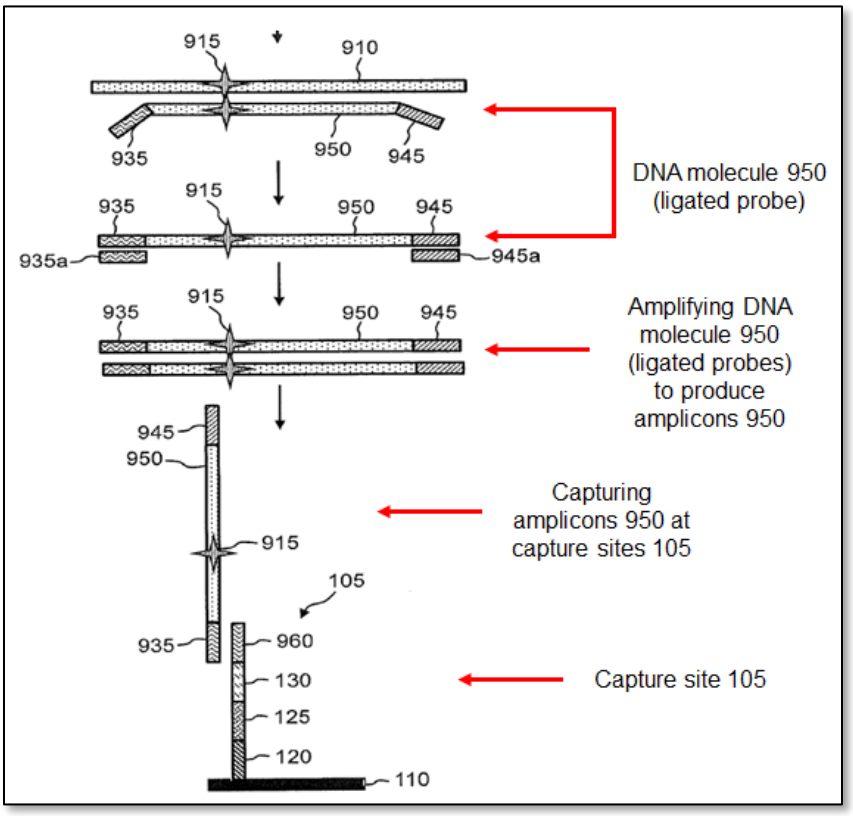


Figure 9

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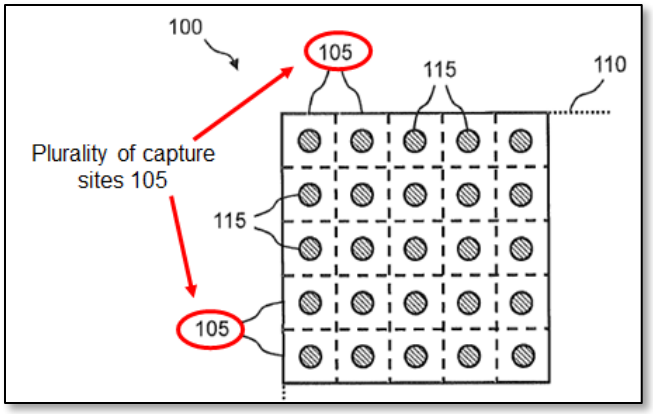


Figure 1A

EX1002, ¶135; EX1005, FIGs. 1A, 9.

So-456's workflow is performed simultaneously at multiple locations of the tissue sample and consequently at multiple capture sites on the array. EX1005, ¶¶[00141], [00183], FIGs. 1A, 9; EX1002, ¶¶136-137. Thus, So-456's method collects *whole* ligated primary probes from the *whole* tissue sample at the same time, as claimed according to NanoString's construction. EX1002, ¶¶136-137; EX1008, 19-20; EX1020, 53-54.

5. "e) [and (f)] performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample into each of the ligated probes, or portions thereof, collected in step (c) [and (d)], thereby forming a first [and second] plurality of extension products that comprise the ligated probes, or portions thereof, collected in step (c) [and (d)] and the at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample"

So-456 teaches claim 16's extension steps (e) and (f). EX1002, ¶¶138-152. Specifically, So-456's methods require an extension reaction to incorporate a

spatial barcode sequence into the captured ligated probes, thereby tagging the ligated probes for spatial identification and analysis. EX1005, ¶¶[0089], [00141], [00158], FIG. 9; EX1002, ¶¶139-140. Although So-456's method does not explicitly describe the extension in Figures 8-9, So-456's method inherently performs extension to achieve spatially barcoded nucleic acids for analysis. "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharm., Inc*., 339 F.3d 1373, 1379 (Fed. Cir. 2003).

The overall workflow of So-456's methods in Figure 2 specifies that after capturing nucleic acids on the array (Step 220), a "sequencing library is prepared" (Step 225) for use in a subsequent sequencing step (Step 230) and an analysis and decoding step (Step 235). EX1005, ¶[00156]-[00158]. So-456's workflow requires (1) encoding the "spatial origin of a nucleic acid in a tissue sample" in "the process of preparing the nucleic acid for sequencing," and (2) performing sequencing to obtain data that is "analyzed . . . and the spatial information is decoded." EX1005, ¶¶[0089], [00131], [00132], [00158]. So-456 explains that the nucleic acids are "*tagged by probes* including location-specific sequence information (a '*spatial address*')," which results in the spatial origin information being "*encoded in the nucleic acid[s]*." EX1005, ¶[0089]; EX1002, ¶141.

However, So-456's ligated probes (950) captured on the array in the previous step are not yet tagged with a spatial barcode and do not include functional sequences (*i.e.*, a pair of SBS primer-binding sites) necessary for performing sequencing-by-synthesis (SBS) in subsequent steps. EX1002, ¶142. Therefore, during sequencing library preparation (Step 225)—the only step remaining before the sequencing step (Step 230)—So-456's method necessarily generates molecules containing a spatial barcode and sequencing primer-binding sites, such that the molecules are ready for sequencing, analysis, and decoding in the subsequent steps (Steps 230, 235). EX1005, ¶¶[00156]-[00158], FIG. 2; EX1002, ¶142.

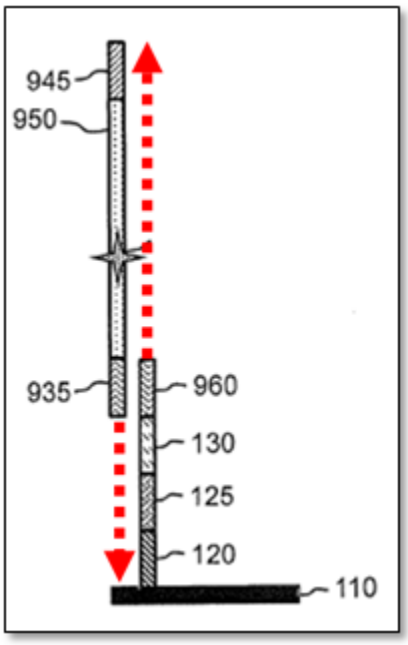
So-456 discloses that its capture probes (115) comprise a unique "spatial address region" containing a "spatial address sequence" (*i.e.*, spatial barcode). EX1005, ¶[00141], FIG. 1; EX1002, ¶¶143-144. Additionally, So-456 (an Illumina publication) discloses using SBS (sequencing-by-synthesis), *e.g.*, "developed by [] Illumina, Inc." EX1005, ¶¶[00156]-[00158], FIG. 2. Illumina's SBS method utilizes SBS primer pairs. EX1030, 6. The ligated probes captured on the array, however, include the binding site for only one SBS primer ("SBS primer region 945 (e.g., SBS12)"). EX1005, ¶¶[00182], [00141]. The other SBS primer-binding site is included in the capture probes. *See* EX1005, FIG. 1, ¶[0141] ("SBS primer

region 125 [] SBS3"), FIG. 9, ¶[00182] ("SBS primer region 130 [] SBS3"); EX1002, ¶¶145-147.

When tagging the oligonucleotides captured on the array with the spatial barcode of the capture probes and incorporating both SBS primer-binding sites in the same molecule, So-456's method necessarily extended the capture probes (using the captured ligated probes as template) and the captured ligated probes (using the capture probes as template). EX1002, ¶148. So-456 confirms this, stating that when the capture probe is "used as a primer," the captured "DNA molecule … is copied," and when the captured DNA molecule is "used as a primer," the "spatial address region" is copied. EX1005, ¶[00173], FIG. 6; EX1002, ¶¶148-149. So-456 further confirms that "*[b]oth extension products* can be used for downstream library generation." *Id.*

This bi-directional extension in So-456's method is the "*natural result* flowing from [So-456's] explicit disclosures" because So-456 did not teach methods for preventing the extension from occurring. *Schering*, 339 F.3d at 1379. So-456 discloses immobilizing the "*capture primers* … such that a 3'-end is available for *enzymatic extension*…." EX1005, ¶[00109]; EX1002, ¶149. So-456 does *not* disclose blocking or otherwise modifying the 3'-ends of either the ligated probes (950) or capture probes (115) to preclude their extension. Compare this with So-456's other disclosures, in which So-456 specifically and expressly

discloses modifying the 3'-end of nucleic acids, e.g., to prevent 3'-end ligation or further nucleotide incorporation during sequencing. *See e.g.,* EX1005, ¶¶[00484], [00491], FIGs. 48-49, ¶[00601]; EX1002, ¶¶148-149. Accordingly, So-456's extension reaction disclosed in the method of Figure 9 necessarily proceeded in *both* directions—extending the 3'-end of the capture probe in one direction and the 3'-end of the captured ligated probe in the other direction. EX1005, ¶¶[00109], [00182]-[00183], FIG. 9; EX1006, Fig. 7; EX1002, ¶¶148-152. This is shown in Dr. Spellman's annotations of So-456's Figure 9:



EX1002, ¶150; EX1005, FIG. 9. The resulting extension products are DNA molecules comprising the sequences of the captured ligated probe (935, 950, and SBS site 945), the spatial barcode 130, and SBS site 125. EX1005, ¶¶[00141], [00182], FIG. 9; EX1002, ¶151-152.

Accordingly, So-456 teaches claim 16's extension steps.

6. "g) identifying the first plurality of extension products and the second plurality of extension products by sequencing the first plurality of extension products and the second plurality of extension products, thereby spatially detecting the at least one target analyte in the first location of the tissue sample and the second location of the tissue sample."

So-456 teaches claim 16's sequencing step (g) under NanoString's interpretation. EX1002, ¶¶153-157. NanoString agrees that "spatially detecting" means "identifying the presence of a specific target analyte within a specific region of interest in a sample." EX1024, 31.

After the sequencing library is prepared, So-456 teaches that "the library is sequenced" and "the sequence data is *analyzed* … and the *spatial information is decoded*." EX1005, ¶¶[0089], [00157]-[00158]; EX1002, ¶¶153-157. The decoded spatial information is "used to provide *information as to the location* of the nucleic acid in the tissue section" (*i.e.*, spatially detecting at least one target analyte in a first and second location of the tissue sample, as claimed). EX1005, ¶¶[0089], [00158]; EX1002, ¶¶153-157. To achieve this, the "sequence-identical nucleic acid molecules originating from *different regions* in a tissue sample can be distinguished based on their spatial address and can be *mapped onto their regions of origin* in the tissue sample." EX1005, ¶¶[0089]; EX1002, ¶¶153-157. So-456 further teaches that its methods "enable the identification of *the location of a cell*

or a cell cluster in a tissue" sample. EX1005, ¶[0002], [0088]. Accordingly, So-456 teaches claim 16's sequencing step.

In sum, So-456 teaches every limitation of claim 16 under NanoString's interpretation, arranged as claimed. So-456's methods are presumed enabled. *In re Antor Media Corp*., 689 F.3d 1282, 1290-91 (Fed. Cir. 2012). Accordingly, So-456 anticipates claim 16.

B. Claim 1

For the same reasons discussed above for claim 16, claim 1 is also anticipated by So-456 under NanoString's interpretation.

1. Preamble: "A method for spatially detecting …"

The preamble of claim 1 is identical to claim 16. So-456 thus discloses the preamble of claim 1 for the reasons discussed above for claim 16. EX1005, ¶¶[00150]-[00151], [00177]-[00183], FIGs. 2, 8, 9; EX1002, ¶159; *see supra*, Section IX.A.

2. "a) contacting the tissue sample with a plurality of nucleic acid probes …"

As discussed above for claim 16, So-456's method contacts a tissue sample with a first plurality and a second plurality of nucleic acid probes comprising a target-binding domain, and treats the tissue sample to facilitate binding of the probes to the target analyte. EX1005, ¶¶¶[0002], [0003], [0085], [00152]-[00154], [00141], [00182], FIGs. 1B, 2, 8, 9; EX1002, ¶¶160-165; *see supra*, Section IX.A.

Claim 1 only requires contacting the tissue sample with a "plurality of nucleic acid probes." EX1001,145:54-60; EX1002, ¶¶160-165. Thus, So-456 teaches claim 1's contacting step for the reasons discussed above for claim 16's contacting step.

3. "b) [and (c)] collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a first location [and second location] of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the first location [and second location] of the tissue sample…"

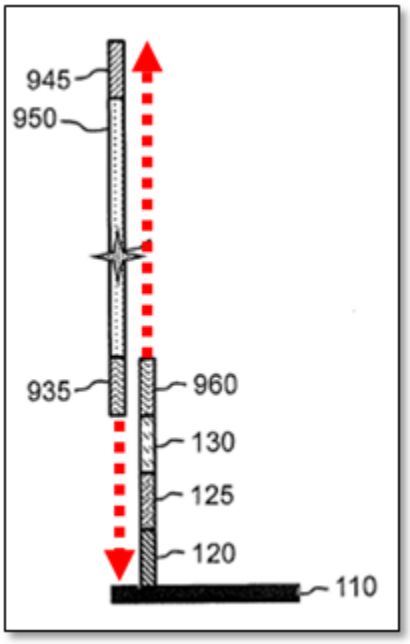
According to NanoString, the collecting steps read on the Visium FFPE capturing step, in which *whole* ligation product (not a portion) generated from ligating the primary probe pairs are diffused from and captured across the *whole* tissue sample, all at the same time. EX1020, 22-27; EX1008, 19-20; EX1002, ¶¶166-169. So-456 teaches claim 1's collecting steps for the reasons discussed above for claim 16. After ligating the probe pairs, So-456 discloses amplifying the ligated primary probes and then diffusing and capturing the whole ligated probes across the whole tissue sample, all at the same time. EX1005, ¶¶[00182]-[00183], [00215], FIGs. 8, 9; EX1002, ¶¶166-169; *see supra*, Section IX.A. Accordingly, So-456 teaches claim 1's collecting steps under NanoString's interpretation.

4. "d) [and (e)] performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (b) [and (c)], thereby forming a first [and second] plurality of extension products that comprise the nucleic acid probes, or portions thereof, collected in step (b)

[and (c)] and the at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample…"

So-456 teaches claim 1's extension steps (d) and (e) for the same reasons discussed above for claim 16's extension steps (e) and (f). EX1002, ¶¶170-184; *see supra*, Section IX.A.

So-456's methods necessarily performed the claimed extension reaction to incorporate the spatial barcode and SBS sequencing primer from the capture probe into the captured ligated probe. EX1002, ¶¶170-184. As discussed above in claim 16, upon their capture on the array, So-456's ligated probes (950) had not yet been tagged with a spatial barcode and do not include a pair of SBS primer-binding sites for sequencing-by-synthesis. EX1002, ¶¶170-184. So-456's extension reaction necessarily extended the 3'-end of the immobilized capture probes and the 3'-end of the captured ligated probes to incorporate these features in the captured products on the array. EX1005, ¶¶[00141], [00109], [00156], [00173], FIGs. 2, 6, 9; EX1002, ¶¶170-184. This is shown in Dr. Spellman's annotations of So-456's Figure 9:



EX1002, ¶182; EX1005, FIG. 9, ¶¶[00141], [00182].

Accordingly, So-456 teaches claim 1's extension steps.

5. "f) identifying the first plurality of extension products and the second plurality of extension products by sequencing the first plurality of extension products and the second plurality of extension products, thereby spatially detecting the at least one target analyte in the first location of the tissue sample and the second location of the tissue sample."

So-456 teaches claim 1's sequencing step (f) for the same reasons discussed above for claim 16's sequencing step. EX1002, ¶¶185-189; *see supra*, Section IX.A. As discussed above, So-456's method includes performing sequencing-by-synthesis, analyzing the sequencing data, and decoding the spatial information. EX1005, ¶¶[0002], [0088], [0089], [00156]-[00158], [00182]-[00183], FIG. 9; EX1002, ¶¶185-189. Accordingly, So-456 teaches the sequencing step of claim 1 under NanoString's interpretation. *Id.*

In sum, So-456 teaches every limitation of claim 1 under NanoString's interpretation, arranged as claimed, and So-456 is presumed enabled. Accordingly, So-456 anticipates claim 1.

C. Claims 2-8, 11-15, 17-23, and 26-30

Claims 2 and 17 depend from claims 1 and 16, respectively, and further require that "the tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample." EX1001, 147:12-13, 148:48-49. **Claims 3 and 18** depend from claims 1 and 16, respectively, and further require that "the tissue sample is immobilized onto a microscope slide." EX1001, 147:14-15, 148:50-51. So-456 teaches these limitations.

So-456 discloses fixing, sectioning, and mounting a "tissue sample" on "a *microscope slide*" and that "[t]he tissue sample can be a *formalin-fixed paraffin-embedded (FFPE) tissue sample*." EX1005, ¶¶[00125]-[00126]; EX1002, ¶¶190-192. Moreover, So-456's method in Figure 2 discloses that "the tissue sample is a *FFPE tissue* sample that is sectioned onto a *slide*." EX1005, ¶[00152], FIG. 2; EX1002, ¶¶190-192. Accordingly, So-456 anticipates claims 2, 3, 17, and 18. EX1002, ¶192.

Claims 4 and 19 depend from claims 3 and 18, respectively, and further require that "the microscope slide comprises a plurality of primers immobilized on the microscope slide." EX1001, 147:16-18, 148:52-54. So-456 teaches this

limitation. So-456 discloses that "the tissue sample is contacted with capture probe 115 that is *fixed on the surface* of capture site 105." EX1005, ¶[00183], FIG. 9; EX1002, ¶¶193-194. So-456 also discloses that "*any number* of capture probes 115 can be *immobilized on solid support* 110 at each capture site 105" and that the solid support has "an *array of capture sites*" that include "*a plurality of capture probes*." EX1005, ¶¶[00141], [00154], FIGs. 1A-1B; EX1002, ¶¶193-194. Accordingly, So-456 anticipates claims 4 and 19. EX1002, ¶194.

Claims 5 and 20 depend from claims 4 and 19, respectively, and further require that "the plurality of primers is immobilized on the microscope slide at their 5' ends." EX1001, 147:20-21, 148:55-57. So-456 specifies that the "[o]ligonucleotides to be used as capture primers … can be immobilized such that a *3'-end is available for enzymatic extension*." EX1005, ¶[00109]; EX1002, ¶¶195-196. In other words, So-456's oligonucleotides are immobilized on the microscope slide at their 5' ends for the 3' ends to be "available for enzymatic extension." EX1005, ¶[00109], FIGs. 1, 9 EX1002, ¶¶195-196. Accordingly, So-456 anticipates claims 5 and 20. EX1002, ¶196.

Claims 6 and 21 depend from claims 5 and 20, respectively, and further require that the extension steps "comprise performing a solid-phase amplification reaction" on the "microscope slide using the plurality of primers immobilized on the microscope slide." EX1001, 147:22-26, 148:58-62. So-456 specifies that its

"capture probes" immobilized on the microscope slide can be "*amplification primers … immobilized* such that a 3'-end is available for enzymatic extension." EX1005, ¶[00109], [00173]; EX1002, ¶¶197-198. So-456 further specifies that the "[l]ibrary preparation may be accomplished *on the capture array substrate*." EX1005, ¶[00156]. Thus, So-456 teaches solid-phase amplification on the microscope slide and anticipates claims 6 and 11. EX1002, ¶¶197-198. So-456 anticipates claims 6 and 21. *Id.*

Claims 7 and 22 depend from claims 1 and 16, respectively, and further require that "the sequencing step is performed using a next generation sequencing reaction." EX1001, 147:27-28, 148:63-64. So-456 discloses this claim element because So-456 discloses that the "spatially-tagged DNA molecules are released from the array and analyzed, for example, by high throughput *next generation sequencing* (NGS), such as sequencing-by-synthesis (SBS)." EX1005, ¶[00127]; EX1002, ¶¶199-200; *see also* EX1005, ¶¶[00156], [00595]. Accordingly, So-456 anticipates claims 7 and 22. EX1002, ¶200.

Claims 8 and 23 depend from claims 1 and 16, respectively, and further require "amplifying a library using the first plurality of extension products and the second plurality of extension products as templates." EX1001, 147:29-31, 148:65-67. So-456 teaches these limitations. So-456 further specifies that its capture probes comprising a "spatial address region 130" also comprises an "SBS

[sequencing-by-synthesis] *primer binding site 125*" that "can also be used in an *amplification reaction* to generate a sequencing library." EX1005, ¶¶[00141], [00142], [00182]; EX1002, ¶¶201-202. Particularly, the SBS primer region 125 "can comprise an SBS primer sequence (e.g., SBS12 or SBS3)" that can be used to amplify the extension product using the extension product as template, as claimed. EX1005, ¶[00141]; EX1002, ¶¶201-202. Accordingly, So-456 anticipates claims 8 and 23. EX1002, ¶202.

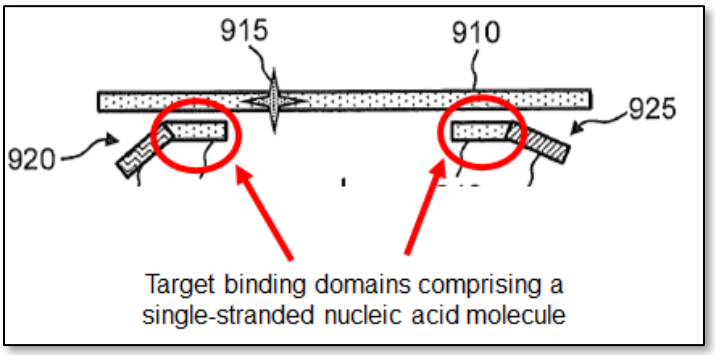
Claims 11 and 12 depend from claim 1, and **claim 27** depends from claim 16, and further require that the "nucleic acid sequence" that "identifies the first location" (claim 11), "second location" (claim 12), and "first location," "second location," or "both" first and second locations (claim 27) of the tissue sample comprise "at least one amplification primer binding site." EX1001, 147:40-47, 149:18-150:9. Thus, these claims require that the oligonucleotide comprising a spatial barcode also comprises "at least one amplification primer binding site." EX1002, ¶¶203-205. So-456 teaches these limitations.

So-456 specifies that its capture probes comprising a spatial address region 130 (*i.e.*, a sequence that *identifies the first and second locations* of the tissue sample) also comprise an "SBS [sequencing-by-synthesis] *primer binding site 125*" that "can also be used in an *amplification reaction* to generate a sequencing library." Thus, So-456's capture probes comprise at least one amplification primer

binding site, as claimed. EX1005, ¶[00141]; EX1002, ¶¶203-205. Accordingly, So-456 anticipates claims 11, 12, and 27. EX1002, ¶¶203-205.

Claims 13 and 28 depend from claims 1 and 16, respectively, and require that "the target binding domains" of the nucleic acid probes (claim 13) and the first and second plurality of nucleic acid probes (claim 28) "comprise[s] a single-stranded nucleic acid molecule." EX1001, 147:48-49, 150:10-13. So-456 teaches these limitations.

As discussed above for claims 1 and 16, So-456's method uses probe pairs comprising a target-binding domain that hybridizes to a complementary site on the target DNA molecules. *See supra,* Sections IX.A-B; EX1002, ¶¶206-208. The target-binding domain in the probe is single stranded because it hybridizes to a complementary site on the target DNA. EX1002, ¶¶206-208. This is depicted in, *e.g.*, So-456's Figure 9, as annotated by Dr. Spellman:



EX1002, ¶207; EX1005, FIG. 9.

Accordingly, So-456 anticipates claims 13 and 28. EX1002, ¶¶206-208.

Claims 14 and 29 depend from claims 1 and 16, respectively, and further require that collecting steps (b)-(c) (claim 14) and (c)-(d) (claim 29) are "performed simultaneously." EX1001, 147:50-51, 150:14-15. So-456 teaches this limitation. So-456's method uses a "capture *array*" comprising capture sites arranged in "rows and columns" (*i.e.*, first and second locations). EX1005, ¶[00141]. So-456 specifies simultaneously capturing (*i.e.*, collecting) at different locations the amplified ligated probes (amplicons 950) when the probes are "transferred *onto an array and captured* by hybridization to universal capture regions on *the array*." EX1005, ¶[00181]; EX1002, ¶¶209-210; *see also* EX1005, ¶[00182] ("genomic amplicons 950 are captured onto the capture site 105"). Accordingly, So-456 anticipates claims 14 and 29. EX1002, ¶¶209-210.

Claims 15 and 30 depend from claims 1 and 16, respectively, and further require that extension steps (d)-(e) (claim 15) and (e)-(f) (claim 30) are "performed simultaneously." EX1001, 147:52-53, 150:16-17. So-456 teaches this limitation. So-456 specifies simultaneously extending by disclosing that the "*capture primers*" at the capture sites on an array are "available for *enzymatic extension*." EX1005, ¶[00109]; EX1002, ¶¶211-212. So-456 further specifies that the spatial barcodes "can be *encoded in the nucleic acid* in the process of preparing the nucleic acid for sequencing." EX1005, ¶[0089]; EX1002, ¶¶211-212. Thus, So-

456's method performs the extension step at multiple capture sites on the array. Accordingly, So-456 anticipates claims 15 and 30. EX1002, ¶¶211-212.

Claim 26 depends from claim 16, and further requires that the "nucleic acid probes" in the "first plurality," "the second plurality," or "both" "comprise an amplification primer binding site." EX1001, 149:9-17. So-456 teaches this limitation.

As discussed above in Section IX.A, So-456's method uses primary probe pairs (capture oligonucleotides). Probe pairs comprise a "universal capture region 935" or an "SBS primer region 945 (e.g., SBS12)"—both these regions are amplification primer binding sites in the subsequent steps. EX1005, ¶[00182], FIG. 9; EX1002, ¶¶213-215. The ligated probes (DNA molecules 950) comprise the universal capture region 935 and SBS primer region 945, and the ligated probes are "amplified by in situ isothermal amplification" "using a *primer* region 935a that is complementary to universal capture region 935 and a *primer* region 945a that is complementary to SBS primer region 945." *Id*. Accordingly, So-456 anticipates claim 26. EX1002, ¶¶213-215.

In sum, So-456 teaches every limitation of claims 2-8, 11-15, 17-23, and 26-30 under NanoString's construction, arranged as claimed, and So-456 is presumed enabled. Accordingly, So-456 anticipates claims 2-8, 11-15, 17-23, and 26-30.

X. GROUND 2: CLAIMS 1-30 WOULD HAVE BEEN OBVIOUS OVER SO-456

To the extent NanoString argues that So-456 does not disclose all the elements of claims 1 and 16, such as the claimed extension steps, claims 1-30 still would have been obvious over So-456 under NanoString's interpretation. EX1002, ¶¶217-254.

A. Claims 1 and 16

The claimed extension steps would have been obvious to a POSA in view of So-456, which teaches including the claimed extension steps in its methods. EX1002, ¶¶218-233. Figure 2—which provides an overall workflow for So-456's methods—specifies that after capturing nucleic acids on the array (Step 220), a "sequencing library is prepared" (Step 225) for use in a subsequent sequencing (Step 230), analysis and decoding (Step 235). EX1005, ¶[00156]. So-456's workflow requires (1) encoding the "spatial origin of a nucleic acid in a tissue sample" in "the process of preparing the nucleic acid for sequencing" and (2) performing sequencing to obtain data that is "analyzed . . . and the spatial information is decoded." EX1005, ¶¶[0089], [00131], [00132], [00158]. To accomplish this, So-456 teaches that the nucleic acids are "tagged by probes including location-specific sequence information (a 'spatial address')." EX1005, ¶[0089]; EX1002, ¶¶218-221.

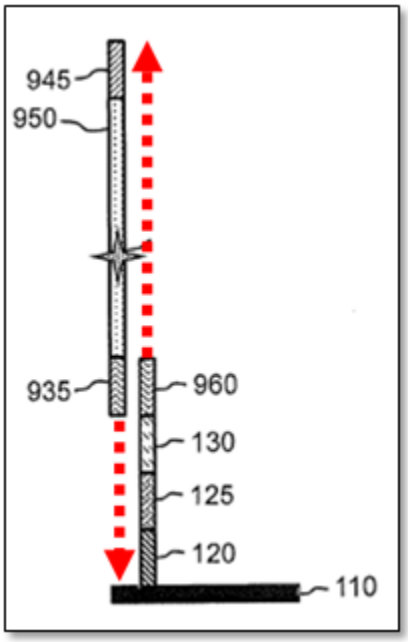
However, So-456's ligated probes (950) captured on the array in the previous step had not yet been tagged with a spatial barcode and do not include the functional SBS primer binding sites necessary for sequencing-by-synthesis in the subsequent steps. EX1002, ¶218-222. Thus, a POSA would have known that during sequencing library preparation (Step 225), the ligated probe sequence (a proxy for the target DNA molecules), the spatial barcode, and the pair of SBS primer-binding sites are incorporated into the same molecule for sequencing and analysis. EX1005, ¶¶[00156]-[00158], FIG. 2; EX1002, ¶222.

So-456 discloses using Illumina's SBS method, which was well known in the art for using a pair of SBS primers for paired-end sequencing. EX1005, ¶¶[00156]-[00158], FIG. 2; EX1030, 6. The ligated probes captured on the array, however, include only one SBS primer binding site ("SBS primer region 945 (e.g., SBS12)"). EX1005, ¶¶[00182], [00141]. The other SBS primer binding site ("SBS primer region 125 [] SBS3") is present on the capture probes, along with the spatial barcode sequence. EX1005, ¶¶[00141], [00109], FIGs. 1, 9; EX1002, ¶¶223-228.

So-456 discloses that the 3'-ends of its capture probes are "available for *enzymatic extension*." EX1005, ¶¶[00141], [00109], FIGs. 1, 9; EX1002, ¶¶229-231. A POSA would have known that because So-456's method uses ligated probes or capture probes with unblocked or unmodified 3'-ends, it extends the 3'-ends of both the ligated probes and capture probes. EX1005, ¶¶[00109], [00182]-

[00183], FIG. 9; EX1002, ¶¶229-231. Indeed, So-456 discloses that when the capture probe is "used as a primer," the captured "DNA molecule … is copied," and when the captured DNA molecule is "used as a primer," the "spatial address region" is copied. EX1005, ¶[00173]; EX1002, ¶¶229-231. So-456 explains that "*[b]oth extension products* can be used for downstream library generation." *Id.*

Thus, So-456 suggests the enzymatic extension of the 3'-ends of the capture probes and the ligated probe to incorporate a spatial barcode, a pair of SBS primer-binding sites, and the ligated probes into the same molecule during library preparation. This is shown in Dr. Spellman's annotations of So-456's Figure 9:



EX1002, ¶230; EX1005, FIG. 9. The resulting extension products are DNA molecules comprising the sequences of the captured ligated probe (935, 950, and SBS primer-binding site 945), the spatial barcode (130), and the second SBS

primer-binding site (125). EX1005, ¶¶[00141], [00182], FIG. 9; EX1002, ¶¶231-232.

Thus, even if So-456 does not disclose performing an extension step (it does) in its method, So-456 still renders it obvious to do so.

Motivation: A POSA would have been motivated to practice So-456's method in Figures 2, 8, and 9 (including the use of extension reaction steps) because the purpose of So-456's methods is to create a sequencing library of sequences that are (i) tagged with spatial barcodes and (ii) include the necessary pair of SBS primer-binding sites for NGS. EX1005, ¶¶[0002], [0089], [0092], [00137], [00141]; EX1002, ¶¶234-236. The use of an extension reaction to extend So-456's capture (and captured) probes was a well-known, obvious, and routine technique for incorporating the spatial barcode (and necessary second sequencing primer) into the resulting extension reaction products to produce the desired finished sequencing library. EX1005, ¶[00173]; EX1002, ¶¶234-236.

So-456 teaches using well-known, commercially available Illumina SBS forward and reverse primers—SBS3 and SBS12. EX1005, ¶¶[00141], [00199], [00201], [00211], [00229], [00496]-[00497]. A POSA would know that SBS3 and SBS12 are the commercially available forward and reverse (respectively) sequencing primers used in Illumina next-generation sequencing (NGS) products. EX1002, ¶¶234-236; EX1030, 6, Fig. 1.

So-456 also teaches using commercially available Illumina sequencing library prep kits, tools, and NGS/SBS sequencers (e.g., "MiSeq") in So-456's methods. EX1005, ¶¶[00127], [00137], [00156]-[00157], [00611]; EX1002, ¶¶234-236. The art taught that to sequence a library on an Illumina NGS sequencer, the sequences in that library must include a pair of Illumina sequencing primers—e.g., SBS3 and SBS12. EX1030, 5-6; EX1002, ¶¶234-236. This is why So-456 teaches using the SBS12 sequencing primer on the captured/ligated probe and the complement of the SBS3 sequencing primer on the capture probe—so that an extension reaction will incorporate both primers of the pair (and the spatial barcode) into both products of the extension reaction. EX1002, ¶¶234-236; EX1005, FIG. 9.

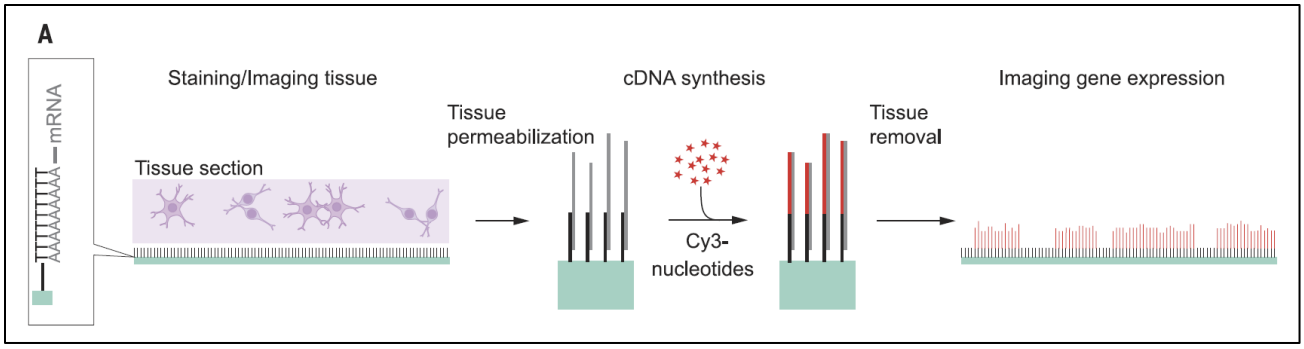
So-456 repeatedly teaches the importance of incorporating the pair of SBS primer sequences into a finished library so it can be sequenced. EX1005, e.g., ¶¶[00199], [00201], [00211], [00229], [00266], [00496]-[00497], [00611]; EX1002, ¶¶234-236.

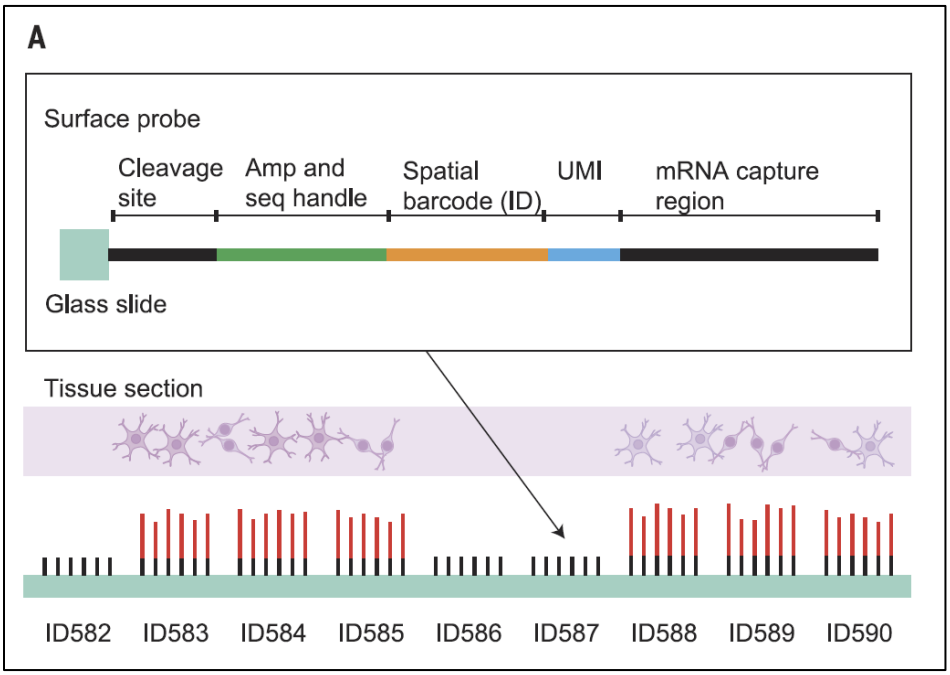
Reasonable Expectation of Success: A POSA would have had a reasonable expectation of successfully practicing the methods of claim 1 and 16 as disclosed by So-456 (including the extension reaction steps) because (i) So-456 provides ample guidance and direction as detailed above, and (ii) the use of extension reactions to extend the captured/ligated (and capture) probes in So-456 to create

the spatially tagged sequencing library was common in the art and required only routine skill. EX1002, ¶¶237-240.

So-456 confirms extension reactions were known, including for preparation of NGS/SBS sequencing libraries. EX1005, ¶¶[00109] ("capture primers...available for enzymatic extension"), [00595]. So-456 also teaches multiple commercially available products for conducting sequencing library prep reactions and subsequent sequencing. EX1005, ¶¶[00127], [00137], [00156]-[00157], [00611]. By the time of So-456 (and the 689 patent), Illumina sequencers were the most well-known and widely used NGS sequencing solutions in the art. EX1002, ¶¶237-240. And POSA's routinely used laboratory protocols (or commercial solutions) for such library preparation extension reactions. EX1002, ¶¶237-240.

The POSA's expectations of success were further bolstered by examples in the art of successfully using immobilized capture probes as primers and captured nucleic acids as templates in extension reactions. EX1016, FIGs. 1A, 2A; EX1002, ¶¶237-240. For example, Stahl's "spatial resolution" method used an extension technique (referred to as "cDNA synthesis" in the figure below) to tag captured target nucleic acids with a spatial barcode:





EX1016, FIGs. 1A, 2A, Abstract; EX1002, ¶239.

Accordingly, claims 1 and 16 would have been obvious.[2]

[2] NanoString did not rely on objective indicia during prosecution. EX1004, 253-272, 469-477; EX1012, 1550-1564.

B. Claims 2-8, 11-15, 17-23, and 26-30

As discussed above for Ground 1, So-456 discloses all of the limitations of claims 2-8, 11-15, 17-23, and 26-30 under NanoString's interpretation. A POSA would have been motivated to practice So-456's method with a reasonable expectation of success for the same reasons discussed above in Sections X.A. and IV.A-C. EX1002, ¶241. Accordingly, claims 2-8, 11-15, 17-23, and 26-30 would have been obvious over So-456. *Id*.

C. Claims 9-10 and 24-25

Claims 9-10 depend from claim 1, and **claims 24-25** depend from claim 16. Claims 9-10 and 24-25 further require that "the at least one nucleic acid sequence that identifies the first location" (claims 9 and 24) or "second location" (claims 10 and 25) "of the tissue sample comprises *at least one unique molecular identifier*." EX1001, 147:32-38, 149:1-8. Claims 9-10 and 24-25 would have been obvious over So-456.

As discussed above in Section IX, a POSA would have known that the spatial barcode ("spatial address region 130") in So-456's capture probe is the "nucleic acid sequence that identifies the first [or second] location of the tissue sample," as claimed. EX1005, ¶[00141], FIGs. 1, 9; EX1002, ¶¶242-245. Although So-456's method of Figures 8-9 does not include a UMI with a spatial barcode in the capture probes, it includes a "UMI region" in the primary probes (capture

oligonucleotide) that is ultimately included in the ligated primary probes (DNA molecules 950). EX1005, ¶[00182]; EX1002, ¶¶242-245. So-456 also discloses including a UMI in the capture probes containing spatial barcodes in other embodiments. For example, So-456's method of Figures 23A and 23B discloses that capture probes "include … a spatial address region 2325, *a unique molecular identifier (UMI)* 2330, and a capture region 2335." EX1005, ¶[00302], FIG. 23; EX1002, ¶¶242-245. Thus, So-456 teaches or suggests all elements of claims 9-10 and 24-25.

Motivation: A POSA would have been motivated to include a UMI in the capture probes in So-456's method of Figures 8-9 for several reasons.

First, UMIs were well known to a POSA. EX[Kivioja2012] Fig. 1A, 72; EX[Stahl], Fig. S5; EX1031, ¶[0030] EX1032, 108:6-15; EX1033, 3:55-4:10; EX1034, ¶[0025]; EX1035 7:39-64; EX1036, ¶[0037]; EX1002, ¶246. The art taught that UMIs incorporate a unique barcode onto each molecule within a given sample library, and by doing so, variant alleles present in the original sample (true variants) can be distinguished from errors introduced during library preparation, target enrichment, or sequencing. EX1002, ¶246.

Second, So-456 teaches including UMIs with the spatial barcodes in its capture probes in other embodiments. EX1005, ¶[00302], FIG. 23; EX1002, ¶247.

Third, So-456 teaches that its disclosed embodiments can be modified, stating that "[o]ther embodiments having different structures and operations do not depart from the scope of the present disclosure" and "various details of the present disclosure can be changed without departing from the scope of the disclosed embodiments." EX1005, ¶[00612]; EX1002, ¶¶248-251. Thus, it would have been obvious for a POSA to try to incorporate the UMI in the capture probes containing the spatial barcode. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (When "there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.").

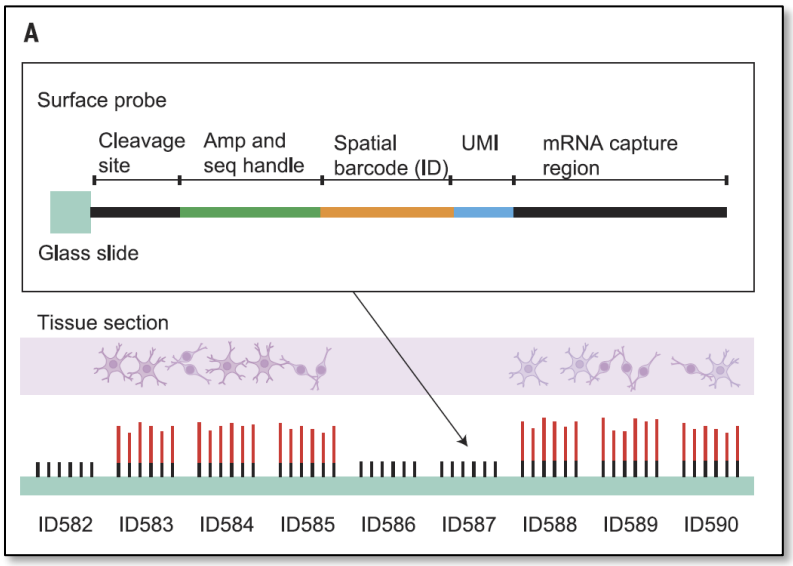
Reasonable expectation of success: A POSA would have had a reasonable expectation of successfully modifying So-456's method of Figures 8-9 to include a UMI with the spatial barcode in the capture probe. EX1002, ¶¶252-254. This is because So-456 discloses other embodiments that successfully used the same approach. EX1005, ¶[0302], FIG. 23. As did other prior art references. EX1016, FIG. 1A; EX1002, ¶¶252-254. For example, Stahl explained that the UMI in the capture probes enabled successful "amplification duplicate removal" via "UMI-filtering." EX1016, Suppl. Data, 21, FIG. S5; EX1002, ¶¶252-254.

Accordingly, claims 9-10 and 24-25 would have been obvious.

XI. GROUND 3: CLAIMS 9-10 AND 24-25 WOULD HAVE BEEN OBVIOUS OVER SO-456 AND STAHL

As discussed above for Grounds 1 and 2, So-456 discloses all of the elements of claims 1-8, 11-23, and 26-30, or renders obvious claims 1-30. Even is, *arguendo*, the UMI claims 9-10 and 24-25 were not obvious over So-456 alone, they were obvious over So-456 in combination with Stahl. EX1002, ¶¶255-268.

So-456 and Stahl together teach or suggest modifying So-456's capture probe to include the UMI disclosed in Stahl's capture probes. As described above, Stahl's "spatial resolution" method uses arrays of capture probes in spots. EX1016, 78, FIG. 2A; EX1002, ¶¶256-258. Each capture probe contains spatial barcodes and UMIs as shown in Figure 2A:



EX1016, FIG. 2A, 78; EX1002, ¶256-257. After reverse transcription, the spatial barcodes and UMIs are incorporated into the cDNA extension product, which is then amplified, generated into a sequencing library, and sequenced. *Id.* Once sequenced, the spatial barcode sequence provides the information to identify which spot the gene transcript came from, and the UMI provides a sequence to identify how many true unique transcripts are present in each spot to "provide quantitative gene expression data." EX1016, Abstract.

Stahl discloses the results of its transcriptomics method, including, Figure S5 which compares Stahl's gene expression data to that in an ISH database and includes in (A) "distributions of unique transcripts captured per feature (UMI-filtered) under the tissue during an experiment on the Spatially barcoded array." Figure S4 and S6 also provide the average number of "unique transcripts." EX1016, Fig. S5; EX1002, ¶258.

Motivation To Combine

A POSA would have been motivated to modify So-456's Figure 8-9 methods to include a UMI sequence in the capture probe as in Stahl's capture probe for several reasons.

First, the use of UMIs was generally well known as shown above for Ground 2. EX1002, ¶260; *see* Section X.C.

Second, So-456 confirms there are two options for incorporating the UMI sequences into the final product to be sequenced: (1) as part of the primary probe (in the method of Figures 8-9) or (2) as a part of the capture probe (along with the spatial barcode) as described in Figure 23 (capture probes that "include … a spatial address region 2325, *a unique molecular identifier (UMI)* 2330, and a capture region 2335"). EX1005, ¶[00302], FIG. 23; EX1002, ¶¶261-264. Further, because So-456 discloses that its methods "can be changed without departing from the scope of the disclosed embodiments," a POSA would have understood that the incorporation of the UMI in different examples was intended to be exemplary and was flexible. *Id.*; EX1005, ¶[00612].

Further, So-456 recognized that "[t]he present disclosure is further based, in part, on the realization that the robustness and data quality of spatial transcriptomics experiments can be enhanced by facilitating the transfer of nucleic acids from a tissue sample onto a capture array, e.g., a capture array of spatially addressed capture probes."). EX1005, ¶¶[2016], [0093]. A POSA reading So-456 would have been aware of Stahl's spatial transcriptomics method, including that the UMI was incorporated in the capture array probes in Stahl. EX1002, ¶¶264-265.

For these reasons, it would have been obvious to incorporate the UMI in So-456's array probe containing the spatial barcode, like Stahl. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

Reasonable Expectation of Success

A POSA would have reasonably expected to modify successfully So-456's method of Figures 8-9 to include a UMI and a spatial barcode in the capture probe because So-456 discloses embodiments that successfully used the same approach (EX1005, ¶[0302], Fig. 23) and, as explained above, spatial detection methods in the prior art successfully included a UMI with a spatial barcode sequence in array capture probes. EX1002, ¶¶266-368.

Accordingly, claims 9-10 and 24-25 would have been obvious.

XII. GROUND 4: CHELL ANTICIPATES CLAIMS 1-30

As discussed below, Chell was filed and published before the 689 patent was filed, and is intervening prior art because the 689 patent is not entitled to any of its claimed priority dates.

A. Claims 1-30 are not entitled to the benefit of any priority date earlier than September 16, 2021

The 689 patent claims are not entitled to priority benefit from any of the priority applications because none of those applications provides written description support for the full scope of the claims. EX1002, ¶¶271-293.

Challenging priority based on lack of written description is appropriate in an IPR. *See e.g., SAP America, Inc. v. Arunachalam*, IPR2014-00414, Paper 24, at 20-21 (P.T.A.B. Aug. 17, 2015); *Nissan North America, Inc. v. The University of Texas System Board of Regents*, IPR2012-00037, Paper 24, at 9 (P.T.A.B. Mar. 19, 2013). There is no priority benefit for claims that are broader than the invention disclosed in the subject application such that they would fail the written description requirement of § 112. *D Three Enters., LLC v. SunModo Corp*, 890 F.3d 1042, 1045, 1051 (Fed. Cir. 2018). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co*. 598 F.3d 1336, 1351 (Fed. Cir. 2010). Where the patentee claims a genus covering multiple potential embodiments, the written description must "indicate that the inventors possessed the full scope of the genus that they chose to claim." *Juno Therapeutics, Inc. v. Kite Pharma, Inc*., 10 F.3d 1330, 1337 (Fed. Cir. 2021).

The claims of the 689 patent were broadened beyond the written description in the specification in two material ways. ***First***, all challenged claims recite "collecting the [] probes, or portions thereof," which on its face encompasses two distinct sets of options—collecting *whole* probes, or portions of probes. However, the priority applications uniformly disclose collecting only portions of probes and

never the whole probe. *E.g.* EX1009, ¶¶[00174]-[00177], [0005]-[0007], [0014], [0015], [0021], [0022], [0024]- [0027], [0033]-[0036], [0043]-[0048], [00108], [00128], [00146], [00160], [00178]-[00180], [00185], [00201], [00212], [00222], [00230], [00235], [00317], [00409], [00411], [00413], [00415], [00417], [00424]; EX1002, ¶¶278-286. This is for good reason: the disclosed primary probes are made up of two separable parts, a target-binding domain (that specifically hybridizes to a target analyte in a tissue) and an identifier oligonucleotide (an oligonucleotide tag that identifies the target analyte). *See, e.g.,* EX1009, ¶¶[0005]-[0007], [0014]-[0015], [0021]-[0022], [0024]-[0027], [0033]-[0036], [0043]-[0048], [00106], [00123], [00126], [00140], [00144], [00155], [00158], [00174], [00178], [00183], [00199], [00210], [00220], [00228], [00231]-[00232], [00235]-[00236], [00246], [00310], [00315], [00317], [00409], [00411], [00413], [00415]; EX1002, ¶¶278-286. When a user wishes to identify the target analytes in a given region of interest, a force is applied only to that region and the identifier oligonucleotide portions of only that local set of probes are cleaved and collected. *Id.* at EX1009, ¶¶[00174]-[00177]. The cleavable nature of the probes is what permits the disclosed "force" to release the portions of probes that are identified within the region, and allow for region-by-region target mapping.

The applications never disclose releasing or collecting *whole* probes, nor do they disclose applying forces to release entire probes. The challenged claims are

drawn to two distinct types of embodiment—collected whole probes and collected cleaved probes. Disclosure of only one embodiment does not evidence possession of a broader claim that also covers different embodiments, particularly where the patent does not describe cleavage as an optional feature. *D Three*, 890 F.3d at 1048-50 (affirming summary judgment of invalidity and lack of priority where one "washerless" assembly was disclosed but claims covered other, undisclosed configurations). Claims 1-30 cannot properly claim the benefit of any of the priority applications.

Second, as discussed above in Section IX.A–IX.B, claims 16-30 are drawn to a particular arrangement and usage of primary (analyte-binding) probes that is not disclosed in the priority applications. Claims 16-30 require hybridizing pairs of primary probes ("nucleic acid probes") to target nucleic acids on the sample followed by ligation of the same probe pairs, all taking place *on the target analyte* before release or collection. EX1002, ¶¶287-292. Thus, the claims require on-analyte ligation to create a new and undisclosed entity—the ligated primary probe.

The 689 patent's priority application neither describes using ligation on the analyte nor binding primary probes to each other. Instead, the priority applications describe distinct on-analyte and off-analyte steps. The on-analyte step requires *in situ* hybridization of cleavable "probes" comprising a target-binding domain and an identifier oligonucleotide. *See, e.g.,* EX1009, ¶¶[0005]-[0007], [0014]-[0015],

[0021]-[0022], [0024]-[0027], [0033]-[0036], [0043]-[0048], [00106], [00123], [00126], [00140], [00144], [00155], [00158], [00174], [00178], [00183], [00199], [00210], [00220], [00228], [00231]-[00232], [00235]-[00236], [00246], [00310], [00315], [00317], [00409], [00411], [00413], [00415]; EX1002, ¶¶287-292. Once the identifier oligonucleotides are cleaved using a force, the released oligonucleotides are collected off the tissue and analyzed (i.e., an off-analyte step). *Id*. As part of the off-analyte step, pairs of *secondary* "nucleic acid probes" are hybridized to the collected identifier oligonucleotides, ligated together, and detected/analyzed. *See, e.g.,* EX1009, ¶¶[0024]-[0027], [0033]-[0036], [0047], [00161], [00168]-[00169], [00174]-[00177], [00178]-[00180], [00183]-[00186], [00389]. But the priority applications do not describe on-analyte ligation. *See, e.g*., EX1009, ¶¶[0024]-[0027], [0033]-[0036], [0047], [00161], [00168]-[00169], [00174]-[00180], [00183]-[00186], [00389]; EX1002, ¶¶287-292.

The priority applications reinforce the distinction between the *singular* primary probes (that hybridize to analytes within the tissue—i.e., on-analyte) and the *pairs* of secondary probes (that hybridize to an identifier oligonucleotide cleaved off from the primary probes—i.e., off- analyte) by giving them different names. Each priority application uses "probes" to describe the oligonucleotides that hybridize to a target analyte in a tissue (*i.e.,* primary probes), and "nucleic acid probes" to describe the pairs of oligonucleotides that hybridize to an identifier

oligonucleotide that was released from the primary probe, and are then ligated together. *See, e.g.,* EX1009, ¶[0024]; EX1010, ¶[0024]; EX1011, ¶[0024]; EX1002, ¶¶287-292. Thus, in the priority applications, the ligation of probe pairs occurs *off-analyte*, while the claims require ligation of probe pairs *on-analyte*. EX1009, ¶¶[0024]-[0027], [0033]-[0036], [0047], [00161], [00168]-[00169], [00174]-[00180], [00183]-[00186], [00389]; EX1010, ¶¶[0023]-[0026], [0032]-[0035], [0046], [00159], [00166]-[00167], [00174], [00178], [00184], [00192]-[00193], [00347], [00357]; EX1011, ¶¶[0023]-[0026], [0032]-[0035], [00131], [00136]-[00137], [00144], [00152]-[00153], [00290], [00293], [00300] , [00303]; EX1002, ¶¶287-292.

Accordingly, claims 1-30 of the 689 patent are not entitled to priority benefit of any of the priority applications because there is no priority support for release or collection of whole probes (rather than portions of probes), and claims 16-30 lack priority for the independent and additional reason that the priority applications fail to disclose pairs of primary probes that are ligated on-analyte. The challenged claims should be accorded a filing date no earlier than September 16, 2021—the date the 707 application was filed. EX1002, ¶¶271-293. Chell thus intervenes and anticipates claims 1-30 under NanoString's interpretation.

B. Claim 16

1. Preamble

Chell teaches methods for spatially detecting at least one target analyte in a tissue sample under NanoString's interpretation. Chell relates to "*methods for spatial analysis* using RNA-templated ligation." EX1006, Title. In particular, Chell discloses "methods of *detecting an analyte of interest* to interrogate *spatial gene expression* in a sample using RNA-templated ligation." EX1006, Abstract; EX1002, ¶¶295-297. Chell's method in Example 1 (depicted in Figures 6 and 13) follows Figure 1's overall workflow and preforms "[s]patial gene expression analysis of FFPE-fixed samples using RNA-templated ligation." EX1006, 80:14-15, FIGs. 1, 6, 13; EX1002, ¶¶295-297. Chell's Figure 13 is reproduced below.

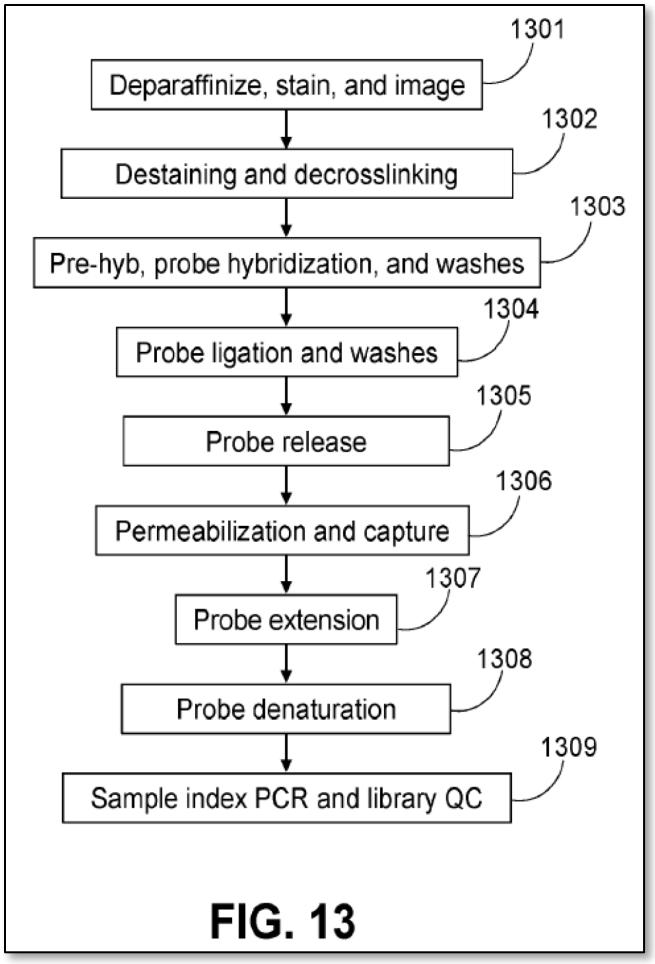


FIG. 13

EX1006, FIG. 13. Chell teaches each of the contacting, ligation, collecting, extension, and sequencing steps of claim 16, arranged as claimed. EX1002, ¶296.

2. "a) contacting the tissue sample …"

Chell teaches claim 16's contacting step. Chell teaches that pairs (a first plurality and second plurality) of "probes are *added to the [biological] sample* and hybridize to an analyte." EX1006, 23:30-32; *see also id*., 80:21-26 (contacting probes with "FFPE-fixed samples"), 81:16-82:7, FIGs. 1, 6, 13; EX1002, ¶¶298-300. Chell's first plurality and second plurality of "probes" 601 and 604 (*i.e.*,

nucleic acid probes) comprise a "target hybridization sequence" (*i.e.*, target-binding domain) that hybridizes at least one target mRNA (*i.e.*, target analyte), as claimed. EX1006, 24:4-9, FIG. 6; EX1002, ¶¶298-300. Chell's Example 1 specifies that "*20,056 probe pairs*" were added "to each *tissue sample* to capture 19,490 different genes," such that the probe pairs that "were added simultaneously" "hybridized to adjacent sequences of the target mRNA." EX1006, 81:18-21; EX1002, ¶298-300. Thus, Chell teaches contacting a plurality of primary probe pairs at multiple locations in a tissue sample. These aspects are shown in Dr. Spellman's annotations of Chell's Figures 6 and 5:

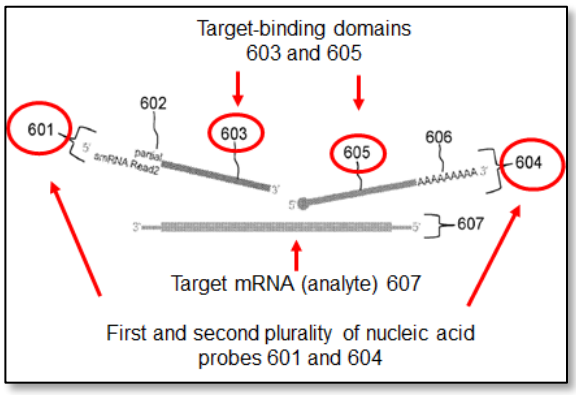


Figure 6

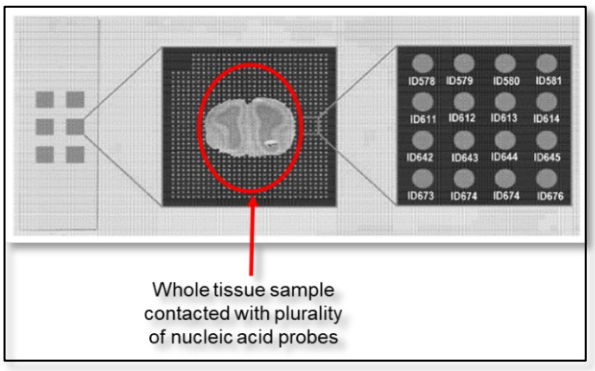


Figure 5

EX1002, ¶300; EX1006, FIGs. 5, 6.

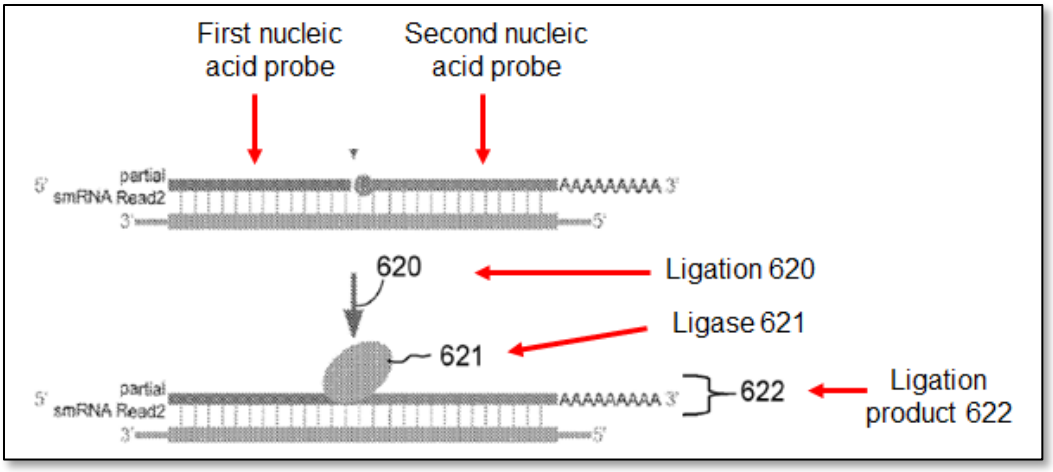
"wherein the tissue sample is treated …"

Chell discloses treating the tissue sample to "facilitate binding" of the probes to the target mRNA, as claimed. Chell teaches that the tissue sample is "deparaffinized," "decrosslinked," and then "*treated with pre-hybridization buffer*" before contacting the tissue with the probes. EX1006, 80:21-26, 23:30-32;

EX1002, ¶301-302. These processes allow water-soluble solutions (such as those containing the probes) to penetrate the tissue and bind the target analyte. EX1002, ¶¶301. Indeed, Chell teaches that after these treatments, the probe pairs hybridized to the target mRNAs, confirming that the tissue was "treated" as claimed. EX1004, 80:26, FIG. 13. Accordingly, Chell teaches claim 16's contacting step.

3. "b) forming ligated probes by ligating …"

Chell teaches claim 16's ligation step. The 689 patent discloses "ligating" probe pairs that are "adjacent and are not overlapping" by "performing a nick repair reaction," by using, for example, ligase. EX1001, 25:60-65, 70:63-71:6, 5:54-6:8, 6:9-44, 8:28-52, 8:63-9:23, 12:39-57, 27:41-47, 28:34-40, 30:53-58, 30:59-65. Chell's method specifies that after the primary probe pairs hybridize to the target mRNA, "[a] ligase 621 *ligates 620 the first probe to the second probe* thereby generating a ligation product 622." EX1006, 24:9-10; *see also id*., 80:26-27 ("[ligase] was added to the samples to ligate hybridized probes to generate a ligation product"), 82:15-83:3, FIGs. 1, 6, 13; EX1002, ¶¶303-305. Dr. Spellman's annotation of Chell's Figure 6 is reproduced below:



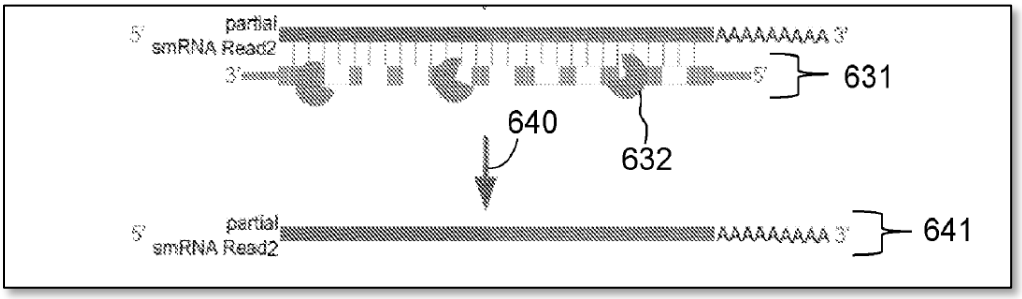
EX1006, FIG. 6; EX1002, ¶304. Accordingly, Chell teaches claim 16's ligation step.

4. "c) [and (d)] collecting the ligated probes…"

Chell teaches claim 16's collecting steps under NanoString's interpretation. As discussed above, according to NanoString, the collecting steps encompass diffusion and capture of *whole* probes or *whole* oligonucleotides across the *whole* tissue sample, all at the same time. EX1020, 53-54; EX1008, 19-20; EX1002, ¶¶306-312.

Chell discloses that, after ligation, the "ligation products" are "*released* from the analyte by contacting the biological sample *with RNAse H.*" EX1006, 80:28-29, 23:33-34, 83:4-15, 24:9-13, FIGs. 1, 6, 13; EX1002, ¶¶306-312. Chell's "[s]amples were then *permeabilized to facilitate capture* of the ligation product by the capture probes on the substrate" wherein the ligation product diffuses on to the substrate. EX1006, 80:29-30, 83:4-15; EX1002, ¶¶306-312. Thus, Chell's method diffuses

and captures the *whole* ligated primary probes from the *whole* tissue sample at adjacent locations on the array, all at the same time. EX1006, 80:21-33, 83:4-8, 83:13-15, FIG. 13; EX1002, ¶¶306-312. Chell depicts this step in Figure 6:



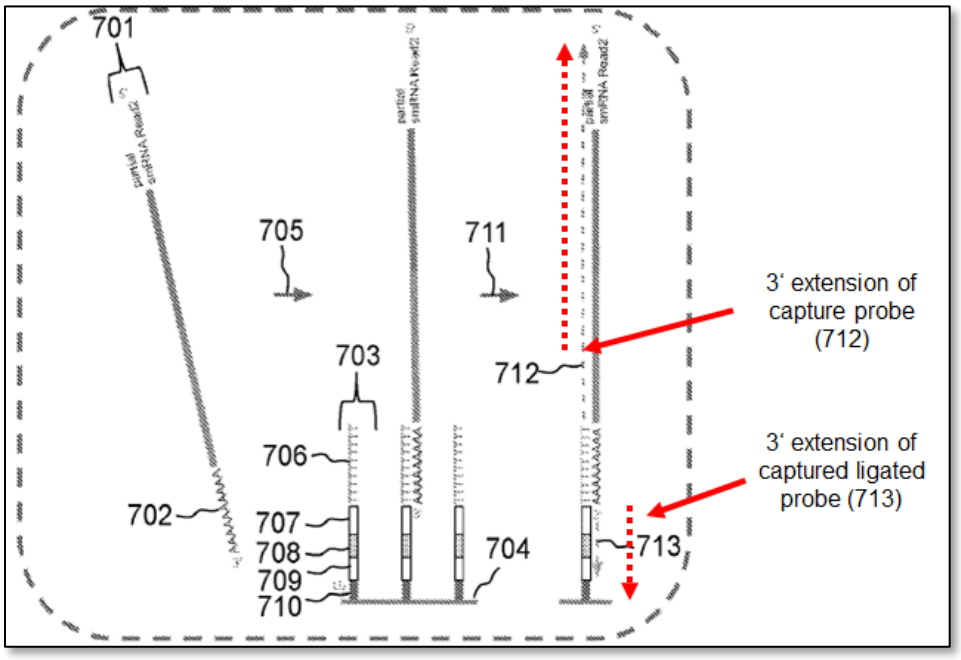
EX1006, FIG. 6; EX1002, ¶310. Accordingly, Chell teaches claim 16's collecting steps under NanoString's interpretation.

5. "e) [and (f)] performing an extension reaction …"

Chell teaches claim 16's extension steps. Chell teaches that the "[l]igation products that hybridized to the capture probes *were then extended*" to generate "extended capture probes" (*i.e.*, extension products). EX1006, 80:30-31, 83:13-84:3, FIG. 13; EX1002, ¶¶313-320. Chell's capture probes include a "spatial barcode" and therefore the extension products comprise the ligation products (i.e., ligated probes) and the spatial barcode of the capture probes. EX1006, 24:31-33, FIG. 7.

As depicted in Figure 7, Chell's method performs bi-directional extension of the ligated probes (701) that were captured in the previous steps on the capture probes (703) containing the spatial barcode (708). EX1006, 24:25-25:8, FIG. 7;

EX1002, ¶¶313-320. The 3'-end of the capture probes (703) is extended in one direction to generate extension products 712, and the 3'-end of the captured ligated probes is extended the other direction to generate the extension products 713, as shown below. *Id.*



EX1006, FIG. 7; EX1002, ¶318.

Indeed, Chell teaches that "[i]ncubation with the [reverse transcription] reagents can *extend the capture probes* [Step] 711 to produce *spatially-barcoded full-length cDNA* 712 and 713." EX1006, 25:4-6, FIG. 7; EX1002, ¶¶313-320. Accordingly, Chell teaches claim 16's extension steps.

6. "g) identifying the first plurality of extension products …."

Chell teaches claim 16's sequencing step under NanoString's interpretation. Chell teaches that the "extended capture probes were denatured" and the

"[d]enatured, extended capture probes" were "indexed" and "subjected to quality control … before *being sequenced*." EX1006, 80:31-33, 84:7-9 ("samples were indexed … [n]ucleic acids were then *sequenced and analyzed*."), 23:12-29, FIGs. 1, 13; EX1002, ¶¶321-323. Chell also teaches spatially detecting at least one target analyte in a first and second location of the tissue sample because Chell's method determines "the abundance *and location* of an analyte." EX1006, 24:2-3, FIG. 1 ("*[d]etermine sequence* of ligation product … *[i]dentify location* of analyte in sample"), 84:12-28, FIGs. 14-19; EX1002, ¶¶321-323. Accordingly, Chell teaches claim 16's sequencing step.

In sum, Chell teaches every limitation of claim 16 under NanoString's interpretation, arranged as claimed, and Chell is presumed enabled. Accordingly, Chell anticipates claim 16.

C. Claim 1

Claim 1 is similar to claim 16, but broader in scope. Thus, because Chell anticipates claim 16, it also anticipates claim 1 under NanoString's interpretation.

1. Preamble

The preamble of claim 1 is identical to claim 16. Chell teaches claim 1's preamble for the reasons discussed above for claim 16. EX1006, Title, Abstract, 80:14-15, 80:21-22, FIGs. 1, 13; EX1002, ¶325; *see supra*, Section XI.B.

2. "a) contacting …"

Chell teaches claim 1's contacting step. As discussed above for claim 16, Chell's method contacts a tissue sample with a first plurality and a second plurality of nucleic acid probes comprising a target-binding domain. EX1006, 19:11-16, 23:30-32, 24:4-9, 80:21-33, 81:16-82:7, FIGs. 1, 5, 6, 13; EX1002, ¶¶326-330; *see supra*, Section XI.B. Claim 1 more broadly requires contacting the tissue sample with a "plurality of nucleic acid probes." EX1001, 147:57-148:4; EX1002, ¶¶326-330 Thus, Chell teaches claim 1's contacting step for the reasons discussed above for claim 16's contacting step.

3. "b) [and (c)] collecting…"

Chell teaches claim 1's collecting steps for the same reasons discussed above for claim 16's collecting steps. EX1002, ¶¶331-336; *see supra*, Section XI.B. As discussed above, according to NanoString, claim 1's collecting steps encompass diffusion and capture of *whole* probes or *whole* oligonucleotides across the *whole* tissue sample, all at the same time. *See* Section VIII.A. After ligation, Chell's method releases the ligated primary probes from a first and second location of the tissue sample by treating the sample with RNAse H and then permeabilizing the tissue to facilitate capture of the ligation products on the immobilized capture probes. EX1006, 80:21-33, 83:4-15, 24:9-13, FIGs. 1, 6, 13; EX1002, ¶¶331-336. Thus, Chell's method diffuses and captures the *whole* ligated primary probes from the *whole* tissue sample at adjacent locations on the array all at the same time. *Id*.

Accordingly, Chell teaches claim 1's collecting steps under NanoString's interpretation.

4. "d) [and (e)] performing an extension reaction …"

Chell teaches claim 1's extension steps for the same reasons discussed above for claim 16's extension steps. EX1002, ¶¶337-345; *see supra*, Section XI.B. As discussed above, Chell's method extends both the 3'-end of the captured ligated probes and 3'-end of the capture probes to generate "extended capture probes" (*i.e.*, extension products), which incorporate a spatial barcode and the target mRNAs sequence. EX1006, 80:30-31, 83:13-84:3; 24:31-33, 25:4-6, FIGs. 1, 7, 13; EX1002, ¶¶337-345. Accordingly, Chell teaches claim 1's extension steps.

5. "f) identifying …"

Chell teaches claim 1's sequencing step for the same reasons discussed above for claim 16's sequencing step. EX1002, ¶¶346-349; *see supra*, Section XI.B. As discussed above, Chell's method includes indexing, sequencing, and analyzing the sequences. EX1006, 80:31-33, 84:7-9, 23:12-29, FIGs. 1, 13; EX1002, ¶¶346-349. Chell's method also determines "the abundance *and location* of an analyte," and thus spatially detects at least one target analyte in a first and second location of the tissue sample. EX1006, 24:2-3, FIG. 1, 84:12-28, FIGs. 14-19; EX1002, ¶¶346-349. Accordingly, for the reasons discussed above in claim 16,

Chell discloses the sequencing and spatial detection steps of claim 1 under NanoString's interpretation.

In sum, Chell teaches every limitation of claim 1 under NanoString's interpretation, arranged as claimed, and Chell is presumed enabled. Accordingly, Chell anticipates claim 1.

D. Claims 2-15 and 17-30

Claims 2 and 17 depend from claims 1 and 16, respectively, and further require that "the tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample." EX1001, 147:12-13, 148:48-49. **Claims 3 and 18** depend from claims 1 and 16, respectively, and further require that "the tissue sample is immobilized onto a microscope slide." EX1001, 147:14-15, 148:50-51. Chell teaches these limitations. Specifically, Chell's method in Example 1 performs "[s]patial gene expression analysis of *FFPE-fixed samples* using RNA-templated ligation." EX1006, 80:14-15, 21-23, FIG. 13; EX1002, ¶¶351-352. Example 1 specifies that the "FFPE-fixed samples" were "deparaffinized, stained (e.g., H&E stain), *and imaged*" and that the workflow uses "FFPE sectioned mouse *brain tissue slides*" (*i.e.*, microscope slides). EX1006, 80:22-23, 81:1; EX1002, ¶¶351-352. Accordingly, Chell anticipates claims 2-3 and 17-18. EX1002, ¶¶351-352.

Claims 4 and 19 depend from claims 3 and 18, respectively, and further require that "the microscope slide comprises a plurality of primers immobilized on

the microscope slide." EX1001, 147:16-18, 148:52-54. Chell teaches this limitation. Chell's method uses "spatially-barcoded arrays" comprising "plurality of capture probes" and specifies that the "[s]amples were [] permeabilized to facilitate capture of the ligation product by the *capture probes on the substrate*." EX1006, 23:13-18, 80:29-30, 24:11-13; EX1002, ¶¶353-354. Chell further specifies that "[t]he released, ligated DNA probes that served as a proxy for the target mRNA were allowed to hybridize to the capture domain on the *capture probe immobilized on the spatial array*…." EX1006, 83:13-15; EX1002, ¶¶353-354. Chell's "plurality of capture probes" constitute the claimed "a plurality of primers" because Chell's probes are used as primers for polymerase extension reactions in the extension steps. EX1006, 23:13-18, 80:30-31, 83:15-16; EX1002, ¶¶353-354. Accordingly, Chell anticipates claims 4 and 19. EX1002, ¶¶353-354.

Claims 5 and 20 depend from claims 4 and 19, respectively, and further require that "the plurality of primers is immobilized on the microscope slide at their 5' ends." EX1001, 147:20-21, 148:55-57. Chell teaches this limitation. Chell's Example 1 specifies that the "[l]igation products that hybridized to the capture probes were then *extended*" to obtain the "extended capture probes." EX1006, 80:30-31; EX1002, ¶¶355-356. Chell specifies that the extended capture probes are capture probes having additional nucleotides added, for example, "*to the most 3' nucleotide* of the capture probe to extend the length of the capture probe."

EX1006, 17:24-28; EX1002, ¶¶355-356. For Chell's capture probes to be extended at 3' ends, they are immobilized at their 5' ends on the array slide. EX1006, Fig. 7; EX1002, ¶¶355-356. Accordingly, Chell anticipates claims 5 and 20. EX1002, ¶¶355-356.

Claims 6 and 21 depend from claims 5 and 20, respectively, and further require that the extension steps "comprise performing a solid-phase amplification reaction" on the "microscope slide using the plurality of primers immobilized on the microscope slide." EX1001, 147:22-26, 148:58-62. **Claims 8 and 23** depend from claims 1 and 16, respectively, and further require "amplifying a library using the first plurality of extension products and the second plurality of extension products as templates." EX1001, 147:29-31, 148:65-67. Chell teaches these limitations. EX1002, ¶¶357-358, 360-361.

Chell discloses that the "*extended capture probes* are *amplified* (e.g., in bulk solution or *on the array*)"—*i.e.*, solid-phase amplification. EX1006, 18:3-6. The "*extended capture probes* (e.g., DNA molecules) act as *templates* for an *amplification reaction* (e.g., a polymerase chain reaction)." *Id*.; EX1002, ¶¶357-358, 361-362. Similarly, Chell's Example 1 specifies that the "[d]enatured, *extended captured probes* were *indexed* and the *amplified libraries* were subjected to quality control 1309 before being sequenced." EX1006, 80:31-33, FIG. 13

("[s]ample index *PCR*"); EX1002, ¶¶357-358, 361-362. Accordingly, Chell anticipates claims 6, 8, 21, and 23. EX1002, ¶¶357-358, 361-362.

Claims 7 and 22 depend from claims 1 and 16, respectively, and further require that "the sequencing step is performed using a next generation sequencing reaction." EX1001, 147:27-28, 148:63-64. Chell teaches this limitation. Chell's "methods for sequencing genetic material include … *next-generation sequencing* methods…." EX1006, 79:8-12, 5:30-31, 16:2-5; EX1002, ¶¶359-360. Accordingly, Chell anticipates claims 7 and 22. EX1002, ¶¶359-360.

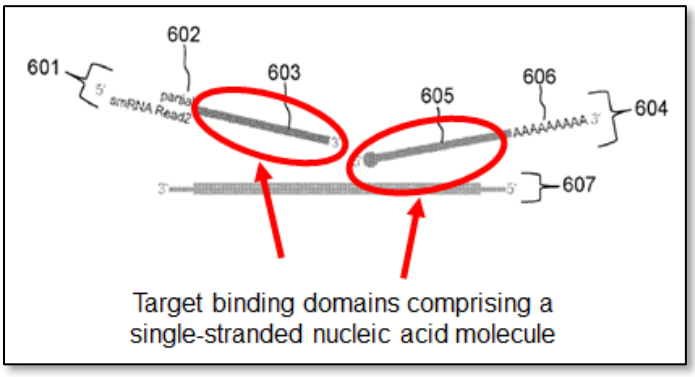
Claims 9-10 depend from claim 1, and **claims 24-25** depend from claim 16. Claims 9-10 and 24-25 further require that "the at least one nucleic acid sequence that identifies the first location" (claims 9 and 24) or "second location" (claims 10 and 25) "of the tissue sample comprises *at least one unique molecular identifier*." EX1001, 147:32-38, 149:1-8. Chell teaches these limitations. Chell's capture probes include "a *spatial barcode and*/or a *unique molecular identifier (UMI)*) and a capture domain." EX1006, 12:12-14, 24:31-33 ("[t]he capture probe can also include a *unique molecular identifier (UMI)* 707, a *spatial barcode* 708…."), FIG. 7; EX1002, ¶¶363-364. Chell's "spatial barcode" is "a nucleic acid sequence that provides information as to the location or position of an analyte within a cell or a tissue sample." EX1006, 10:6-10; EX1002, ¶¶363-364. Accordingly, Chell anticipates claims 9-10 and 24-25. EX1002, ¶¶363-364.

Claims 11 and 12 depend from claim 1, and **claim 27** depends from claim 16, and further require that the "nucleic acid sequence" that "identifies the first location" (claim 11), "second location" (claim 12), and "first location," "second location," or "both" first and second locations (claim 27) of the tissue sample comprise "at least one amplification primer binding site." EX1001, 147:40-47, 149:19-150:9. Chell teaches these limitations because Chell discloses that its capture probes, which comprise a spatial barcode sequence, can also include at least one amplification primer binding site. EX1002, ¶¶365-367.

As discussed above for claims 1 and 16, Chell's capture probes comprise the claimed "nucleic acid sequence that identifies the first [and second] location of the tissue sample" because they comprise a "*spatial barcode*." EX1006, 10:6-10, 12:11-14, 15:15-16; EX1002, ¶¶365-367; *see supra,* Section XI.B-C. Chell's "capture probe[s] can include … a *functional domain* (e.g., *a primer-binding site*….)." EX1006, 12:14-16, 15:16-17; EX1002, ¶¶365-367. Indeed, Chell's method in Example 1 specifies that "[t]he captured ligated probes *were copied* [*i.e.*, amplified], using the capture probe as a template," and that, "[f]or *library preparation*, samples were indexed using an *Amp Mix* that included *dual indexing primers* and an Amp Mix." EX1006, 83:15-16, 84:7-8; EX1002, ¶¶365-367. Accordingly, Chell anticipates claims 11, 12, and 27. EX1002, ¶¶365-367.

Claims 13 and 28 depend from claims 1 and 16, respectively, and require that "the target binding domains" of the nucleic acid probes (claim 13) and the first and second plurality of nucleic acid probes (claim 28) "comprise a single-stranded nucleic acid molecule." EX1001, 147:48-49, 150:10-13. Chell discloses these limitations.

As discussed above for claims 1 and 16, Chell teaches probe pairs comprising a "target hybridization sequence" (*i.e.*, target binding domain) that binds to the target mRNAs. EX1006, 24:4-9, FIG. 6; *see supra,* Section XI.B-C; EX1002, ¶¶368-370. Chell's probe pairs "were designed to *hybridize to adjacent sequences of each analyte* (e.g., mRNA sequence)…." EX1006, 81:16-82:2; EX1002, ¶¶368-370. For each of the probes to hybridize to the target mRNA, its target-binding domain must comprise a single-stranded region. EX1002, ¶¶368-370. Chell exemplifies this in Figure 6, as annotated by Dr. Spellman:



EX1006, FIG. 6; EX1002, ¶369. Accordingly, Chell anticipates claims 13 and 28. EX1002, ¶¶368-370.

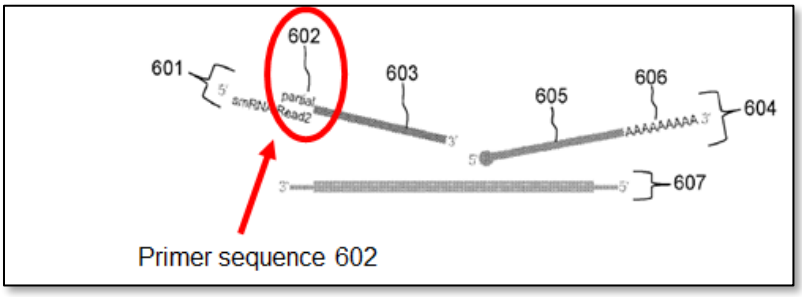
Claims 14 and 29 depend from claims 1 and 16, respectively, and further require that the collecting steps (b)-(c) (claim 14) and (c)-(d) (claim 29) are "performed simultaneously." EX1001, 147:50-51, 150:14-15. **Claims 15 and 30** depend from claims 1 and 16, respectively, and further require that extension steps (d)-(e) (claim 15) and (e)-(f) (claim 30) are "performed simultaneously." EX1001, 147:52-53, 150:16-17. Chell teaches these limitations.

Chell's method in Example 1 releases the ligated primary probes by "incubating the *samples* with RNase H mix"—thus, releasing the probes simultaneously from multiple locations. EX1006, 82:15-83:12; EX1002, ¶¶371-374. Likewise, Chell's method captures the released ligated probes from multiple locations of the tissue simultaneously on the array of capture probes. EX1006, 83:13-15; EX1002, ¶¶371-374. Chell specifies that the "*[s]amples* were then permeabilized to *facilitate capture* of the ligation product *by the capture probes* on the substrate." EX1006, 80:29-30, 83:4-15; EX1002, ¶¶371-374. Accordingly, Chell discloses performing the collecting steps simultaneously, as claimed, and anticipates claims 14 and 29. EX1002, ¶¶371-374.

Chell's method also performs the extension reactions simultaneously at multiple locations on the array. EX1006, 80:30-31, 83:17-18, FIG. 13; EX1002, ¶¶371-374. Chell specifies that the "*[l]igation products* that hybridized to the capture probes *were then extended*" by incubating "the *tissues* … with a second

strand *extension mix*." EX1006, 80:30-31, 83:17-18, FIG. 13; EX1002, ¶¶371-374. Thus, Chell anticipates claims 15 and 30. EX1002, ¶¶371-372.

Claim 26 depends from claim 16, and further requires that "the nucleic acid probes" in the "first plurality," "the second plurality," or "both" the first and second plurality of the nucleic acid probes, "comprise an amplification primer binding site." EX1001, 149:9-17. Chell teaches this limitation because Chell's primary probes in its probe pairs have "a target-hybridization sequence 603 and a *primer sequence* 602." EX1006, 24:4-13, 81:19-22, FIG. 6; EX1002, ¶¶375-377. Chell exemplifies this in Figure 6, as annotated by Dr. Spellman:



EX1006, FIG. 6; *see also id.*, 30:1-2 ([i]n some embodiments, a first probe includes a functional sequence" that "includes a *primer sequence*."); EX1002, ¶¶375-377. Accordingly, Chell anticipates claim 26.

XIII. DISCRETIONARY DENIAL IS NOT APPROPRIATE HERE

A. The Petition satisfies 35 U.S.C. § 325(d)

The Board's two-part framework set forth in *Advanced Bionics* does not apply here because neither So-456, Stahl, nor Chell were previously presented to

the Office by the Applicant or ever considered by the Examiner. EX1004, 205-213, 236, 242-250, 273, 514; EX1012, 202-208, 1380, 1386, 1533, 1538-1546, 2457, 2463-2464; *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8-9 (P.T.A.B. Feb. 13, 2020) (precedential).

Further, the Examiner erred during prosecution in failing to recognize that the challenged claims lacked written description support in the priority applications and thus are not entitled to any of the 689 patent's claimed priority dates. EX1004, 222-235, 493-503; EX1012, 1517-1532, 2436-2456. Indeed, the Office did not raise any written description (or prior art) rejections during prosecution of the 689 patent or its parent application. EX1004, 222-235, 493-503; EX1012, 1517-1532, 2436-2456. And the enablement rejection under § 112 had nothing to do with the written description bases identified in Section XI.A above. EX1004, 224-233; EX1012, 1517-1532, 2436-2456; *see supra*, Section XII.A. Thus, this Petition satisfies 35 U.S.C. § 325(d).

B. *Fintiv* does not support discretionary denial under 35 U.S.C. § 314(a)

The *Fintiv* factors do not support discretionary denial of institution. *Commscope Technologies LLC v. Dali Wireless, Inc*., IPR2022-01242, Paper 23 (P.T.A.B. Feb. 27, 2023) (precedential) ("*Commscope*"); *Apple Inc. v. Fintiv, Inc.*, IPR2020-0019, Paper 11, 6 (P.T.A.B. Mar. 20, 2020) (precedential).

Here, the 689 patent district court litigation is still in the early stages and the parties have not significantly invested in the litigation. The trial date for the 689 patent is currently projected to be December 9, 2024—approximately two months before a Final Written Decision would be reached in this IPR. *See* EX1023. Thus, the substantive briefing, discovery, and potentially even the oral hearing in this IPR may be complete before the projected trial date.

Moreover, the Petition demonstrates compelling unpatentability bases for multiple independent reasons. "[W]hen determining whether there is a compelling unpatentability challenge, the Board evaluates whether the Petition presents challenges 'in which the evidence, if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence.'" *Commscope* at 3; EX1029, 4. As demonstrated above, under NanoString's interpretations, all challenged claims are "highly likely" anticipated and/or obvious over the prior art. *Commscope* at 4. *Fintiv* simply does not apply here.

XIV. MANDATORY NOTICES (37 C.F.R. § 42.8(A)(1))

A. Real Party-in-Interest 37 C.F.R. § 42.8(b)(1)

The real party-in-interest is 10x Genomics, Inc.

B. Related Matters (37 C.F.R. § 42.8(b)

The 689 patent was asserted as a counterclaim in *10x Genomics, Inc. and President and Fellows of Harvard College v. NanoString Technologies, Inc*., Case No. 1:22-cv-00261 (D. Del.). Subsequently, the 689 patent counterclaim was severed from Case No. 1:22-cv-00261 and consolidated with *NanoString Technologies, Inc. v. 10x Genomics, Inc.*, Case No. 1:22-cv-01375 (D. Del.).

C. Lead and Back-up Counsel (37 C.F.R. § 42.8(b)

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D. Service Information (37 C.F.R. § 42.8(b)

Please direct all correspondence regarding this Petition to counsel at the above addresses and PTAB@sternekessler.com. 10x consents to service by email at the addresses above.

E. Procedural Statements

This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith are a Power of Attorney and Exhibit List under 37 C.F.R. §§ 42.10(b) and 42.63(e), respectively. The required fee is paid through Deposit Acct. No. 19-0036 (Customer ID No. 45324). The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 19-0036 (Customer ID No. 45324).

XV. CONCLUSION

Claims 1-30 should be canceled.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. This Petition for *Inter Partes* Review complies with the type-volume limitation of 14,000 words, comprising 13,815 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).

2. This Petition for *Inter Partes* Review complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman font.

Respectfully submitted,

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CERTIFICATE OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

I certify that the above-captioned **PETITION FOR *INTER PARTES* REVIEW FOR U.S. PATENT NO. 11,377,689** and associated Exhibits 1001-1013, 1016-1021, and 1023-1037 were served in their entireties upon the Patent Owner on August 16, 2023, via FedEx® Express at the following address:

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Patent Owner's Correspondence Address of Record for U.S. Patent No. 11,377,689

Respectfully submitted,

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