**IN THE UNITED STATES BANKRUPTCY COURT**
**FOR THE DISTRICT OF DELAWARE**

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| In re: | : | Chapter 11 |
| NANOSTRING TECHNOLOGIES, INC., *et al.*,[1] | : | Case No. 24-10160 (CTG) |
| | : | (Jointly Administered) |
| Debtors. | : | **Objection Deadline: February 29, 2024 at 4:00 p.m. EST**<br>**Hearing Date: March 7, 2024 at 1:00 p.m. EST** |

**MOTION OF 10X GENOMICS, INC. FOR ENTRY OF AN ORDER (I) MODIFYING THE AUTOMATIC STAY WITH RESPECT TO THE 653 ACTION AND THE IPR PROCEEDINGS AND (II) GRANTING RELATED RELIEF**

10x Genomics, Inc. ("**10x**") hereby submits this motion (the "**Motion**") and respectfully states as follows:

## RELIEF REQUESTED

1. By this Motion, 10x seeks entry of an order substantially in the form attached hereto as **Exhibit A** (the "**Order**") (i) granting relief from the automatic stay pursuant to section 362(d)(1) of title 11 of the United States Code (the "**Bankruptcy Code**") and Rule 4001 of the Federal Rules of Bankruptcy Procedure (the "**Bankruptcy Rules**") with respect to: (A) *10x Genomics, Inc. and Prognosys Biosciences, Inc. v. NanoString Technologies, Inc.*, Case No. 21-cv-653 (MFK) (D. Del. 2021) (the "**653 Action**"), a patent infringement action pending in the United States District Court for the District of Delaware (the "**Delaware District Court**"), solely for the purpose of permitting the Delaware District Court to rule on the post-trial motions filed by

[1] The Debtors in these Chapter 11 Cases, along with the last four digits of their U.S. federal tax identification numbers, to the extent applicable, are NanoString Technologies, Inc. (4687), NanoString Technologies International, Inc. (2723), NanoString Technologies Netherlands B.V., and NanoString Technologies Germany GmbH. The Debtors' headquarters is located at 530 Fairview Avenue North, Suite 2000, Seattle, WA 98109.

10x and Debtor NanoString Technologies, Inc. ("**NanoString**") and to enter final judgment, but not for enforcement of any judgment or other adjudication of claims; and (B) two administrative actions pending in the United States Patent and Trademark Office (the "**USPTO**") before the Patent Trial and Appeal Board (the "**PTAB**"): (I) Case IPR2023-01298 (the "**689 IPR Proceeding**") whereby 10x has challenged the validity of NanoString's U.S. Patent No. 11,377,689 (the "**689 Patent**") and (II) Case IPR2023-01300 (the "**142 IPR Proceeding**" and together with the 689 IPR Proceeding, the "**IPR Proceedings**") whereby 10x has challenged the validity of NanoString's U.S. Patent No. 11,473,142 (the "**142 Patent**");[2] and (ii) granting related relief. A summary of the current U.S. litigation between 10x and the Debtors relevant to the Chapter 11 Cases is attached hereto as **Exhibit B**.

## PRELIMINARY STATEMENT

2. Since May 2021, 10x, the Debtors' largest unsecured creditor, has sought to defend its patents in several jurisdictions to protect its valuable intellectual property rights against the Debtors' wrongful infringement. Indeed, each of the German Federal Patent Court in Munich, the United States District Court in Delaware, and the Unified Patent Court in the European Union, have determined that the Debtors' products infringe at least ten of 10x's patents. Contrary to the Debtors' position that 10x's "flimsy" claims are a veiled attempt at stomping out competition, these rulings in 10x's favor would indicate that the Debtors are the ones whose conduct is problematic.[3] The Debtors assert that ongoing litigation with 10x was a key driver of the Debtors'

[2] The PTAB has yet to render a decision regarding whether the IPR Proceedings are in fact stayed and, if so, which court will decide whether to lift the stay.

[3] *See Motion of Debtors for Relief from the Automatic Stay with Respect to the U.S. CosMx Action* (the "**Debtors' Lift Stay Motion**"), Dkt. No. 125 at ¶ 24. ("The Debtors believe that their counterclaims and affirmative defenses effectively dismantle 10x's flimsy claims and reveal their true nature: that a much larger company is trying to remove the Debtors from the market to further tighten their hold on the biotechnology space and monopolize the SST market to the detriment of the scientific community at large and the Debtors' stakeholders.").

decision to file for bankruptcy, yet also acknowledge that the Debtors have not recognized any net profit since their inception, have consistently missed their revenue goals, and, for the nine months ended September 2023, had net losses of approximately $122.3 million with a total accumulated deficit of $931.6 million.[4] In other words, the ongoing litigation notwithstanding, the Debtors concede they are facing an imminent liquidity crisis and have experienced a precipitous drop in their stock price.

3. The Debtors now seek to address their precarious financial situation by pursuing "a value-maximizing sale transaction" in the Chapter 11 Cases on an expedited basis with an auction to take place, including potentially with respect to infringing product lines, within 90 days of the Petition Date, a sale order to be entered within 100 days of the Petition Date, and a sale to be consummated within just 30 days thereafter.[5]

4. Contrary to the Debtors' assertions, the relief sought herein will facilitate the sale process and the efficient administration of the Debtors' estates by providing clarity for potential bidders with respect to whether the product lines that the Debtors now seek to sell are subject to valid patents or, instead, should be enjoined from further distribution. As such, 10x's request to lift the stay as to the 653 Action and the IPR Proceedings is in the best interest of the Debtors' estates and stakeholders.

5. The Debtors have three product lines: nCounter, GeoMx, and CosMx. GeoMx and CosMx constitute the Debtors' "spatial business" and are the two product lines that have been

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[4] *See Declaration of R. Bradley Gray in Support of Chapter 11 Petitions and First Day Pleadings* (the "**Gray Declaration**"), Dkt. No. 26 at ¶¶ 44, 48; *see also* NanoString Technologies, Inc. Quarterly Report (Form 10-Q) (Nov. 6, 2023).

[5] *See* Gray Declaration at ¶ 43; *see also Debtors' Motion for Entry of Interim and Final Orders (I) Authorizing the Debtors to Obtain Postpetition Financing, Granting Senior Postpetition Security Interests and According Superpriority Administrative Expense Status Pursuant to Sections 364(c) and 364(d) of the Bankruptcy Code, (II) Authorizing the Use of Cash Collateral, (III) Granting Adequate Protection, (IV) Modifying the Automatic Stay, and (V) Granting Related Relief*, Dkt. No. 24.

found to infringe 10x patents. During the first day hearing, the Debtors confirmed: "critically, we believe that any potential buyer of our spatial business will want to see the matters that are in dispute resolved sooner, rather than later."[6] 10x agrees and supports the lifting of the automatic stay to permit this critical litigation to proceed, including to allow final judgment to be entered following the Delaware District Court's consideration of fully briefed post-verdict motions in the 653 Action.[7]

6. However, the Debtors' aforementioned strategy to bring clarity to its sale process by resolving disputes with 10x only includes the 261 Action (which relates to the Debtors' CosMx product line), and intentionally excludes the 653 Action (which relates to the Debtors' GeoMx product line) and the IPR Proceedings (which were initiated in response to NanoString's infringement claims against 10x pending in the 1375 Action[8]). The Debtors go as far as stating, on the one hand, that "[t]he ability to bring the [261 Action] to trial on or substantially close to its existing schedule is likely to be attractive to bidders in the Debtors' sale process because the anticipated result would create significant value for a successful bidder who purchases CosMx,"[9] while, on the other hand, that lifting the stay pursuant to this Motion would cause an unexplained "potentially negative impact" on the sale process.[10] The Debtors also ignore the potential for an adverse ruling in the 261 Action and appear to accept that the potential negative impact is no reason to keep the 261 Action stayed. 10x expects that any potential buyer that seeks to participate in the

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6 *See February 6, 2024* Hr'g Tr., at 18:7-18:10.

7 To be clear, 10x is not seeking authority to execute on any final judgment entered at this time.

8 *See* Case No. 22-cv-1375 (MFK) (D. Del. 2022) (the "**1375 Action**").

9 Debtors' Lift Stay Motion at ¶ 20.

10 *See* Debtors' Lift Stay Motion at ¶ 4 ("[A]ny motion by 10x to lift the stay in the U.S. GeoMx Action will not be [consensual]. In fact, due to the potentially negative impact such relief could have on the Debtors' sale process, the Debtors vehemently oppose lifting the stay with respect to the U.S. GeoMx Action.").

Debtors' sale process will insist on full clarity with respect to *both* the GeoMx and CosMx product lines. Absent a global resolution of these issues, the overhang of unresolved claims is likely to chill bids and depress the value of the Debtors' estates given the uncertainty that would accompany the purchase of assets that several courts have already determined infringe 10x's patents.

7. Importantly, 10x would face significant prejudice if the 653 Action and the IPR Proceedings are not permitted to proceed while the Debtors would face little to no harm if, instead, the stay is lifted. Post-trial briefing in the 653 Action has already been completed and allowing the 653 Action to proceed will provide clarity to potential bidders to maximize the value of a potential sale. While 10x has requested a final judgment in its favor, a doubling of damages, and injunctive relief, the Debtors could, instead, prevail in their request to overturn the jury's $31 million verdict, while also preserving appeal rights thereafter. And while the Debtors may argue that permitting the entry of a final judgment would cause them harm because 10x may be awarded monetary or injunctive relief, the automatic stay is not a license for the Debtors' continuing infringement in violation of non-bankruptcy law. No matter the outcome, a resolution of the 653 Action would allow potential buyers to submit bids with full knowledge of relevant facts. Conversely, permitting the stay to remain in place would be detrimental to the Debtors' sale process given the cloud over the assets and the likelihood 10x would continue to pursue patent infringement claims against any buyer that purchases infringing products from the Debtors.

8. Meanwhile, the IPR Proceedings are intertwined with the 1375 Action, with the same patents at issue in both, and absent the continuation of the IPR Proceedings, 10x would be denied the preferred venue to challenge the validity of the patents that was specifically created by Congress for this purpose. If the Debtors plan to continue to assert the 142 Patent and 689 Patent in the 1375 Action, allowing the IPR Proceedings to proceed concurrently is crucial to 10x's ability

to have the patent validity resolved in a comprehensive and fair manner, including in a tribunal specifically created for validity challenges. Doing so will inform the merits of NanoString's patent infringement claims against 10x pending in the 1375 Action, which will determine whether the 142 Patent and 689 Patent have any value for NanoString, and relatedly, for a potential buyer or successor. It is against this backdrop that 10x files this Motion seeking relief to proceed with the 653 Action and the IPR Proceedings. The Debtors are not prejudiced by the relief sought because resolution will only bring clarity to bidders regarding the value of the assets the Debtors are seeking to sell and, absent such relief, 10x will be severely prejudiced.[11]

## JURISDICTION

9. This Court has jurisdiction over the Debtors' Chapter 11 Cases and the Motion pursuant to 28 U.S.C. §§ 157 and 1334 and the *Amended Standing Order of Reference* from the United States District Court for the District of Delaware dated February 29, 2012. Consideration of the Motion constitutes a core proceeding pursuant to 28 U.S.C. § 157(b)(2). Venue is proper pursuant to 28 U.S.C. §§ 1408 and 1409.

10. The statutory predicates for the relief sought herein include section 362(d)(1) of the Bankruptcy Code, Bankruptcy Rule 4001, and Rule 4001-1 of the Local Bankruptcy Rules of the United States Bankruptcy Court for the District of Delaware.

## BACKGROUND

### I. General Background

11. On February 4, 2024 (the "**Petition Date**"), each of the above captioned debtors (the "**Debtors**") filed voluntary petitions under chapter 11 of the Bankruptcy Code (the "**Chapter**

[11] On February 17, 2024, the Debtors confirmed via e-mail that they would not stipulate to the stay relief sought in this Motion with respect to the 653 Action. As of the filing of this Motion, the Debtors have not responded to confirm whether they would stipulate to the stay relief sought with respect to the IPR Proceedings.

**11 Cases**") in the Bankruptcy Court. The Debtors are authorized to operate their business and manage their properties as debtors and debtors in possession pursuant to sections 1107(a) and 1108 of the Bankruptcy Code.

12. On February 15, 2024, the Office of the United States Trustee appointed an official committee of unsecured creditors (the "**Creditors Committee**"). No request has been made for the appointment of a trustee or an examiner.

13. On February 21, 2024, the Debtors filed the Debtors' Lift Stay Motion, pursuant to which the Debtors are seeking to lift the automatic stay with respect to *10x Genomics, Inc. and President and Fellows of Harvard College v. NanoString Technologies, Inc.*, Case No. 22-cv-00261 (MFK) (D. Del. 2022) pending in the Delaware District Court, pursuant to which 10x has asserted patent infringement claims against the Debtors with respect to one of their spatial business lines, the CosMx product line (the "**261 Action**"). 10x does not object to this relief.

## II. Background Regarding 10x and Patent Litigation

14. 10x is a life sciences technology company that was founded in 2012 in Pleasanton, California. 10x has invested hundreds of thousands of hours and at least $1.5 billion in research and development to invent, design, and develop its proprietary line of products for understanding biology at an unprecedented resolution and scale. 10x is a worldwide leader in genomics, the comprehensive study of biological systems at a molecular and cellular level. 10x launched its first commercial product in 2015, and over 7,000 scientific articles have been published based on data generated from 10x products. 10x's Visium and Xenium products have catalyzed the field of spatial analysis by providing commercial offerings that enable true spatial discovery. Spatial analysis allows the large-scale interrogation of biological analytes in their spatial context, allowing

researchers and clinicians to build a comprehensive map—a kind of Google Earth—of where each analyte is located, so that function can be tied to location.

15. 10x has been actively engaged in litigation with the Debtors over various patent disputes. Since May 2023, the Debtors have been found liable for patent infringement in three separate courts, including pursuant to a jury verdict in the Delaware District Court in the 653 Action granting monetary damages to 10x for lost profits associated with the Debtors' willful infringement[12] and injunctive relief in two European venues enjoining the Debtors from continuing to sell their infringing products. The Debtors have argued that 10x's actions to defend its patents represent an "unfair" use of the judicial system.[13] While 10x welcomes fair competition, the Debtors' actions have been far from fair, and they should not be permitted to continue their infringing conduct unabated by hiding behind the cloak of a bankruptcy filing—the intended outcome of filing the Debtors' Lift Stay Motion.[14]

### A. 10x's Affirmative Litigation Regarding Debtors' GeoMx Product: The 653 Action

16. On May 6, 2021, 10x along with Prognosys Biosciences Inc. ("**Prognosys**") filed the 653 Action against NanoString in the Delaware District Court asserting claims of patent infringement related to the Debtors' GeoMx product line. The seven patents subject to the 653 Action relate to studying the spatial distribution of genetic material at a cellular level within tissues.

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[12] *See 10x Genomics, Inc. v. NanoString Technologies, Inc.*, Case No. 21-cv-653 (MFK) (D. Del. Nov. 22, 2023), 653 Action, Dkt. No. 312; *see also* Press Release, PR Newswire, "10x Genomics Wins Another Patent Infringement Case Against NanoString Technologies" (Nov. 17, 2023).

[13] *See* Gray Declaration at ¶¶ 34-35.

[14] *See* Debtors' Lift Stay Motion at ¶ 18 ("…absent the protection of the automatic stay, the District Court could soon enter a judgment enforcing the $31.6 million jury verdict against the Debtors and potentially award other relief (such as enjoining the Debtors' sales of GeoMx or imposing an ongoing royalty rate).").

17. The 653 Action has been litigated for over two years and was nearing conclusion prior to institution of the automatic stay. A jury trial was held in November 2023, and, on November 17, 2023, the jury found that NanoString had willfully infringed all of the asserted patents, that the asserted patents were valid, and that 10x was entitled to over $31 million in damages, including lost profits for sales resulting from NanoString's willful infringement.

18. At present, 10x's and NanoString's post-trial motions are the sole outstanding items left for adjudication in the 653 Action. In its post-trial motion, NanoString requested judgment as a matter of law or a new trial while 10x requested the Delaware District Court award enhanced damages and attorneys' fees based on NanoString's willful infringement, award pre-judgment and post-judgment interest, and enjoin NanoString from continuing to sell its infringing GeoMx products and award an on-going royalty for any sales not enjoined. A wide range of outcomes could occur as a result of the post-trial briefing. For example, the judgment amount could be reduced to $0 or it could increase beyond $31 million. Additionally, an injunction could be entered or not. The post-trial briefing concluded on January 17, 2024. The Debtors filed the Chapter 11 Cases before the Delaware District Court ruled on either party's motion or entered final judgment, and, on February 8, 2024, the Delaware District Court confirmed that it was staying consideration of the post-trial motions pending a decision by the Bankruptcy Court to lift the automatic stay with respect to the 653 Action. *See 10x Genomics, Inc. v. NanoString Technologies, Inc.*, Case No. 21-cv-653 (MFK) (D. Del. Feb. 8, 2024), 653 Action Dkt. No. 336.

### B. Cross-Party Litigation: The 261 Action, the 1375 Action and the IPR Proceedings

#### (i) 10x's Affirmative Litigation Regarding Debtors' CosMx Product: The 261 Action

19. On February 28, 2022, 10x and President and Fellows of Harvard College ("**Harvard**") filed the 261 Action against NanoString in the Delaware District Court asserting

claims of patent infringement related to the Debtors' CosMx product line.[15] The Debtors have contested the claims regarding patent infringement on several different grounds and have sought to invalidate 10x's patents. The parties have been engaged in discovery on all claims and counterclaims in this case. On January 30, 2024, just before the Debtors filed the Chapter 11 Cases, NanoString filed an IPR petition against one of the patents asserted in the 261 Action. Prior to the imposition of the automatic stay, trial on these issues was scheduled to begin in September 2024. As mentioned above, the Debtors have filed a motion seeking to lift the automatic stay with respect to the 261 Action.

**(ii) Debtors' Affirmative Litigation: The 1375 Action**

20. NanoString asserted its own patents, the 142 Patent and 689 Patent, in the 1375 Action. Specifically, NanoString has accused 10x's Visium products of infringement. 10x contends that its products do not infringe the asserted patents, and that the patents are invalid for failing to comply with statutory requirements, among other grounds. Prior to the filing of the Chapter 11 Cases, the 1375 Action was in the middle of fact discovery, with fact depositions having begun and the close of fact discovery set for March 15, 2024. The 1375 Action is not subject to the automatic stay.

**(iii) 10x's Affirmative Administrative Actions: IPR Proceedings**

21. In conjunction with the 1375 Action, 10x petitioned the PTAB at the USPTO to consider the validity of the 689 Patent and 142 Patent via two separate *inter partes* review ("**IPR**") proceedings. The IPR procedure enables defendants in patent litigation to challenge the validity of patents at the PTAB while they face infringement allegations in district court if the defendant

[15] These asserted patents are related to the patents that the Debtors were found to infringe in the German Federal Patent Court in Munich and the Unified Patent Court in the European Union, which led to two injunctions against the Debtors in those jurisdictions.

requests an IPR within one year of the service of a complaint. 35 U.S.C. § 315(b). On February 6, 2024, NanoString notified the PTAB that the IPR Proceedings were stayed due to filing of the Chapter 11 Cases.

22. The IPR Proceedings and 1375 Action are interrelated, and are proceeding alongside each other. 10x pursued the IPR path because of the quick and predictable timeframe to decide validity within the statutorily required one year period and because the PTAB is well-suited for determining the validity of the 142 Patent and the 689 Patent due to its specialized expertise.

23. An IPR occurs in two stages and is not automatically granted. First, a party must petition for an IPR, which requires a showing and finding that there is a reasonable likelihood that a challenged claim will be found unpatentable. 35 U.S.C. § 314(a); *see also SAS Institute, Inc. v. Iancu*, 138 S.Ct. 1348, 1356 (2018) ("[Section 314(a)] simply requires [PTAB] to decide whether the petitioner is likely to succeed on 'at least 1' claim."). Once that occurs, the petition is instituted, and a trial commences. The petitioner then must prove by a preponderance of the evidence that the patent should be deemed invalid. 35 U.S.C. § 316(e). If the PTAB makes such a finding, the patent is then deemed invalid and the petitioner may move for dismissal in the related district court proceeding on the grounds that the patent in question is no longer valid.

24. 10x filed its IPR petition for the 689 Patent (IPR2023-01298) on August 16, 2023, and its IPR petition for the 142 Patent (IPR2023-01300) on September 25, 2023.

25. On February 1, 2024, the PTAB instituted the 689 IPR Proceeding, making the requisite finding that there is a reasonable likelihood of invalidity of the patent. *See 10x Genomics, Inc. v. NanoString Technologies, Inc.*, Case IPR2023-01298 (PTAB, Feb. 1, 2024) (Newman, APJ)[, 689 IPR Proceeding, Paper 14]. Absent a stay, 10x expected a final written decision with respect to the 689 IPR Proceeding no later than February 1, 2025.

26. In the IPR Proceeding related to the 142 Patent, while 10x has filed its petition, the PTAB had not yet issued its institution decision as of the Petition Date. Absent a stay, 10x would expect the PTAB would issue its institution decision by April 2024, with a final written decision expected between February 2025 and April 2025 if the 142 IPR Proceeding resumes promptly.

27. If the Debtors plan to continue to assert the 142 Patent and the 689 Patent in the 1375 Action, allowing the IPR Proceedings to proceed concurrently is crucial to 10x's ability to have the patent validity resolved in a comprehensive and fair manner, in a tribunal specifically created for such validity challenges. To deny 10x the ability to fully defend itself with respect to the patents the Debtors are asserting in the ongoing 1375 Action would be extremely prejudicial to 10x.

## BASIS FOR RELIEF

28. Bankruptcy Code section 105(a) authorizes the Bankruptcy Court to "issue any order, process, or judgment that is necessary or appropriate to carry out the provisions of this title." 11 U.S.C. § 105(a).

29. Under the Bankruptcy Code, the filing of a bankruptcy petition automatically stays "the commencement or continuation . . . of a judicial . . . action or proceeding against the debtor that was or could have been commenced before the commencement of the [bankruptcy]." 11 U.S.C. § 362(a)(1). The moving party bears the initial burden to establish a *prima facie* case that "cause" exists, which the party opposing relief must then rebut. *Matter of Rexene Prods. Co.*, 141 B.R. 574, 577 (Bankr. D. Del. 1992).

30. "Cause" is not defined in the Bankruptcy Code; rather, courts have found that "[c]ause is a flexible concept and courts often conduct a fact intensive, case-by-case balancing test, examining the totality of the circumstances to determine whether sufficient cause exists to lift the stay." *In re SCO Grp., Inc.*, 395 B.R. 852, 856 (Bankr. D. Del. 2007). The automatic stay "is not

meant to be absolute, and in appropriate instances relief may be granted." *Id.* The Third Circuit has instructed courts to use "wide latitude" in determining whether to grant relief from stay. *In re Myers*, 491 F.3d 120, 129 (3d Cir. 2007). "The purpose of the automatic stay is to maintain the status quo that exists at the time of the debtor's bankruptcy filing." *In re APF Co.*, 274 B.R. 408, 417 (Bankr. D. Del. 2001).

31. To establish cause, the party seeking relief from the stay must show that the balance of hardships from not obtaining relief tips in its favor. *See id.* (citing *In re Am. Classic Voyages, Co.*, 298 B.R. 222, 225 (D. Del. 2003)); *see also In re Aleris Int'l, Inc.*, 456 B.R. 35, 47 (Bankr. D. Del. 2011) (applying a hardship balancing test to assess the existence of "cause"). "The three prongs of the balance test are (1) whether any great prejudice to either the bankrupt estate or the debtor will result from lifting the stay; (2) whether the hardship to the non-bankrupt party by the maintenance of the stay considerably outweighs the hardship to the debtor if the stay is lifted; and (3) whether it is probable that the creditor will prevail on the merits of its case against the debtor." *In re Aleris Int'l, Inc.*, 456 B.R. at 47-48.

32. However, as this Court has recognized, "when the debtor files a bankruptcy case immediately on the eve of trial in a dispute over ownership of the debtor's critical assets, these circumstances (and the risk of misuse of the bankruptcy process) make it incumbent on the debtor to provide good reasons why stay relief should not be granted." *In re AP Orangevale, LLC*, No. 23-10687 (CTG), 2023 WL 5093819 at *10 (Bankr. D. Del. Aug. 8, 2023). In *AP Orangevale*, this Court held that the timing of the debtor's chapter 11 filing warranted "more careful scrutiny" under principles of the Bankruptcy Code. *Id.* at *9. Given the advanced state of outside proceedings and the necessity of liquidating the movant's claim concerning critical assets, this Court found that stay relief was warranted based on a "common-sense judgment about whether it

makes good sense to have the case proceed in the court where it was pending…" *Id.* at *7 (quoting *In re Medical Tech. Assocs. II*, No. 22-50389 (CTG), 2022 Bankr. LEXIS 3088 at *15 (Bankr. D. Del. Nov. 2, 2022)).

33. Here, the ongoing dispute between 10x and the Debtors relates to two of the Debtors' core assets. As discussed above, 10x's claims must be liquidated before confirmation, and doing so now will provide clarity to the Debtors' sale process and the Chapter 11 Cases generally. Both the Delaware District Court and the PTAB "have developed familiarity with the claim by presiding over the lawsuit before the bankruptcy" and, particularly in the case of the PTAB, "have specialized expertise in [the] particular area of law." *Id*. at *9. And the 653 Action has advanced past the eve of trial – even past trial itself – such that the jury verdict need only be reduced to judgment following the Delaware District Court's consideration of the fully-briefed post-trial submissions.[16] Even considering the Debtors' cash-flow and liquidity challenges, this Court should be wary of anything that might resemble a "litigation tactic to obtain a potentially more favorable forum for resolving a dispute" and, particularly with respect to the 653 Action, "a last-ditch effort by the debtor to stave off impending defeat in another forum."[17] The Debtors' own assertions make clear that this is likely the case. By arguing that the stay should not be lifted for the 653 Action to proceed to judgment simply because trial "has already taken place" and the "District Court could soon enter a judgment" is completely backwards and a clear indication that the Debtors are attempting to improperly use the stay as a litigation tactic.[18] Given the

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[16] *See* Non-Final Judgment Following Jury Verdict (the "**Non-Final Judgment**") attached hereto as **Exhibit C**.

[17] *See AP Orangevale*, 2023 WL 5093819 at *8 ("Accordingly, while every motion for relief from stay will turn on the particular facts and circumstances of the case, the case for granting stay relief is a relatively strong one when the debtor is not, in fact, seeking to obtain a breather from that litigation, but instead intends to pursue the very same litigation, only in a different forum.").

[18] *See* Debtors' Lift Stay Motion at ¶ 18.

circumstances of this case, the burden should shift to the Debtors to explain their intentions with respect to 10x's claims and to show why the pending actions should not be concluded in their existing forums.

34. Further, to the extent that 10x must carry the burden, "cause" exists here to lift the stay to allow 10x to litigate (i) the 653 Action before the Delaware District Court and (ii) the IPR Proceedings before the PTAB because the potential harm to 10x from maintenance of the stay far outweighs the prejudice (if any) to the Debtors or their estates from lifting the stay.

### A. The Debtors Will Not be Prejudiced, and Are, In Fact, Benefited by Lifting the Automatic Stay for Both the 653 Action and the IPR Proceedings

(i) *There is no prejudice in allowing the 653 Action to proceed*

35. Allowing the 653 Action to proceed will benefit the Debtors because the case is at the final post-jury verdict stage, and proceeding with the case will create minimal additional expense for the Debtors since post-trial briefing has already concluded and these claims will ultimately need to be adjudicated to finality regardless of the venue.[19]

36. As outlined above, allowing the relief requested will facilitate efficient administration of the Debtors' estates. The relief requested herein allows the Debtors to have an opportunity to modify or overturn 10x's favorable verdict in post-trial briefing, while preserving appeal rights thereafter. Additionally, allowing the 653 Action to proceed, and a final judgment to be entered, will provide clarity to potential bidders to maximize the value of a potential sale.[20] While the Debtors claim that lifting the stay may have a "negative impact" on the sale, they are

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[19] Courts have recognized that reducing a verdict to judgment is "a simple ministerial task that does not constitute the continuation of a judicial proceeding, which would be stayed under § 362(a)(1)." *In re ABC Learning Centres Ltd.*, 445 B.R. 318, 336-39 (Bankr. D. Del. 2010) (citing *In re Rexnord Holdings, Inc.*, 21 F.3d 522, 527 (7th Cir. 1994)). Relatedly, courts routinely grant stay relief so that a verdict can be reduced to judgment when certain post-verdict matters must be adjudicated. *In re Nugent*, 254 B.R. 14, 40 (Bankr. D.N.J. 1998); *In re Beguelin v. Volcano Vision, Inc.*, 220 B.R. 94, 97-98 (B.A.P. 9th Cir. 1998).

[20] *See* Debtors' Lift Stay Motion at ¶ 20.

not able to articulate why.[21] If the Debtors are correct that a judgment will be entered against them in the 653 Action, then they are improperly using the Bankruptcy Court to stave off impending defeat. Conversely, if there is uncertainty regarding the outcome of the 653 Action, lifting the stay will provide necessary clarity in the Debtors' sale process. Further, permitting the stay to remain in place increases the likelihood that 10x may need to continue to pursue patent infringement claims against any successor or buyer that purchases infringing products from the Debtors and intends to continue to sell them, thereby potentially chilling the Debtors' sale efforts.

(ii) *There is no prejudice in allowing the IPR Proceedings to proceed*

37. Regarding the IPR Proceedings, receiving a final determination inures to the Debtors' benefit. The result of the IPR Proceedings will yield one of two outcomes. *First*, the PTAB could hold that one or both of the Debtors' patents are valid, thus effectively insulating the Debtors' patents from many invalidity attacks in the 1375 Action. *Second*, the PTAB could hold the patents are invalid, providing clarity to any prospective buyers of the Debtors' assets.

38. Allowing the 1375 Action to proceed while the IPR Proceedings remain stayed is inefficient and would not achieve the clarity that the Debtors seek in order to maximize value for their sale process. This scenario would leave any ruling in the Debtors' favor subject to later attack because the patents on which the claims are premised could ultimately be found to be invalid by the PTAB, after the stay is lifted.

39. The 1375 Action will only provide a ruling on the validity of a subset of patent claims, leaving open validity challenges to the remaining patent claims. Where a defendant files an IPR petition, the same **patents** will be at issue in both the district court proceeding and the IPR proceeding; however, the specific patent **claims** addressed in each is likely to vary, with the district

[21] *See id*. at ¶ 4.

court addressing a subset of the claims at issue in the IPR proceeding. Here, the Delaware District Court will only address the validity of 5 patent claims of each patent while the PTAB will address all 30 claims of the 689 Patent and all 13 claims of the 142 Patent. Since the PTAB will determine the validity of *all* of the patent claims, the IPR Proceedings will provide more clarity to prospective buyers than will the 1375 Action standing alone.

40. There is very little work for the Debtors or 10x to do or funds to expend before a decision can be rendered in the IPR Proceedings. The institution process has concluded with respect to the 689 Patent and has been almost fully briefed with respect to the 142 Patent (and no hearing is likely before institution in the 142 IPR Proceeding). Following institution, some additional briefing will occur with limited discovery and an oral hearing, none of which should entail significant expense, particularly when weighed against the benefits set forth above.

41. Lastly, and as discussed in more detail below, the PTAB is the best body to adjudicate the validity of the patents in question. The PTAB has specialized knowledge that would be difficult for the Bankruptcy Court to replicate and makes it well positioned to provide finality on this issue.

42. In sum, neither the Debtors nor their estates will be prejudiced (and rather the Debtors will likely be benefited) by lifting the stay to allow the 653 Action and the IPR Proceedings to proceed.

**B. Hardship to 10x from Denial of the Relief Sought Considerably Outweighs Any Conceivable Hardship to the Debtors if the Stay is Lifted**

(i) *There is hardship to 10x if the 653 Action is not allowed to proceed*

43. Courts find prejudice to creditors like 10x where not lifting the automatic stay of a pending litigation would force the creditor to "duplicate all of its efforts in the bankruptcy court."

*Matter of Fernstrom Storage & Van Co.*, 938 F.2d 731, 736-37 (7th Cir. 1991) (finding such duplication to be "unfair").

44. With respect to the 653 Action, 10x will be severely prejudiced if the automatic stay is not lifted. Absent relief, 10x could be required to re-prosecute a duplicative proceeding in the Bankruptcy Court—a gross waste of private and judicial resources. The 653 Action, which is extremely close to completion, would involve the same facts, witnesses, documents and issues as the proceeding that would then take place in the Bankruptcy Court. Importantly, with regards to the 653 Action, this Motion is only seeking relief to allow it to proceed to judgment – not to enforce such a judgment. *See In re Briarpatch Film Corp.*, 281 B.R. 820 (Bankr. S.D.N.Y. 2002) (the automatic stay cannot "be used to prevent the entry of judgment against the debtor on a lawsuit in which its rights have been fully litigated."). At this juncture in the 653 Action, 10x's claim needs to be liquidated, and it would be administratively inefficient and burdensome to have the claim liquidated by the Bankruptcy Court at such a late stage in the litigation. Conversely, the Debtors achieve a significant benefit by having an opportunity to modify or overturn the verdict in post-trial briefing.

45. With respect to injunctive relief, if the stay is not lifted, the Debtors would effectively be allowed to operate their business in willful violation of applicable non-bankruptcy law (*i.e.*, continue to infringe 10x's patents) and without monetary compensation to 10x in the form of a royalty. While that appears to be the Debtors' goal,[22] the Debtors should not be able to hide behind the automatic stay in order to accomplish objectives that are inconsistent with the Bankruptcy Code. Additionally, the Debtors should not be allowed to circumvent an otherwise valid claim for injunctive relief unless the Debtors agree not to take any actions in violation of the

[22] *See* Debtors' Lift Stay Motion at ¶ 18.

injunction 10x is seeking. 10x reserves the right to seek further stay relief, such as an appeal or steps to enforce or collect, and/or further affirmative relief, such as seeking to enjoin continuing postpetition infringement and/or a royalty escrow. The harm to 10x by allowing the 653 Action to remain stayed is significant.

(ii) *There is hardship to 10x if the IPR Proceedings are not allowed to proceed*

46. If the IPR Proceedings are stayed and remain stayed, 10x will suffer severe harm that far outweighs any harm to the Debtors if the stay is lifted.

47. One of 10x's defensive mechanisms in the 1375 Action would be hamstrung if the stay is not lifted. This presents a scenario where the Debtors are permitted to proceed with an action seeking judgment that 10x infringed upon a patent without 10x being able properly to defend itself by arguing that such patent is not valid in the venue best-suited for such validity challenges.[23] Validity challenges at the PTAB are reviewed by a panel of three judges with scientific background and the burden to prove invalidity at the PTAB is lower than that in district court (preponderance of the evidence compared with clear and convincing evidence). Additionally, while patent validity may be challenged during the district court litigation, due to the limited number of hours allocated for trial testimony, 10x will have to limit the number of defenses it presents at trial and 10x may never be able to present the prior-art-based grounds for invalidity at issue in the IPR Proceedings. Additionally, allowing both the IPR Proceedings and the 1375 Action to proceed in parallel would ensure the parties take consistent positions on infringement and validity in both forums; the

[23] *See A.P. Orangevale*, 2023 WL 5093819 at *8 ("For example, where the debtor initiates a prepetition suit against a defendant (which is not subject to the stay) and that defendant asserts certain counterclaims in the same case, courts should be cognizant of the fact that, while the defendant's counterclaims are subject to the automatic stay, in practice it may make sense to allow both claims to proceed outside of bankruptcy to ensure that the same facts are not litigated twice **and that one side is not forced into a fight with one hand tied behind its back**.") (emphasis added).

Debtors should not be permitted to stay the IPR Proceedings and avoid taking positions on the invalidity of the 689 Patent and the 142 Patent that are inconsistent with the infringement positions the Debtors takes in the Delaware District Court. The Debtors' admissions in the IPR Proceedings are likely to be material and persuasive in the co-pending 1375 Action. Entities against whom a debtor proceeds in an offensive posture are permitted to initiate judicial or adversary proceedings in order to defend their legal rights as long as such litigation is not designed to seize or exercise control over property of the estate.[24] Therefore, 10x should not be limited in how it defends itself in the 1375 Action through maintenance of the stay.

48. And absent relief, the IPR Proceedings cannot be conducted in a different forum because the USPTO is the *only* tribunal that can conduct an IPR proceeding (though it is not the only tribunal that can assess the validity of a patent). Conversely, the Debtors would suffer little to no prejudice if the stay were lifted and the IPR Proceedings were allowed to proceed. *See In re Scarborough St. James Corp.*, 535 B.R. 60 (Bankr. D. Del. 2015) (finding that the debtor would "not suffer great prejudice" by lifting the stay to allow litigation pending in Michigan state court to proceed where the state court was in a position to make a determination, the state court "has familiarity with the parties and the facts of the case," and the debtor would be permitted to "raise in the Michigan Court any and all arguments in support of its position").

49. While the Bankruptcy Court could theoretically assess the validity of the 689 Patent and the 142 Patent, it is unlikely that the Bankruptcy Court possesses the resources to adjudicate the validity of a patent and doing so would likely entail significant inefficiencies for all stakeholders. The PTAB was formed precisely so that it could decide, based on the expertise of

[24] *See Martin-Trigona v. Champion Federal Sav. and Loan Ass'n*, 892 F.2d 575, 577 (7th Cir. 1989) ("There is, in contrast, no policy of preventing persons whom the bankrupt has sued from protecting their legal rights. True, the bankrupt's cause of action is an asset of the estate; but as the defendant in the bankrupt's suit is not, by opposing that suit, seeking to take possession of it, subsection (a)(3) [of Section 362] is no more applicable than (a)(1) is.").

its administrative law judges, the same issues as the District Courts in a more timely and efficient way. For many of the same reasons that the Debtors seek to lift the stay on the 261 Action, allowing the IPR Proceedings to proceed to a final determination just makes sense.

50. For these reasons, the potential harm to 10x from maintenance of the stay far outweighs the prejudice (if any) to the Debtors or their estates from lifting the stay.

**C. 10x is Likely to Prevail on the Merits**

51. In considering the probability of success on the merits, courts in this district have found that "[e]ven a slight probability of success on the merits may be sufficient to support lifting an automatic stay in an appropriate case." *Am. Airlines, Inc. v. Continental Airlines, Inc. (In re Continental Airlines, Inc.)*, 152 B.R. 420, (D. Del. 1993); *see also Rexene Prods.*, 141 B.R. at 577 (stating that the required showing on the probability of success is "very slight"); *Fernstorm Storage & Van*, 938 F.2d at 737 (stating that because "suit is not frivolous" this factor weighs in favor of granting relief). All that is required is that the movant "make more than a 'vague initial showing' that he can establish a prima facie case." *In re 15375 Memorial Corp.*, 382 B.R. 652, 691 (Bankr. D. Del. 2008).

52. As further explained below, 10x would plainly clear the "slight" probability of success threshold for both the 653 Action and the IPR Proceedings.

(i) *10x is likely to prevail on the merits in the 653 Action*

53. In the 653 Action, 10x has received a jury verdict in its favor (the "**653 Action Jury Verdict**"), attached hereto as **Exhibit D**, and Non-Final Judgment, and has a high likelihood of prevailing on the merits in the post-trial briefing before the Delaware District Court such that the verdict is upheld and reduced to final judgment. Courts routinely find that judicial results short of a jury verdict are more than sufficient to meet this standard. *See, e.g., Rexene Prods.*, 141 B.R. at 578 (noting that the prong "is easily met by the fact that there has already been a denial of

defendants' motion for summary judgment in the lawsuit."); *SCO Grp.*, 395 B.R. at 859 (finding a "reasonable probability of success on the merits" where plaintiff had obtained partial summary judgment); *In re Tribune Co.*, 416 B.R. 116, 129 (Bankr. D. Del. 2009) (finding that movant's ability to introduce relevant evidence was "sufficient, under the circumstances, to support a slight showing on the probability of success on the merits."). The court in *Scarborough St. James* addressed a situation similar to the circumstances here, as the movant was seeking to proceed with state litigation that was, in effect, merely entering judgment based an existing arbitration award. 535 B.R. at 63-66. As in this case, a finder of fact had already considered the evidence and made findings that went to the ultimate merits of the case. *See id*. The *Scarborough St. James* court found that the existence of the arbitration award, notwithstanding the debtor's ability to appeal, "made (at least) the requisite slight showing of the probability of success on the merits." *Id*. at 69-70. Therefore, the existence of the 653 Action Jury Verdict and the Non-Final Judgment is more than sufficient to satisfy this prong.

(ii) *10x is also likely to prevail on the merits in the IPR Proceedings*

54. As noted above, an IPR consists of two stages: (1) the decision of the PTAB to institute the IPR, which requires a showing of reasonable likelihood of invalidity of the patent, and (2) a merits determination, which often, but not always, mirrors the decision made at stage one.

55. 10x has passed the institution stage of the IPR process in the 689 IPR Proceeding and the PTAB "determine[d] that Petitioner has demonstrated that there is a reasonable likelihood that at least one of the challenged claims is unpatentable based on the last ground presented by Petition" according to its institution decision (the "**689 IPR Institution Decision**"), attached hereto as **Exhibit E**. *See 10x Genomics, Inc. v. NanoString Technologies, Inc.*, Case IPR2023-01298 (PTAB, Feb. 1, 2024) (Newman, APJ)[, 689 IPR Proceeding, Paper 14]. 10x therefore has

already established a prima facie case to invalidate the 689 Patent, representing a likelihood of succeeding on the merits.

56. While the 142 IPR Proceeding has not received an institution decision from the PTAB, 10x likewise clears the threshold required to demonstrate that it is likely to prevail on the merits. The threshold "merely requires a showing that [the movant's] claim is not frivolous." *Levitz Furniture Inc. v. T. Rowe Price Recovery Fund L.P.* (*In re Levitz*), 267 B.R. 516, 523 (Bankr. D. Del. 2000). On September 25, 2023, 10x filed its petition with the PTAB (the "**142 IPR Proceeding Petition**"). The nearly 100-page 142 IPR Proceeding Petition, attached hereto as **Exhibit F**, sets forth in detail the reasons why the PTAB should grant institution for the 142 IPR Proceeding and evidences 10x's ultimate likelihood of success on the merits.

57. The specific arguments detailed in the 142 IPR Proceeding Petition more than surpass the minimal threshold requirement to establish this factor. As set forth therein, the 10x spatial product that NanoString has accused of infringing its 142 Patent in the co-pending 1375 Action began development years prior to NanoString's patent application. *See 10x Genomics, Inc. v. NanoString Technologies, Inc.*, Case IPR2023-01300 (PTAB, Sept. 25, 2023)[, 142 IPR Proceeding, Paper 2]. The initial version of 10x's product was described in the prominent publication *Science* in 2016, two years before NanoString's patent application.[25] Therefore, NanoString's contention in the 1375 Action that the 142 Patent covers the same thing that existed at least two years before NanoString claims to have invented it is self-defeating. Given these compelling arguments, 10x has a high likelihood of establishing before the PTAB that NanoString's patent claims are invalid because 10x's prior art existed in 2016 (*i.e.*, before

[25] Stahl *et al.*, "Visualization and analysis of gene expression in tissue selections by spatial transcriptomics," *Science* 353(6294):78-82 (July 1, 2016).

NanoString's patent application was filed). Accordingly, there is far greater than a reasonable likelihood that 10x will prevail in the institution and merits stages of the 142 IPR Proceeding if the stay is lifted. The minimal threshold required to support stay relief is satisfied.

58. For each of these reasons, 10x submits that this factor weighs in favor of granting stay relief.

**REQUEST FOR WAIVER OF BANKRUPTCY RULE 4001(A)(3)**

59. 10x requests a waiver of Bankruptcy Rule 4001(a)(3), which provides that "[a]n order granting a motion for relief from an automatic stay made in accordance with Rule 4001(a)(1) is stayed until the expiration of 14 days after the entry of the order, unless the court orders otherwise." Pursuant to the "negative notice" procedures, parties in interest have had 14 days' notice of the relief. Accordingly, it is proper for the Bankruptcy Court to waive the Bankruptcy Rule 4001(a)(3) stay to avoid further prejudice to the parties as a result of delay.

**CONCLUSION**

60. For the foregoing reasons, the balance of the equities demonstrates that cause exists for the automatic stay to be lifted or modified to permit 10x to litigate (i) the 653 Action before the Delaware District Court and (ii) the IPR Proceedings before the PTAB. Additionally, because the factors also provide sufficient grounds to waive the requirements of Bankruptcy Rule 4001(a)(3), 10x respectfully requests that the order modifying the stay be made effective upon issuance so that 10x can proceed with its actions without delay.

**NOTICE**

61. Notice of this Motion has been provided to (a) the Debtors, (b) proposed counsel for the Creditors Committee, (c) the Office of the U.S. Trustee for the District of Delaware, (d) the United States Attorney's Office for the District of Delaware; (e) counsel to the Prepetition 2025 Note Trustee and the Prepetition Trustee and Collateral Agent; (f) counsel to the DIP Agent; (g)

counsel to the DIP Lenders; (h) the Delaware District Court; (i) the USPTO and PTAB; (j) all parties to the 653 Action and the IPR Proceedings; and (k) all other parties entitled to notice pursuant to Bankruptcy Rule 2002. 10x submits that such notice is sufficient, and no other or further notice need be provided.

**NO PRIOR REQUEST**

62. No prior request for the relief sought in this Motion has been made by 10x to this or any other court.

[*Remainder of Page Intentionally Left Blank*]

WHEREFORE, 10x respectfully requests entry of the Order, substantially in the form attached hereto as **Exhibit A**, granting the relief requested herein and such other and further relief as is just and proper.

Dated: February 22, 2024

Respectfully submitted,

*/s/ Sophie Rogers Churchill*

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**IN THE UNITED STATES BANKRUPTCY COURT**
**FOR THE DISTRICT OF DELAWARE**

| | | |
|---|---|---|
| In re: | : | Chapter 11 |
| NANOSTRING TECHNOLOGIES, INC., *et al.*,[1] | : | Case No. 24-10160 (CTG) |
| | : | (Jointly Administered) |
| Debtors. | : | **Objection Deadline: February 29, 2024 at 4:00 p.m. EST** **Hearing Date: March 7, 2024 at 1:00 p.m. EST** |

**NOTICE OF MOTION OF 10X GENOMICS, INC. FOR ENTRY OF AN ORDER (I) MODIFYING THE AUTOMATIC STAY WITH RESPECT TO THE 653 ACTION AND THE IPR PROCEEDINGS AND (II) GRANTING RELATED RELIEF**

**PLEASE TAKE NOTICE** that, on February 22, 2024, 10x Genomics, Inc. ("**10x**") filed the *Motion of 10x Genomics, Inc. for Entry of an Order (I) Modifying the Automatic Stay with Respect to the 653 Action and the IPR Proceedings and (II) Granting Related Relief* (the "**Motion**") with the United States Bankruptcy Court for the District of Delaware (the "**Court**").

**PLEASE TAKE FURTHER NOTICE** that copies of the Motion, including all exhibits thereto, are available free of charge on the website maintained by Kroll Restructuring Administration, LLC, the Debtors' claims and noticing agent, at https://cases.ra.kroll.com/nanostring/ or for a fee via PACER at http://ecf.deb.uscourts.gov

**PLEASE TAKE FURTHER NOTICE** that any responses or objections to approval of the relief requested in the Motion must (a) be in writing; (b) be filed with the Clerk of the Court, 824 Market Street, 3rd Floor, Wilmington, Delaware 19801, on or before **February 29, 2024, at 4:00 p.m. (ET)** (the "**Objection Deadline**"); and (c) served so as to be received on or before the Objection Deadline by the undersigned counsel to 10x.

**PLEASE TAKE FURTHER NOTICE** THAT A HEARING ON THE MOTION WILL BE HELD ON **MARCH 7, 2024, AT 1:00 P.M. (ET)** BEFORE THE HONORABLE CRAIG T. GOLDBLATT AT THE UNITED STATES BANKRUPTCY COURT FOR THE DISTRICT OF DELAWARE, 824 MARKET STREET, 3rd FLOOR, COURTROOM #7, WILMINGTON, DELAWARE 19801.

[1] The Debtors in these Chapter 11 Cases, along with the last four digits of their U.S. federal tax identification numbers, to the extent applicable, are NanoString Technologies, Inc. (4687), NanoString Technologies International, Inc. (2723), NanoString Technologies Netherlands B.V., and NanoString Technologies Germany GmbH. The Debtors' headquarters is located at 530 Fairview Avenue North, Suite 2000, Seattle, WA 98109.

**PLEASE TAKE FURTHER NOTICE** THAT ONLY OBJECTIONS MADE IN WRITING AND TIMELY FILED AND RECEIVED IN ACCORDANCE WITH THE PROCEDURES ABOVE WILL BE CONSIDERED BY THE COURT AT SUCH HEARING.

IF YOU FAIL TO RESPOND IN ACCORDANCE WITH THIS NOTICE, THE COURT MAY GRANT THE RELIEF REQUESTED IN THE MOTION WITHOUT FURTHER NOTICE OR HEARING.

Dated: February 22, 2024

Respectfully submitted,

*/s/ Sophie Rogers Churchill*

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*Counsel to 10x Genomics, Inc.*

**Exhibit A**

Proposed Order

**IN THE UNITED STATES BANKRUPTCY COURT**
**FOR THE DISTRICT OF DELAWARE**

| | | |
|---|---|---|
| In re: | : | Chapter 11 |
| NANOSTRING TECHNOLOGIES, INC., *et al.*,[1] | : | Case No. 24-10160 (CTG) |
| Debtors. | : | (Jointly Administered) |

**ORDER (I) MODIFYING THE AUTOMATIC STAY WITH RESPECT TO THE 653 ACTION AND THE IPR PROCEEDINGS AND (II) GRANTING RELATED RELIEF**

Upon consideration of the motion (the "**Motion**")[2] of 10x Genomics, Inc. ("**10x**") for entry of an order (this "**Order**"): (i) granting relief from the automatic stay pursuant to section 362(d)(1) of title 11 of the United States Code (the "**Bankruptcy Code**") and Rule 4001 of the Federal Rules of Bankruptcy Procedure (the "**Bankruptcy Rules**") with respect to: (A) *10x Genomics, Inc. and Prognosys Biosciences, Inc. v. NanoString Technologies, Inc.*, Case No. 21-cv-653 (MFK) (D. Del. 2021) (the "**653 Action**"), pending in the United States District Court for the District of Delaware (the "**Delaware District Court**"), solely for the purpose of permitting the Delaware District Court to rule on the post-trial motions filed by 10x and Debtor NanoString Technologies, Inc. ("**NanoString**") and to enter final judgment, but not for enforcement of any judgment or other adjudication of claims; and (B) two administrative actions pending in the United States Patent and Trademark Office (the "**USPTO**") before the Patent Trial and Appeal Board (the "**PTAB**"): (I) Case IPR2023-01298 (the "**689 IPR Proceeding**") whereby 10x has challenged the

[1] The Debtors in these Chapter 11 Cases, along with the last four digits of their U.S. federal tax identification numbers, to the extent applicable, are NanoString Technologies, Inc. (4687), NanoString Technologies International, Inc. (2723), NanoString Technologies Netherlands B.V., and NanoString Technologies Germany GmbH. The Debtors' headquarters is located at 530 Fairview Avenue North, Suite 2000, Seattle, WA 98109.

[2] Capitalized terms used but not defined herein have the meaning ascribed to them in the Motion.

validity of NanoString's U.S. Patent No. 11,377,689 (the "**689 Patent**") and (II) Case IPR2023-01300 (the "**142 IPR Proceeding**" and together with the 689 IPR Proceeding, the "**IPR Proceedings**") whereby 10x has challenged the validity of NanoString's U.S. Patent No. 11,473,142 (the "**142 Patent**"); and (ii) granting related relief, all as more fully set forth in the Motion; and this Court having reviewed the Motion; and this Court having jurisdiction to consider the Motion and the relief requested therein in accordance with 28 U.S.C. §§ 157 and 1334 and the *Amended Standing Order of Reference* from the United States District Court for the District of Delaware, dated February 29, 2012; and this Court having found that this is a core proceeding pursuant to 28 U.S.C. § 157(b)(2); and this Court having found that venue of this proceeding and the Motion in this district is proper pursuant to 28 U.S.C. §§ 1408 and 1409; and it appearing that proper and adequate notice of the Motion has been given and that no other or further notice is necessary; and upon the record herein; and after due deliberation thereon; and this Court having determined that there is good and sufficient cause for the relief granted in this Order, therefore, it is hereby:

**ORDERED, ADJUDGED, AND DECREED THAT**:

1. The Motion is **GRANTED** as set forth herein.

2. All objections to the entry of this Order, to the extent not withdrawn or settled, are overruled.

3. The automatic stay is modified pursuant to Bankruptcy Code section 362(d) and Bankruptcy Rule 4001 with respect to *10x Genomics, Inc. and Prognosys Biosciences, Inc. v. NanoString Technologies, Inc.*, Case No. 21-cv-653 (MFK) (D. Del. 2021) solely for the purpose of permitting the Delaware District Court to rule on the post-trial motions filed by 10x and NanoString and to enter final judgment, but not for enforcement of any judgment or other

adjudication of claims. 10x's rights to pursue further stay relief (and the Debtors' right to object to such relief) are reserved.

4. To the extent the automatic stay applies, the automatic stay is modified pursuant to Bankruptcy Code section 362(d) and Bankruptcy Rule 4001 for the purpose of allowing Case IPR2023-01298 challenging the validity of NanoString's U.S. Patent No. 11,377,689 in the United States Patent and Trademark Office before the Patent Trial and Appeal Board to proceed.

5. To the extent the automatic stay applies, the automatic stay is modified pursuant to Bankruptcy Code section 362(d) and Bankruptcy Rule 4001 for the purpose of allowing Case IPR2023-01300 challenging the validity of NanoString's U.S. Patent No. 11,473,142 in the United States Patent and Trademark Office before the Patent Trial and Appeal Board to proceed.

6. This Order is without prejudice to any and all other rights of 10x or the Debtors with respect to the 653 Action and IPR Proceedings, all of which are hereby reserved.

7. The parties are authorized, but not directed, to take all actions necessary to effectuate the relief granted pursuant to this Order.

8. Notice of the Motion as provided therein shall be deemed good and sufficient.

9. The relief granted in this Order shall be effective immediately and shall not be subject to the 14-day stay of enforcement under Federal Rule of Bankruptcy Procedure 4001(a)(3).

10. The Bankruptcy Court retains exclusive jurisdiction with respect to all matters arising from or related to the implementation of this Order.

**Exhibit B**

Litigation Summary Chart

**Current 10x U.S. Litigation Relevant to Chapter 11 Cases**

| Case Number | Plaintiff(s) | Defendant | Product(s) Accused of Infringement | Patents Asserted | Case Status | Related Cases (*Inter Partes Reviews* "IPRs") | Related Cases Status | Automatic Stay Status |
|---|---|---|---|---|---|---|---|---|
| 1:21-cv-00653-MFK ("**653 Action**") | 10x Genomics, Inc. and Prognosys Biosciences, Inc. | NanoString Technologies, Inc. | NanoString's GeoMX | U.S. Patent Nos. 10,472,669; 11,293,917; 10,961,566; 10,983,113; 10,996,219; 11,001,878; 11,008,607 | Jury verdict rendered 11/23; post-trial motions fully briefed | | | Stayed; 10x seeking to lift stay pursuant to this Motion. |
| 1:22-cv-00261-MFK ("**261 Action**") | 10x Genomics, Inc. and President and Fellows of Harvard College | NanoString Technologies, Inc. | NanoString's CosMX | U.S. Patent Nos. 10,227,639; 11,021,737; 11,293,051; 11,293,052; 11,293,054; 11,542,554 | Trial scheduled for end of Q3 2024 | | | Stayed; NanoString filed lift stay motion on 2/21/24. |
| 1:22-cv-01375-MFK ("**1375 Action**") | NanoString Technologies, Inc. | 10x Genomics, Inc. | 10x's Visium | U.S. Patent Nos. 11,377,689; 11,473,142 | Trial scheduled for Q4 2024 | IPR2023-01298 ("**689 IPR Proceeding**") | 689 IPR Proceeding: Instituted by PTAB (pending final merits decision) | 1375 Action not stayed.<br><br>NanoString represented to PTAB that the stay applies to the IPRs.[1] 10x seeking to lift stay pursuant to this Motion, if applicable, for IPRs. |
| | | | | | | IPR2023-01300 ("**142 IPR Proceeding**) | 142 IPR Proceeding: pending institution decision by PTAB (institution briefing complete) | |

[1] *See* IPR202-01298, Paper Nos. 17 and 18; *see also* IPR2023-01300, Paper Nos. 9 and 10.

**Exhibit C**

Non-Final Judgment Following Jury Verdict

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | |
|---|---|
| 10X GENOMICS, INC. and PROGNOSYS BIOSCIENCES, INC.,<br><br>Plaintiffs,<br><br>v.<br><br>NANOSTRING TECHNOLOGIES, INC.,<br><br>Defendant. | C.A. No. 21-cv-653-MFK |

**NON-FINAL JUDGMENT FOLLOWING JURY VERDICT**

WHEREAS, the Court having held a jury trial from November 13, 2023, through November 17, 2023, and the jury having rendered a verdict,

IT IS HEREBY ORDERED as follows:

1. Judgment is entered for the plaintiffs, 10x Genomics, Inc. and Prognosys Biosciences, Inc. (together, "Plaintiffs"), and against the defendant, NanoString Technologies, Inc. ("Defendant"), on Plaintiffs' claims for direct and indirect willful infringement of U.S. Patent No. 10,472,669; U.S. Patent No. 10,961,566; U.S. Patent No. 10,983,113; U.S. Patent No. 10,996,219; U.S. Patent No. 11,001,878; U.S. Patent No. 11,008,607, and U.S. Patent No. 11,293,917 in the amount of $25,611,347.20 in lost profits and $6,061,306.62 in reasonable royalties; and

2. Judgment is entered for Plaintiffs and against Defendant on Defendant's counterclaims for non-infringement and invalidity of U.S. Patent No. 10,472,669; U.S. Patent No. 10,961,566; U.S. Patent No. 10,983,113; U.S. Patent No. 10,996,219; U.S. Patent No. 11,001,878; U.S. Patent No. 11,008,607, and U.S. Patent No. 11,293,917.

Date: Nov. 22, 2023

THE HONORABLE MATTHEW F. KENNELLY
UNITED STATES DISTRICT JUDGE

**Exhibit D**

653 Action Jury Verdict

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | |
|---|---|
| 10X GENOMICS, INC. and PROGNOSYS BIOSCIENCES, INC.,<br><br>Plaintiffs,<br><br>v.<br><br>NANOSTRING TECHNOLOGIES, INC.,<br><br>Defendant. | C.A. No. 21-cv-653-MFK |

**VERDICT FORM**

**INSTRUCTIONS:**

When answering the following questions and filling out this Verdict Form, please follow the directions provided throughout this Verdict Form. Your answer to each question must be unanimous. Some of the questions contain legal terms that are defined and explained in detail in the Jury Instructions. Please refer to the Jury Instructions if you are unsure about the meaning or usage of any legal term that appears in the questions below.

As used in this Verdict Form:

1. "10x" refers to Plaintiff 10x Genomics Inc.
2. "Prognosys" refers to Plaintiff Prognosys Biosciences Inc.
3. "NanoString" refers to Defendant NanoString Technologies Inc.
4. The "669 Patent" refers to U.S. Patent No. 10,472,669.
5. The "566 Patent" refers to U.S. Patent No. 10,961,566.
6. The "113 Patent" refers to U.S. Patent No. 10,983,113.
7. The "219 Patent" refers to U.S. Patent No. 10,996,219.
8. The "878 Patent" refers to U.S. Patent No. 11,001,878.
9. The "607 Patent" refers to U.S. Patent No. 11,008,607.
10. The "917 Patent" refers to U.S. Patent No. 11,293,917.
11. The "Asserted Patents" refers collectively to the 669 Patent, 566 Patent, 113 Patent, 219 Patent, 878 Patent, 607 Patent, and the 917 Patent.

**Please proceed to the next page.**

We, the jury, unanimously agree to the answers to the following questions and return them under the instructions of this Court as our verdict in this case.

**Please proceed to Jury Question 1.**

## QUESTION 1: DIRECT INFRINGEMENT

Did 10x and Prognosys prove by a preponderance of the evidence that NanoString directly infringed any claim of the Asserted Claims?

Please check "Yes" or "No" for each claim. "Yes" is in favor of 10x and Prognosys, and "No" is in favor of NanoString.

| | | | |
|---|---|---|---|
| **669 Patent** | Claim 10: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **566 Patent** | Claim 17: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **113 Patent** | Claim 2: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **219 Patent** | Claim 21: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **878 Patent** | Claim 25: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **607 Patent** | Claim 17: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **917 Patent** | Claim 5: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |

**Please proceed to Jury Question 2.**

**QUESTION 2: INDIRECT INFRINGEMENT**

Did 10x and Prognosys prove by a preponderance of the evidence that NanoString indirectly infringed any claim of the Asserted Patents either by actively inducing another person or entity to directly infringe or contributing to another person or entity's direct infringement?

Please check "Yes" or "No" for each claim. "Yes" is in favor of 10x and Prognosys, and "No" is in favor of NanoString.

| | | | |
|---|---|---|---|
| **669 Patent** | Claim 10: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **566 Patent** | Claim 17: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **113 Patent** | Claim 2: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **219 Patent** | Claim 21: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **878 Patent** | Claim 25: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **607 Patent** | Claim 17: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |
| **917 Patent** | Claim 5: | Yes: ✓ (for 10x & Prognosys) | No:____ (for NanoString) |

**Please Proceed to Jury Question 3.**

**QUESTION 3: WILLFULNESS**

Did 10x and Prognosys prove by a preponderance of evidence that NanoString has willfully infringed any claim of the Asserted Patents after the filing of the Complaint?

"Yes" is a finding for 10x and Prognosys.

"No" is a finding for NanoString

Yes: ✓ No: _____

**Please proceed to Jury Question 4.**

**QUESTION 4: INVALIDITY – LACK OF WRITTEN DESCRIPTION**

Did NanoString prove by clear and convincing evidence that any claim of the Asserted Patents is invalid for lack of written description?

Please check "Yes" or "No" for each claim. "Yes" is in favor of NanoString, and "No" is in favor of 10x and Prognosys.

| | | | |
|---|---|---|---|
| **669 Patent** | Claim 10: | Yes:____ (for NanoString) | No:__✓__ (for 10x & Prognosys) |
| **566 Patent** | Claim 17: | Yes:____ (for NanoString) | No:__✓__ (for 10x & Prognosys) |
| **113 Patent** | Claim 2: | Yes:____ (for NanoString) | No:__✓__ (for 10x & Prognosys) |
| **219 Patent** | Claim 21: | Yes:____ (for NanoString) | No:__✓__ (for 10x & Prognosys) |
| **878 Patent** | Claim 25: | Yes:____ (for NanoString) | No:__✓__ (for 10x & Prognosys) |
| **607 Patent** | Claim 17: | Yes:____ (for NanoString) | No:__✓__ (for 10x & Prognosys) |
| **917 Patent** | Claim 5: | Yes:____ (for NanoString) | No:__✓__ (for 10x & Prognosys) |

**Please proceed to the next page.**

**If you checked "Yes" for any claims in Question 1 or Question 2 and checked "No" for those same claims in Question 4, please proceed to Questions 5 and 6.**

**In other words, please proceed to Questions 5 and 6 only if you found that NanoString infringed at least one claim in Question 1 or Question 2 that you found is not invalid in Question 4.**

**Otherwise, skip and DO NOT answer Question 5 or Question 6, and instead please proceed directly to the Final Page of the Jury Verdict and sign and date that page.**

## QUESTION 5: DAMAGES – LOST PROFITS

**Has 10x proven by a preponderance of the evidence that it is entitled to lost profits?**

"Yes" is a finding for 10x.

"No" is a finding for NanoString.

Yes: ✓ No: _____

**If yes, what is the total amount of lost profits that 10x has shown it is entitled to?**

Amount: $ 25,611,347.20 (75%)

**Please proceed to Jury Question 6.**

**QUESTION 6: DAMAGES – REASONABLE ROYALTY**

**What is the total amount 10x and Prognosys have proven by a preponderance of the evidence that they are entitled to be paid as a reasonable royalty for NanoString's infringement of the Asserted Patents?**

Amount: $ 6,061,306.62 (12.5%)

**Please proceed to the Final Page of the Verdict Form and sign and date that page.**

**Final Page of the Jury Verdict**

You have now reached the end of the verdict form and should review it to ensure it accurately reflects your unanimous determinations. The presiding juror should then sign and date the verdict form in the spaces below and notify the Court Security Officer that you have reached a verdict.

The presiding juror should retain possession of the verdict form and bring it when the jury is brought back into the courtroom.

**Signature of Presiding Juror:** [redacted] **Date: November** 17**, 2023**

**Exhibit E**

689 IPR Institution Decision

Trials@uspto.gov
571-272-7822

Paper 14
Date: February 1, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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10X GENOMICS, INC.,
Petitioner,

v.

NANOSTRING TECHNOLOGIES, INC.,
Patent Owner.

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IPR2023-01298
Patent No. 11,377,689 B2

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Before SUSAN L. C. MITCHELL, DEVON ZASTROW NEWMAN, and JAMIE T. WISZ, *Administrative Patent Judges.*

NEWMAN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
*35 U.S.C. § 314, 37 C.F.R. § 42.4*

## I. INTRODUCTION

### *A. Background and Summary*

Petitioner 10X Genomics, Inc., ("Petitioner") filed a Petition for *inter partes* review of claims 1–30 of U.S. Patent No. 11,377,689 B2 ("the '689 patent"). Paper 2 ("Pet."). Patent Owner NanoString Technologies, Inc., ("Patent Owner") filed a Preliminary Response (Paper 8, "Prelim. Resp.").

With our authorization (Order, Paper 9), Petitioner filed Petitioner's Pre-Institution Reply (Paper 11, "Pet. PI Reply") and Patent Owner filed Patent Owner's Pre-Institution Sur-Reply (Paper 12, "PO PI Sur-Reply").

We have jurisdiction under 35 U.S.C. § 314. Under § 314, an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). The Board determines whether to institute a trial on behalf of the Director. 37 C.F.R. § 42.4(a). A decision to institute is "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition." *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018).

For the reasons set forth below, we determine that Petitioner has demonstrated that there is a reasonable likelihood that at least one of the challenged claims is unpatentable based on the last ground presented by Petitioner. Accordingly, we institute an *inter partes* review of the challenged claims in the Petition.

### *B. Real Parties in Interest*

Petitioner and Patent Owner identify themselves as the real parties-in-interest. Pet. 77; Paper 4, 1 (Patent Owner's Mandatory Notice).

### *C. Related Matters*

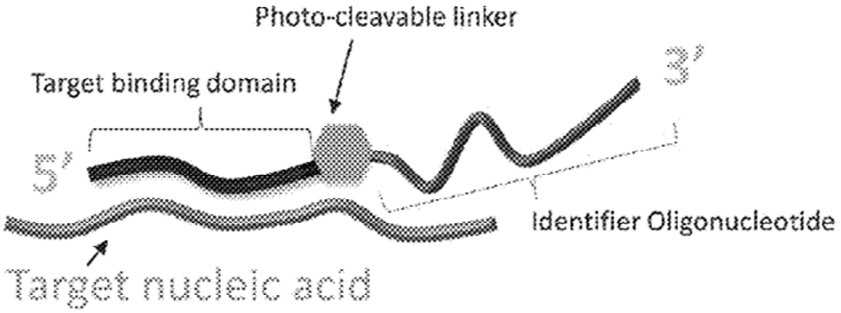
Petitioner identifies a related litigation in which the '689 patent was asserted, *10x Genomics, Inc. and President and Fellows of Harvard College v. NanoString Technologies, Inc.*, Case No. 1:22-cv-00261 (D. Del.). Pet. 78. Petitioner indicates that, following assertion of the '689 patent in that case, "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.)." *Id.*

Patent Owner identifies the same matters. Paper 4, 2.

*D. 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. Ex. 1001, codes (45), (21), (22). The 707 application is a continuation of U.S. Appl. No. 16/272,487 ("487 application"; Ex 1009), filed on February 11, 2019, which claims priority to U.S. Appl. Nos. 62/771,212 (Ex. 1010), filed November 26, 2018, and 62/629,180 (Ex. 1011), filed February 12, 2018. Ex. 1001, codes (63), (60).

The '689 patent is directed to a method for spatially detecting nucleic acids in a tissue sample. *Id.* at 1:44–67. The method uses nucleic acid probes to bind to target nucleic acids ("analytes") within a tissue sample that has been treated to permit binding. *Id.* at 1:44–67; 145:57–58; 148:1–4. The probes contain two segments and a linker, as shown below in an excerpt reproduced below from Figure 12:




Reproduced above is an excerpt of Figure 12 of the patent, showing an oligonucleotide probe having three components: 1) a target binding domain; 2) a cleavable linker; and 3) an identifier oligonucleotide. *Id.*, Figure 12.

The target binding domain "is a region of the probe that specifically binds to at least one target analyte in a sample." *Id.* at 37:16–17. Multiple locations may be probed within the tissue sample using different nucleic acid

probes. *Id.* at 33:33–49. In some embodiments, the probes are bound to the target binding domain, and then ligated to each other, to permit amplification of the target binding domain. *See, e.g., id*. at 6:2–5; 148:5–11.

The cleavable linker joins the two nucleotide regions in the primer and "allows release of an identifier oligonucleotide from a bound target nucleic acid or protein and the identifier oligonucleotide can then be collected and detected." *Id.* at 39:16–18. In one embodiment, the linker permits release of the identifier oligonucleotide when exposed to a sufficient wavelength of ultraviolet light. *Id.* at 17:4–9.

The identifier oligonucleotide is "a nucleic acid molecule that identifies the target analyte bound to the target binding domain. [It] comprises a unique nucleic acid sequence that identifies the target analyte bound to the target binding domain of the probe."[1] *Id.* at 38:29–33.

Figure 20, reproduced below, is a schematic overview of the method of the '689 patent.

[1] Such unique identifying sequences in the references at issue are called unique molecular identifiers (UMIs), unique nucleic acid sequences, and spatial addresses or spatial barcodes, depending on the reference. *See, e.g.*, Ex. 1001, 38:29–33 (unique nucleic acid sequence); Ex. 1005 ¶ 98 (spatial address), and Ex. 1016, 80. (UMI). We understand these various phrases to refer to the use of a nucleic acid with a unique sequence used to identify the source of target DNA.

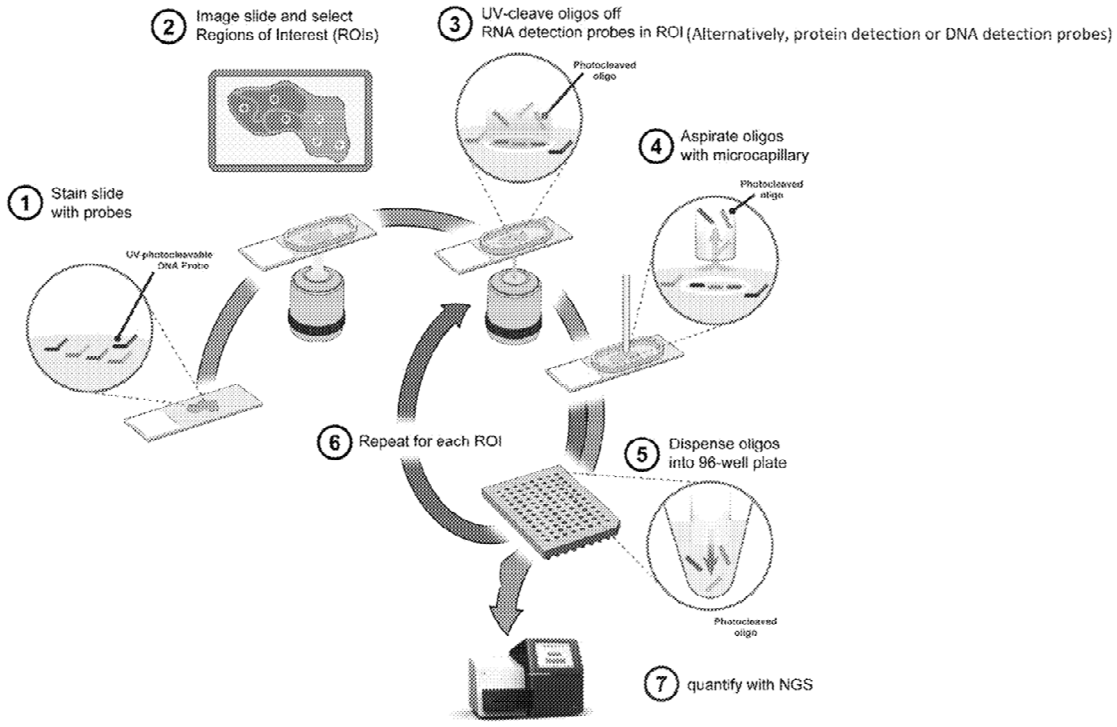



FIG. 20 is an exemplary schematic of overview of the methods of the present disclosure. First, a sample on a microscope slide is contacted with a plurality of probes of the present disclosure (step 1 in FIG. 20). The slide is then imaged and particular regions of interest (ROIs) are selected (step 2 in FIG. 20). A specific ROI is then illuminated by UV light to release identifier oligonucleotides from probes bound within the ROI. The released identifier oligonucleotides are then collected via aspiration with a microcapillary. Following aspiration, the identifier oligonucleotides are transferred to a particular well within a 96 well plate. Steps 4 and 5 are then repeated for each ROI identified in step 2. After all ROIs have been illuminated and all released identifier oligonucleotides collected, the identifier oligonucleotides are sequenced using next generation sequencing methods to spatially detect at least one target analyte in the sample.

*Id.* at 36:62–37:11.

In "a preferred aspect of a direct PCR method of the present disclosure," after cleavage of the linker, the identifier oligonucleotide is

amplified in a manner that facilitates identification of the location of the sample to which the oligonucleotide was bound. *Id.* at 32:27–51. Figure 11, reproduced below, depicts an embodiment in which the identifier nucleotide is amplified, including the portion comprising the unique nucleic acid sequence.

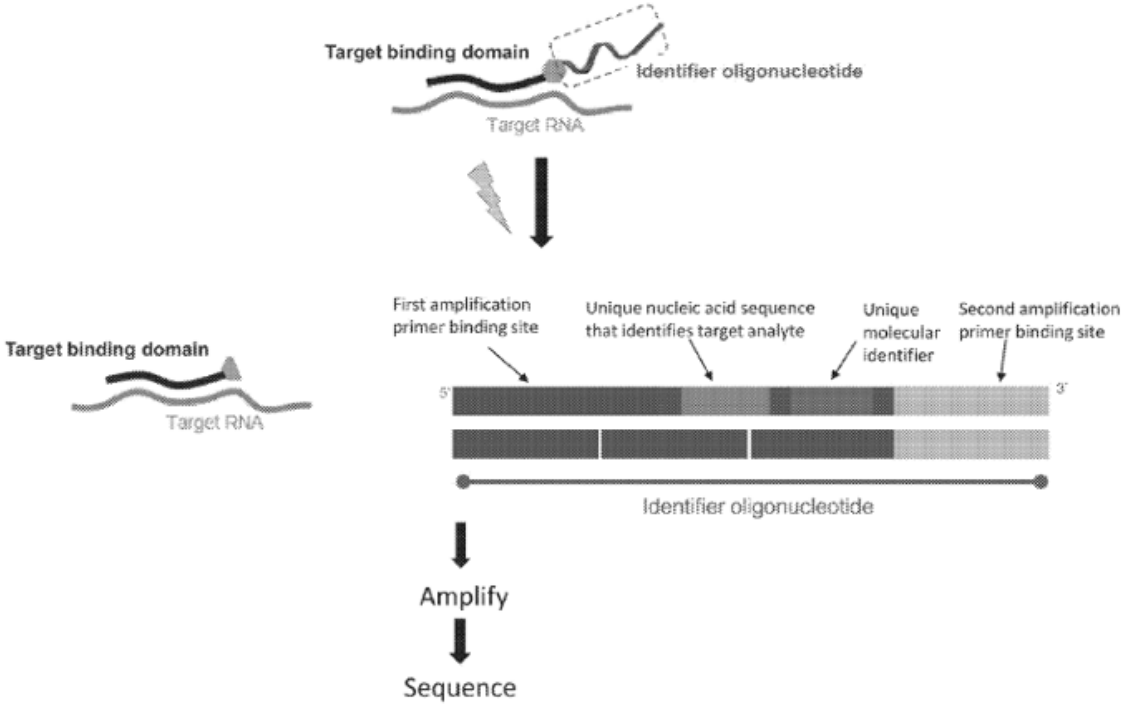



Figure 11 "shows a schematic of a preferred aspect of a direct PCR method" of the '689 patent. *Id.* at 32:27–51. After the probe hybridizes and the identifier nucleotide is cleaved, amplification of the identifier oligonucleotide occurs, which is initiated by binding of amplification primers at the first and second binding sites at the borders of the identifier oligonucleotide. *Id.* "The amplified product is then sequenced to identify the target nucleic acid bound by the probe." *Id.* at 32:50–51. The '689 patent refers to this process as "spatially detecting" a target analyte. *See, e.g., id.* at 30:51–31:5.

### *E. Illustrative Claims*

Claims 1 and 16 are independent. Representative claim 1 is reproduced below:

> 1. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:
>
> a) contacting the tissue sample with a plurality of nucleic acid probes, wherein each of the nucleic acid probes comprise a target binding domain that binds to the at least one target analyte, wherein the tissue sample [has been] is treated to facilitate binding of the nucleic acid probes to the target analyte;
>
> b) collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a first location of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the first location of the tissue sample;
>
> c) collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a second location of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the second location of the tissue sample;
>
> d) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (b), thereby forming a first plurality of extension products that comprise the nucleic acid probes, or portions thereof, collected in step (b) and the at least one nucleic acid sequence that identifies the first location of the tissue sample;
>
> e) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the second location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (c), thereby forming a second plurality extension products that comprise the nucleic acid probes, or portions thereof, collected in step (c) and

> the at least one nucleic acid sequence that identifies the second location of the tissue sample; and
>
> 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.

Ex. 1001, 145:51–147:11.

Whereas claim 1 recites contacting the tissue sample with "a plurality of nucleic acid probes", claim 16 recites using a "first" and a "second plurality of probes" and further adds a ligation step in which the first and second probes are ligated to form "ligated probes," which are then collected. 147:54–148:47. The remainder of the claims depend from either claim 1 or 16 and specify components used in the method or the practice of the method steps themselves (e.g., simultaneous performance of specific recited steps). *Id.* at 147:13–150:18.

### *F. Prior Art and Asserted Grounds*

Petitioner asserts that claims 1–30 would have been unpatentable on the following grounds:

| Claim(s) Challenged | 35 U.S.C. §[2] | Reference(s)/Basis |
|---|---|---|
| 1–8, 11–23, 26–30 | 102 | So-456[3] |
| 1–30 | 103 | So-456 |

[2] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the '689 patent claims priority to a provisional application filed after the effective date of these AIA amendments, we apply the AIA version of 35 U.S.C. § 102 and § 103.

[3] WO 2017/019456, published February 2, 2017 (Ex. 1005, "So-456").

| Claim(s) Challenged | 35 U.S.C. §[2] | Reference(s)/Basis |
|---|---|---|
| 9, 10, 24, 25 | 103 | So-456, Stahl[4] |
| 1–30 | 102 | Chell[5] |

In support of its contentions, Petitioner relies on the Declaration of Paul T. Spellman, Ph.D. (Ex., 1002).

## II. ANALYSIS

### *A. Legal Standards*

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")).

"A claim is anticipated [under 35 U.S.C. § 102] only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Moreover, "[b]ecause the hallmark of anticipation is prior invention, the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Whether a reference anticipates is

[4] Stahl et al., *Visualization and analysis of gene expression in tissue selections by spatial transcriptomics*, SCIENCE 353(6294):78–82, July 1, 2016 (Ex. 1016, "Stahl").
[5] WO 2021/133849, published July 1, 2021 (Ex. 1006, "Chell").

assessed from the perspective of an ordinarily skilled artisan. *See Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003).

A patent claim is unpatentable under 35 U.S.C. § 103 when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when available, evidence such as commercial success, long felt but unsolved needs, and failure of others.[6] *Graham v. John Deere Co*., 383 U.S. 1, 17–18 (1966); *see KS*R, 550 U.S. at 407 ("While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls."). The Court in *Graham* explained that these factual inquiries promote "uniformity and definiteness," for "[w]hat is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context." 383 U.S. at 18.

The Supreme Court made clear that we apply "an expansive and flexible approach" to the question of obviousness. *KSR*, 550 U.S. at 415. Whether a patent claiming the combination of prior art elements would have been obvious is determined by "whether the improvement is more than the

[6] Patent Owner does not presently assert objective indicia supporting non-obviousness of the challenged claims. *See generally* Prelim. Resp.; PO PI Sur-reply.

predictable use of prior art elements according to their established functions." *Id.* at 417. To support this conclusion, however, it is not enough to show merely that the prior art includes separate references covering each separate limitation in a challenged claim. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). Rather, obviousness additionally requires that a person of ordinary skill at the time of the invention "would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.*; *see also Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1273 (Fed. Cir. 2018) ("The question is not whether the various references separately taught components of the '330 Patent formulation, but whether the prior art suggested the selection and combination achieved by the '330 inventors.").

"In determining whether there would have been a motivation to combine prior art references to arrive at the claimed invention, it is insufficient to simply conclude the combination would have been obvious without identifying any reason why a person of skill in the art would have made the combination." *Metalcraft of Mayville, Inc. v. Toro Co*., 848 F.3d 1358, 1366 (Fed. Cir. 2017) (emphasis added). As a factfinder, we also must be aware "of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR*, 550 U.S. at 421.

Applying these general principles, we consider the evidence and arguments of the parties.

### *B. Level of Ordinary Skill in the Art*

Petitioner proposes that a person of ordinary skill in the art of the '689 patent

> 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.

Pet. 14 (citing Ex. 1002 ¶¶ 24–25).

For the purposes of its Preliminary Response, Patent Owner does not provide its own proposed level of skill. Prelim. Resp. 10. For purposes of this Decision, we apply Petitioner's unchallenged definition as it is consistent with the cited prior art and disclosure of the '689 patent.

### *C. Claim Construction*

Petitioner provides no claim construction for any term, but asks that we apply Patent Owner's interpretations of the '689's patent claims from the concurrent litigation. Pet. 14–15. Petitioner alleges "[i]n 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." *Id.* at 20 (citing Ex. 1020, 22–27, 53–54; Ex. 1008, 19–20; Ex. 1002 ¶¶ 116, 132). Petitioner provides Patent Owner's infringement contentions (Ex. 1020) and Answer and Counterclaim (Ex. 1012) as evidence of Patent Owner's interpretations. Patent Owner states that it "does not dispute that the 'collecting' steps in claims 1 and 16 include the capture of entire probes" and that no claim construction order has been entered by the district court in the concurrent litigation. Prelim. Resp. 14.

For purposes of institution, we discern that we must interpret "collecting the nucleic acid probes," which we do below in relation to Petitioner's allegations of anticipation by So-456. Any final written decision

entered in this case may include a final claim construction based on the full trial record that differs from this preliminary construction, or from any discussion of claim scope provided in our analysis below.

### *D. Anticipation by So-456*

Petitioner alleges that So-456 anticipates claims 1–8, 11–23, and 26–30. Pet. 15–18.

#### *1. So-456 (Ex. 1005)*

So-456 is a published patent application directed to "methods and compositions for spatial detection and analysis of nucleic acids in a tissue sample." Ex. 1005, Abstract. Patent Owner does not dispute the prior art status of So-456. *See* Prelim. Resp. 10–13.

So-456 discloses that its methods provide for "characterization of analytes in tissue while preserving spatial information related to the origin of target analyte in the tissue." *Id.* ¶ 85. Specifically, "spatial addressing of nucleic acids from a tissue sample can involve two-dimensional spatial addressing, e.g., to correlate the position of a nucleic acid on a two-dimensional capture array with the position of the nucleic acid in a two-dimensional tissue section." *Id.* ¶ 94. So-456 discloses the method steps in Figure 2, reproduced below:

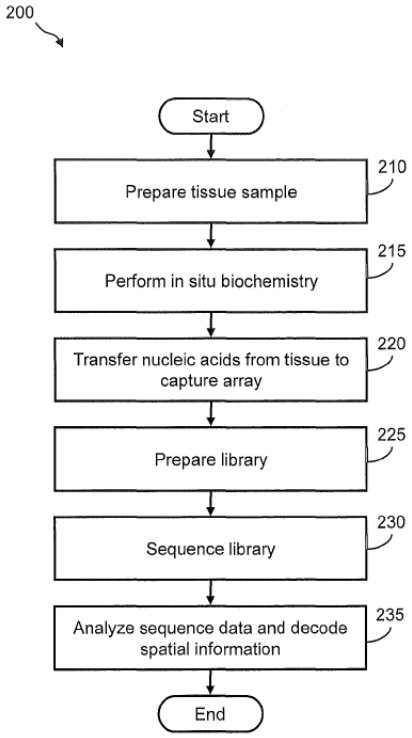



Figure 2 "illustrates a flow diagram of an exemplary embodiment of a method of spatial detection and analysis of nucleic acid in a tissue sample." *Id.* ¶ 12.

So-456 discloses encoding information identifying the spatial origin of a nucleic acid in a tissue sample during the process of preparing the nucleic acid for sequencing:

> nucleic acids from a tissue sample can be tagged by probes including location-specific sequence information (a "spatial address"). Spatially addressed nucleic acid molecules from a tissue sample can then be sequenced in bulk. 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.

*Id.* ¶ 89.

So-456 discloses a "capture probe" as shown below in Figure 1B, which is used to capture the nucleic acids or "DNA amplicons" in a sample

that are generated by in situ amplification of a target nucleic acid, and then analyzed on a "capture array," also shown below in Figure 1A. *Id.* ¶ 18.

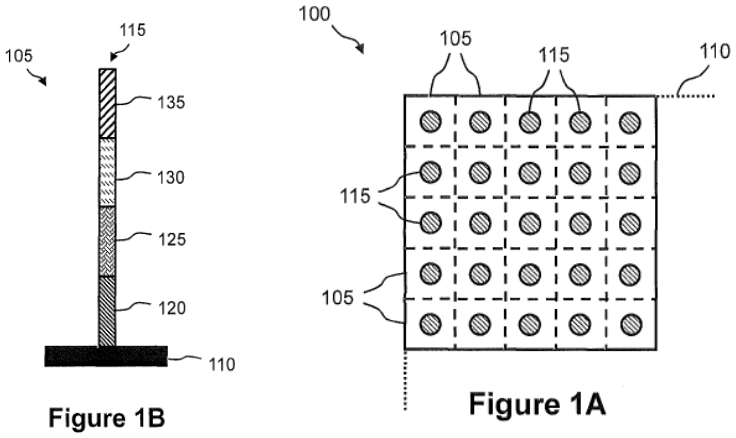



Figure 1B

Figure 1A

Reproduced above is Figure 1B, a "side view of one capture site of the capture array, wherein the one capture site comprises at least one capture probe for capture of nucleic acid in a tissue sample." *Id.* ¶ 10. "Capture probe 115 may optionally comprise a cleavable sequence in a cleavable region 120, an SBS [sequencing-by-synthesis] primer sequence in a SBS primer binding site 125, a spatial address sequence in a spatial address region 130, and a capture sequence in a capture region 135." *Id.* ¶ 141.

Also reproduced above is Figure 1A, which illustrates a "plan view of an exemplary embodiment of a capture array for capture of nucleic acid in a tissue sample." *Id.* ¶ 9. Capture probe 115 is "immobilized" at each of the capture sites 105 of capture array 100, meaning it is fixed by "direct or indirect attachment to a solid support via covalent or non-covalent bond(s)." *Id.* ¶¶ 109, 141.

Figures 8 and 9, reproduced below, illustrate a flow diagram (Figure 8) and an exemplary embodiment (Figure 9) of the method of creation of and capture of DNA amplicons generated by in situ amplification of target nucleic acids.

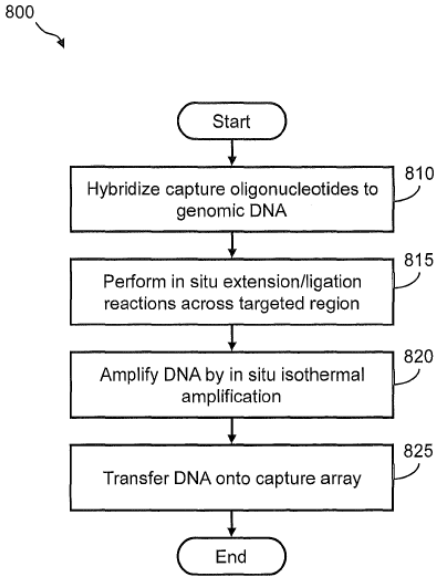



Figure 8

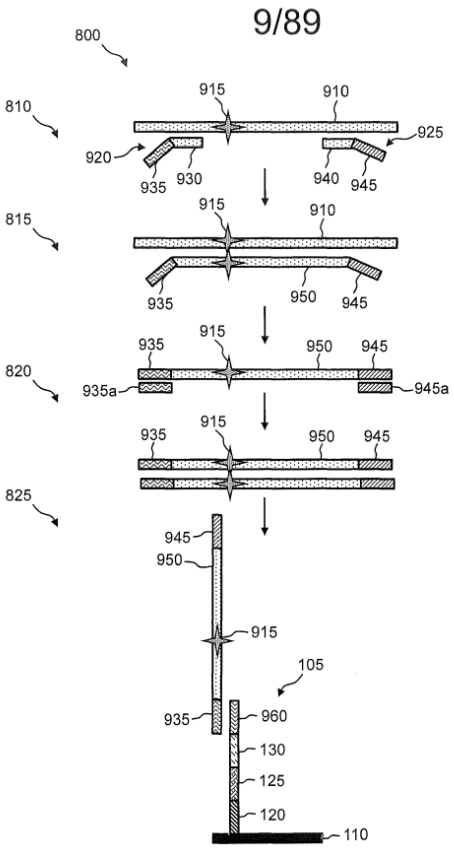



Figure 9

Figure 8, reproduced above, is a flow diagram of the method of creation of and capture of DNA amplicons generated by in situ amplification of target nucleic acids. *Id.* ¶ 19. Figure 9 illustrates an embodiment of the method of capturing DNA amplicons onto an array, wherein the DNA amplicons are generated by in situ amplification of a target nucleic acid. *Id.* ¶¶ 18, 19. "At a step 810, a pair of gene-specific capture oligonucleotides that flank a region of interest [915] are hybridized in situ to genomic DNA." *Id.* ¶ 178. The capture oligonucleotides contain "a gene-specific sequence and a universal capture sequence." *Id.* The capture nucleotide binds (ligates) to the region of interest and the DNA flanked by capture oligonucleotides having bound at the 3' and 5' ends of the target DNA "is amplified by in situ isothermal amplification to generate multiple copies of the region of interest,

i.e., multiple genomic amplicons." *Id.* ¶¶ 179, 180. Genomic amplicons are collected and transferred to an array for capture by hybridization to universal capture regions on the array. *Id.* ¶ 181.

As shown in Figure 9, "capture probe 115 on the capture site 105 comprises a capture region 960 that is complementary to universal capture region 935; SBS primer region 130 is SBS3. DNA amplicons 950 are captured on the capture site 105 by hybridization of universal capture region 935 to capture region 960." *Id.* ¶¶ 182, 183. Following capture, the captured ligation products can undergo an extension reaction to tag the products with spatial barcodes or generate additional molecules for analysis. *Id.* Figure 6, ¶¶ 173, 174, 182.

*2. Disputed Issues*

Petitioner alleges that So-456 anticipates claims 1–8, 11–23, and 26–30. Pet. 15–18. Patent Owner disagrees and alleges that So-456 does not teach four limitations recited in the challenged independent claims. Prelim. Resp. 15–36. Patent Owner focuses its arguments on independent claims 1 and 16. *Id.* As Patent Owner does, we focus our discussion below on the limitations of claims 1 and 16 that Patent Owner alleges So-456 does not teach.

*a) Collecting the Nucleic Acid Probes*

*(1) Allegations of the Parties*

Patent Owner argues that So-456 does not teach "collecting the nucleic acid probes" of claim elements b) or c) of claim 1 (requiring "collecting the nucleic acid probes, or portions thereof, bound to the at least

one target analyte in a first/second location"[7]) or claim elements c) or d) of claim 16 (requiring "collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a first/second location"). *See* Prelim. Resp. 16–19 (citing similar language of claim 16). Patent Owner argues that So-456 instead teaches *amplification* of probes, and capturing of the amplified products, the "genomic amplicons." *Id.* at 17–18.

We next turn to Petitioner's allegations regarding how So-456 discloses "collecting the nucleic acid probes." Petitioner provides annotated versions of Figures 9 and 1A, reproduced below:

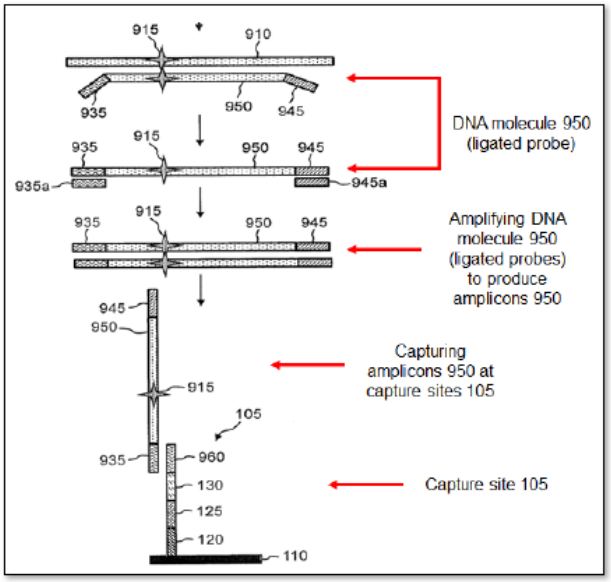



**Figure 9**

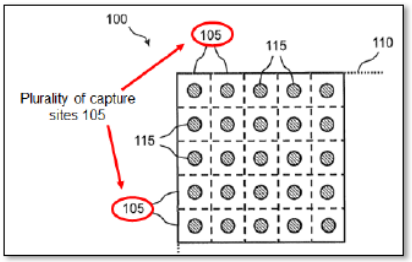



**Figure 1A**

Figure 9 illustrates an exemplary embodiment of the method of creation of and capture of DNA amplicons generated by in situ amplification of target nucleic acids. Ex. 1005 ¶ 19. Figure 1A "illustrates a plan view of an

[7] Claim elements b and c, and d and e are grouped in this discussion for brevity as the only different terms are "first" and "second."

exemplary embodiment of a capture array for capture of nucleic acid in a tissue sample." *Id.* ¶ 9.

Petitioner alleges that So-456's method discloses amplification of the ligated probes (950) to produce "unbound amplified ligated probes" or "amplicons" (also 950), which are free from the target DNA molecules. Pet. 20. These amplicons are then "captured" on a capture array by passive diffusion where they bind to a capture site, 105, as shown in Figure 1A. *Id.* (citing Ex. 1005 ¶¶ 182, 215; Figures 2, 8, 9; Ex. 1002 ¶¶ 134, 135). Petitioner alleges 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)." *Id.* at 20–21 (citing Ex. 1005 ¶¶ 141, 182, 183; Ex. 1002 ¶¶ 135–137). Petitioner alleges So-456's workflow "collects *whole* ligated primary probes from the *whole* tissue sample at the same time" as it is performed in multiple locations on the tissue sample at multiple capture sites on the array. *Id.* at 22 (citing Ex. 1005 ¶¶ 141, 183, Figures 1A, 9; Ex. 1002 ¶¶ 136, 137). *See also* Pet. 29, alleging "So-456 teaches claim 1's collecting steps for the reasons discussed above for claim 16."

*(2) Analysis*

After review of the evidence of record, we conclude that it is necessary to interpret "collecting the nucleic acid/ligated probes" for purposes of institution. Despite its importance to this issue, neither party has construed "collecting the nucleic acid/ligated probes" or "probe," though Petitioner's declarant, Dr. Spellman, opines that the '689 patent Specification discloses two types of probes, 1) "probes" that "are *primary* probes that contain a target-binding domain and hybridize to a target analyte

in the sample (an 'on-analyte' hybridization)" and 2) "nucleic acid probes," which are "pairs of *secondary* probes that do not contain a target-binding domain and are never bound to the target analyte." Ex. 1002 ¶¶ 56, 57 (emphasis original). Dr. Spellman provides the following Table 1, reproduced below, reflecting the types of probes disclosed in the '689 patent.

**TABLE 1: Oligonucleotides disclosed in the 689 patent**

| Oligonucleotide | Disclosure in the specification (excluding the claims) |
|---|---|
| "Probes" | Primary probes having a target-binding domain that binds to the target analytes in a tissue sample (on-analyte binding)<br><br>"The present disclosure provides *probes* comprising a *target binding domain* and an *identifier oligonucleotide*." EX1001, 37:14-16 (emphasis added). |
| "Nucleic acid probes" | Secondary probes: pairs of oligonucleotides that hybridize to the identifier oligonucleotide cleaved off from the "probes" (off-analyte binding)<br><br>"[H]ybridizing to the released identifier oligonucleotide *a first nucleic acid probe and a second nucleic acid probe*, wherein the first nucleic acid probe comprises a nucleic acid complementary to a portion of the identifier oligonucleotide . . . and wherein the second nucleic acid probe comprises a nucleic acid complementary to a portion of the identifier oligonucleotide…." EX1001, 5:44-6:8 (emphasis added). |

*Id.* ¶ 58. Table 1 above, from Dr. Spellman's declaration, describes the types of probes disclosed in the '689 patent. However, Dr. Spellman notes that his classification of the disclosed probes *excludes how the probes are described in the claims*. *Id.*

To interpret "collecting the nucleic acid probes," we turn first to the words of claim 1 itself, to interpret "nucleic acid probe" in claim 1. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1301 (Fed. Cir.

2006) ("[C]laim construction must begin with the words of the claims themselves.").

Claim 1 recites the following about "nucleic acid probe," with the relevant text shown in italics below.

> a) contacting the tissue sample with a plurality of nucleic acid probes, *wherein each of the nucleic acid probes comprise a target binding domain that binds to the at least one target analyte*, wherein the tissue sample [has been] is treated to facilitate binding of the nucleic acid probes to the target analyte
>
> b/c) *collecting the nucleic acid probes*, or portions thereof, *bound to the at least one target analyte* in a first/second location of the tissue sample *under conditions that release the nucleic acid probes*, or portions thereof, from the first/second location of the tissue sample
>
> d/e) performing an extension reaction that *incorporates at least one nucleic acid sequence that identifies the first/second location of the tissue sample into each of the nucleic acid probes*, or portions thereof, collected in step (b), thereby forming a first plurality of extension products that comprise the nucleic acid probes, or portions thereof, collected in step (b) and the at least one nucleic acid sequence that identifies the first/second location of the tissue sample

Ex. 1001, 145:51–147:11 (emphasis added).

Thus, according to claim 1, the "nucleic acid probe" must 1) comprise a target binding domain that binds to the at least one target analyte, 2) be bound to the at least one target analyte; 3) be released in whole or as a portion, and 4) have a location-identifying nucleic acid sequence incorporated into it through an extension reaction. Steps a), b), and c) occur in relation to the target analyte, while steps d) and e) occur after the probe is

collected. *Id.* Claim 16 adds that the probes must be ligated to each other after binding. Ex. 1001, 148:5–10.

Turning to the Specification, we agree with Dr. Spellman that the characterization of "nucleic acid probe" in the '689 patent is at odds with the language of claims 1 and 16. *See, e.g.*, Ex. 1002 ¶ 77. In the disclosure, "nucleic acid probes" bind to cleaved portions from the "probe" (what Dr. Spellman calls the "primary probe") that contain the identifier oligonucleotide, not the target binding domain, which is described as being bound by "probes" rather than "nucleic acid probes." *Compare* Ex. 1001, 37:14–16 ("The present disclosure provides *probes* comprising a target binding domain and an identifier oligonucleotide") with 5:54–56 ("hybridizing to the released identifier oligonucleotide a *first nucleic acid probe* and a *second nucleic acid probe* ...") (emphases added).

Furthermore, all instances of "collecting" and "collected" in the Specification relating to nucleic acids refer to the "released identifier oligonucleotide" or the "collected identifier oligonucleotide" rather than the target binding domain itself. *See, e.g.*, Ex. 1001, regarding "collecting" 2:11; 4:33; 8:27; 22:27; 35:52; and regarding "collected" 13:4; 17:25; 22:45; *see also id.* at 17:17–21 ("identifier oligonucleotides are collected only f[rom] *probes that are bound to targets within that location*, thereby permitting detection of the identities and quantities of the targets (proteins and/or nucleic acids) located only within that location."). Thus, the Specification informs us that "collecting the nucleic acid probes" refers to collecting identifier nucleotides released after application of a force (e.g., conditions that release the nucleic acid probes) from the location of the sample, for example by aspirating solution in which the free-floating oligonucleotide is found. *See, e.g.*, Ex. 1001, 39:33–39 (disclosing that a

"proximal solution may be collected by aspirating, e.g., using a pipette, a capillary tube, a microarray pin, a flow cell comprising holes, or another suitable aspirating system"). After collection, the recited extension reaction is then performed, whereby the "at least one nucleic acid sequence that identifies the first/second location of the tissue sample into each of the nucleic acid probes" is incorporated into the extension product. Ex. 1001, 145:51–147:11.

Turning to other intrinsic evidence, the prosecution history does not have pertinent evidence regarding claim interpretation of *collecting* nucleic acid probes. *See generally*, Ex. 1004.

With this information in hand, we interpret "collecting the nucleic acid probes." "[C]laims are interpreted with an eye toward giving effect to all terms in the claim." *Bicon, Inc. v. Straumann Co*., 441 F.3d 945, 950 (Fed. Cir. 2006).

> Ultimately, the interpretation to be given a [claim] term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.

*Renishaw plc v. Marposs Societa per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

Consistent with the claim language when read in light of the Specification, we interpret a "nucleic acid probe," consistent with its usage in claims 1 and 16, as an oligonucleotide comprising a target binding domain that binds to one or more target analytes, and is modified after collection to comprise a location-identifying nucleic acid sequence for use in identifying the location of the target analyte.

We further interpret "collecting the nucleic acid probes" to mean "releasing all or a portion of the nucleic acid probe bound to the at least one target analyte through application of a force followed by retrieval of the released probe or portion of the probe."

The question then becomes whether So-465, which teaches replication of a probe that was bound and then at least partially released to make genomic amplicons, followed by collection of those genomic amplicons, anticipates collection of probes as recited in claims 1 and 16. On this record, we do not see sufficient evidence that the genomic amplicons disclosed in So-456 that Petitioner identifies as "captured" were ever "bound to the analyte" in part or in whole as required by the claim language, but rather were amplified in situ from the probe or partial probe that was released. Ex. 1005 ¶¶ 181–183. In particular, the process of So-456 differs from the '689 patent claims in that the extension reaction to incorporate the tissue-identifying nucleic acid sequence in So-465 occurs after the identifier nucleotide is cleaved from the tissue sample. "Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference." *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). Petitioner has not demonstrated that So-456 teaches this claim limitation or otherwise demonstrates that this limitation would have been inherent in the disclosure of So-456 for claims 1 and 16. For these reasons, on this record we determine that Petitioner has not shown a reasonable likelihood that So-456 anticipates either of independent claims 1 or 16.

In sum, based on the record before us, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that So-456 anticipates claims 1–8, 11–23, and 26–30. Nevertheless, the Board, in a decision to institute under 35 U.S.C. § 314(b), may not institute

review on fewer than all claims challenged in the petition. *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). In addition, if the Board institutes trial, it will institute on all grounds in the petition. *See* 37 C.F.R. § 42.108(a) ("When instituting . . . review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim."); *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

For the reasons explained below, we determine that Petitioner has met its burden under 35 U.S.C. § 314(a) as to its challenge of at least one claim of the '689 patent on other grounds. Thus, we institute *inter partes* review as to all claims challenged in the Petition, and on all grounds presented, pursuant to *SAS* and 37 C.F.R. § 42.108(a). Because we institute on other grounds, we provide the following additional observations below regarding our evaluation of the evidence of record on the remaining three disputed limitations in claims 1 and 16 for use by the parties in this proceeding.

*b) Treated Tissue Sample*

*(1) Allegations of the Parties*

Patent Owner alleges So-456 does not disclose the claim element "wherein the tissue sample is treated to facilitate binding of the nucleic acid probes to the target analyte" as recited in claims 1 and 16. Prelim. Resp. 20. Patent Owner argues that So-456 discloses only sectioning, staining, and fixing a tissue sample on a slide, but that none of these facilitate binding of nucleic acid probes. *Id.* at 21 (citing Ex. 1005 ¶ 125). Rather, Patent Owner argues that So-456 "describes introducing probes without any treatment to the tissue sample." *Id.* Patent Owner argues that, without such treatment, it

is unclear how a nucleic acid probe would bind paraffin-fixed tissue and contrasts the pre-probe tissue treatment disclosed in Chell, which Patent Owner argues constitutes "treating a tissue sample to facilitate binding of nucleic acid probes to a target analyte." *Id.* at 21–22.

We next turn to Petitioner's allegations regarding how So-456 discloses "wherein the tissue sample is treated to facilitate binding of the nucleic acid probes to the target analyte." Petitioner alleges that So-465 teaches treating the tissue sample because it "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.'" Pet. 18 (citing Ex. 1005 ¶¶ 152–153; Ex. 1002 ¶¶ 125–127) (emphasis in original). Petitioner points to Figures 2 and 8 as evidence of the in situ biochemistry and hybridizing capture oligonucleotides to genomic DNA. *Id.* at 18–19 (citing Ex. 1005, Figures 2, 8, 9, ¶¶ 153, 178, 182; Ex. 1002 ¶¶ 125–127). In support, Dr. Spellman opines consistent with Petitioner's ipso facto position, that the tissue in So-456 must have been prepared to allow binding of the nucleic acid because Figure 8 depicts binding of oligonucleotides to genomic DNA. Ex. 1005 ¶¶ 126–127 (stating that

> Because the capture oligonucleotides hybridized to the target analytes and were processed according to the subsequent steps, So-456's method treated the tissue sample to facilitate binding of the first and second plurality of capture oligonucleotides (i.e., nucleic acid probes of the claim) to the target DNA molecules (i.e., target analytes)).

*(2) Analysis*

After review of the evidence of record, we conclude that the parties have not sufficiently addressed the meaning of "wherein the tissue sample is

treated to facilitate binding of the nucleic acid probes to the target analyte" in claims 1 and 16. We encourage the parties to address the disclosures of the '689 patent with respect to this term as well as the knowledge of an ordinarily skilled artisan at the time of the invention regarding this process.

*c) Required Extension Reaction Steps*

Patent Owner alleges So-456 does not disclose the claim element "performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first/second location of the tissue sample into each of the nucleic acid probes, or portions thereof" ("performing an extension reaction") as recited in claims 1 and 16. Prelim. Resp. 23–33.

*(1) Allegations of the Parties*

Patent Owner argues that Petitioner's evidence for this limitation is based on inherency only, and that Petitioner does not "demonstrate that the protocols disclosed in So-456 *would necessarily* result in incorporating the spatial address region via an extension reaction." *Id.* at 35 (emphasis original).

Petitioner relies on Figure 9 as evidence to show that because the ligated probes that are captured on an array 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," the ligated probe would necessarily be extended *in both directions*, which bi-directional extension would result in the incorporation of the "spatial barcode and sequencing primer-binding sites." Pet. 25–26. Petitioner argues that the extension reaction is inherently bi-directional because So-456 did not teach methods to *prevent* the extension from occurring and all the components needed for bi-directional extension are present. *Id.*

*(2) Analysis*

After review of the evidence of record, we conclude that, on this record, Petitioner does not show sufficient evidence of inherently bi-directional extension. In particular, we do not find that one of ordinary skill in the art would have read So-456 to disclose an extension reaction replicating the spatial barcode due to the lack of disclosure on this issue. We encourage the parties to further develop this issue at trial.

*d) Forming ligated probes*

Patent Owner alleges So-456 does not disclose the claim element "forming a first/second plurality of extension products that comprise the ligated probes" ("forming ligated probes") as recited in claim 16. Prelim. Resp. 33–37.

*(1) Allegations of the Parties*

Patent Owner argues that So-456 does not disclose "forming ligated probes" because, rather than ligating two nucleic acid probes to form a ligated probe, So-456 uses an "extension/ligation reaction" between non-adjacent probes. *Id.* at 33. Patent Owner argues the probes cannot be ligated by a nick ligation process as disclosed in the patent because they are not adjacent, but rather ligate the extension products together *after* the extension reaction occurs. *Id.* at 35–36.

Petitioner, through Dr. Spellman, alleges that So-456 discloses this term 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." Pet. 19 (citing Ex. 1005 ¶ 182, Figures 8, 9; Ex. 1002 ¶¶ 128–130).

*(2) Analysis*

After review of the evidence of record, we conclude that the parties have not sufficiently addressed the meaning of "ligating the probes" in claim 16. We encourage the parties to address the disclosures of the '689 patent with respect to this term as well as the knowledge of an ordinarily skilled artisan at the time of the invention regarding this process.

*E. Obviousness over So-456*

*1. Allegations of the Parties*

Petitioner alleges that, to the extent So-456 does not anticipate claims 1–8, 11–23, and 26–30, So-456 renders all of claims 1–30 obvious. Pet. 39–48 (citing, e.g., Ex. 1002 ¶¶ 218–254). Petitioner argues that an ordinarily skilled artisan would have been motivated to make a sequencing library because the goal of So-456 was 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 [next generation sequencing] NGS." *Id.* at 42. Petitioner argues the artisan would have found it obvious to include the "performing an extension reaction" limitation because using such a reaction to extend 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." *Id.* Petitioner cites evidence of commercially available primer sequences and other supporting components (*id.* at 42–43) and argues that the artisan would have reasonably expected to succeed in making the claimed subject matter because of the "ample guidance and direction" including working examples in the art. *Id.* at 43–45. Petitioner incorporates its allegations regarding anticipation by So-456 of the dependent claims and argues that the ordinarily skilled artisan would have been motivated to

include unique molecular identifiers in the capture probes of So-456, and would have had reasonable success in doing so. *Id.* at 46–48.

Patent Owner disagrees and argues that the claims are not obvious for the same reasons they are not anticipated as addressed above. Prelim. Resp. 15–36 (arguing issues together). The sole argument Patent Owner articulates separately with regard to non-obviousness regards the "performing an extension reaction" claim limitation. *Id.* at 30–33. Patent Owner argues that the proposed extension reaction from the direction of the capture probe would not incorporate a spatial barcode because none exists at that location to incorporate. *Id.* at 31–32. Patent Owner argues that despite the technique for extension being routine in the art, extension of the probe is not necessary or obvious because "an extension of the capture probe would incorporate the target analyte sequence as well as the necessary second SBS primer-binding site from the *captured* probe onto the *capture* probe." *Id.* at 32 (emphasis original). Because such uni-directional extension would create a molecule with both primers, Patent Owner argues, there would be no motivation to find a different method, nor is it inherent that such extension happens. *Id.* at 32–33.

*2. Analysis*

After reviewing the record of evidence, we find Petitioner's case for obviousness is stronger than its case for anticipation from a technical perspective due to the high level of skill in the art that could have assisted an ordinary artisan in understanding how to bridge the gaps between one or more disclosures of So-456 and the challenged claims. For instance, to the extent So-456 did not disclose "wherein the tissue sample is treated to facilitate binding of the nucleic acid probes to the target analyte" as recited in claims 1 and 16, we agree with Petitioner that an ordinarily skilled artisan

would have known how to prepare tissue for in situ histochemistry. *See* Ex. 1003 ¶ 24 (Dr. Spellman's proposed definition of a person of ordinary skill in the art, unopposed by Patent Owner, stating that the artisan "would have possessed a strong understanding 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 section").

However, Petitioner's allegations regarding the obviousness of independent claims 1 and 16 do not address the deficiency discussed above with regard to the limitation "collecting the nucleic acid probes." *See* Section II.D.2.a. Specifically, Petitioner does not allege or provide evidence to support that the skilled artisan would have found it obvious based on the teachings of So-456 to collect the cleaved identifier oligonucleotides rather than the genomic amplicons as alleged. In addition, we share Patent Owner's view that Petitioner, on this record, does not sufficiently show a motivation for the ordinarily skilled artisan to have included a spatial barcode in the capture probes of So-456. We suggest the parties further address these issues at trial.

### *F. Obviousness over So-456 and Stahl*

Petitioner alleges claims 9, 10, 24, and 25 are obvious over So-456 and Stahl. Pet. 49–52.

#### *1. Stahl (Ex. 1016)*

Stahl is a journal article entitled "*Visualization and analysis of gene expression in tissue sections by spatial transcriptomics*." Patent Owner does not dispute the prior art status of Stahl. *See* Prelim. Resp. 13–14.

Stahl discloses a "spatial resolution" method, called "transcriptomics," that "allows visualization and quantitative analysis" of the pattern of proteins or messenger RNAs present in individual tissue sections. Ex. 1016,

78. Stahl discloses the use of capture probes containing spatial barcodes and UMIs to allow both 1) identification of corresponding surface probes on the solid substrate (e.g., tissue sample), and 2) identification of duplicate post-amplification molecules. *Id.*, Figure 2A.

*2. Disputed Issues*

Petitioner alleges claims 9, 10, 24, and 25 are obvious over So-456 and Stahl. Pet. 49–52. In particular, Petitioner alleges that the combined disclosures of So-456 and Stahl teach or suggest modifying So-456's capture probe to include a UMI as disclosed in Stahl's capture probes. *Id.* at 49.

Patent Owner disagrees and alleges that, as discussed above, So-456 does not teach four limitations recited in the challenged independent claims, and Petitioner's obviousness case does not rely on Stahl to provide the missing claim elements. Prelim. Resp. 5.

*3. Analysis*

Challenged claims 9, 10, 24, and 25 depend from independent claims 1 or 16. Petitioner relies on the same allegations it made regarding anticipation and obviousness over So-456 for the disclosure of all limitations of independent claims 1 and 16. Pet. 49. Petitioner does not rely on Stahl to cure the deficiencies for any of the limitations we found lacking in the prior challenges. *See* II.D., II.E. For the same reasons discussed in the prior challenges, on the current record, Petitioner has not shown a reasonable likelihood of success in showing obviousness of claims 9, 10, 24, and 25.

*G. Anticipation by Chell*

*1. Chell (Ex. 1006)*

Chell is a published patent application assigned to Petitioner. Ex. 1006, codes (10), (71). Chell discloses "methods of detecting an analyte

of interest to interrogate spatial gene expression in a sample using RNA-templated ligation." *Id.*, Abstract. Chell discloses:

> a method for determining a location of an analyte in a biological sample including: (a) providing the biological sample on an array including a plurality of capture probes, where a capture probe of the plurality includes: (i) a spatial barcode and (ii) a capture domain; (b) contacting a first probe and a second probe with the biological sample, where the first probe and the second probe each include one or more sequences that are substantially complementary to sequences of the analyte, and where the second probe includes a capture probe capture domain; (c) hybridizing the first probe and the second probe to the analyte; (d) generating a ligation product by ligating the first probe and the second probe; (e) releasing the ligated product from the analyte; (f) hybridizing the ligation product to the capture domain; and (g) determining (i) all or a part of the sequence of the ligation product bound to the capture domain, or a complement thereof, and (ii) all or a part of the sequence of the spatial barcode, or a complement thereof, and using the determined sequence of (i) and (ii) to identify the location of the analyte in the biological sample.

*Id.* at 2:9–22. *See also* Figure 13 (workflow diagram).

*2. Disputed Issues*

Petitioner alleges that Chell discloses all limitations of challenged claims 1–30. Pet. 52–75. Petitioner further alleges that Chell, which was filed and published before the '689 patent was filed, is intervening prior art because the priority application for the '689 patent, the 487 application, does not provide written descriptive support for the full scope of the claims. *Id.* at 52. Patent Owner, for purposes of institution, does not dispute that Chell anticipates claims 1–30, but argues that Chell cannot be prior art because the priority application provides written description support for the full scope of

the claims. Prelim. Resp. 36–42. Because Chell's status as prior art is a threshold issue, we address this first.

*3. Allegations of the Parties*

Petitioner alleges that the 487 application does not provide written descriptive support for the claim limitations 1) collecting whole probes; and 2) hybridizing pairs of primary nucleic acid probes to target nucleic acids in a sample followed by ligation of the same probe pairs, prior to release or collection. Pet. 54–55. Petitioner alleges that because the 487 application does not contain this written description support, the claims are only entitled to the filing date of the application leading to the '689 patent, September 16, 2021, which would render Chell, with a July 1, 2021, publication date, prior art to the '689 patent. *Id.* at 5. Petitioner argues that the 487 application only describes collecting portions of probes that are cleaved off by force (e.g., application of UV light) and not release of whole probes. *Id.* at 53–55 (citing Ex. 1009, e.g., ¶¶ 5–7, 24–27, 174–177; Ex. 1002 ¶¶ 278–286). Petitioner further argues that the challenged claims recite "a particular arrangement and usage of primary (analyte-binding) probes" taking place on the target analyte before release or collection, which differs from the 487 application's disclosure of "distinct on-analyte and off-analyte steps." *Id.* at 55–56 (citing Ex. 1009, e.g., ¶¶ 5–7, 24–27, 231–232; Ex. 1002 ¶¶ 278–292). Petitioner argues that the 487 application does not describe the "on-analyte" ligation recited in the claims. *Id.*

Patent Owner disagrees and argues that the 487 application discloses embodiments wherein "the entire 'intact probe' is collected." Prelim. Resp. 38 (citing Ex. 1009 ¶ 252). Patent Owner argues that the disclosure contemplates both whole and partial probe use. *Id.* at 39 (citing Ex. 1009 ¶ 261). Patent Owner further argues that one of ordinary skill in the art

would have understood the 487 application to disclose the claimed hybridization and ligation methods. *Id.* at 40–42.

On reply, Petitioner argues that the cited paragraphs of the 487 application, paragraphs 252 and 261, do not disclose collecting nucleic acids that are bound to the target analyte for extension through the recited extension reaction, but rather describe a "negative purification" process whereby whole probes are removed to reduce background noise in the nucleic acid detection process. Pet. PI Reply, 1–2. Petitioner cites additional disclosures in the 487 application as support for its interpretation. *Id.* at 2–3.

In response, Patent Owner argues that Petitioner concedes that the 487 application discloses "intact probes" for use in the methods of the disclosure, which adequately describes the probes sufficiently to support its priority claim. PO Prelim. Reply, 1–2. Patent Owner further argues that Petitioner fails to meet its burden to explain why this disclosure would not describe using intact probes sufficiently to enable one of ordinary skill in the art to understand the full scope of the claims. *Id.* at 3.

*4. Analysis*

As discussed above, Petitioner has asked that we apply Patent Owner's interpretations of the '689's patent claims from the concurrent litigation, in which Patent Owner alleges that the "collection" step encompasses diffusion and capture of whole ligation products generated from ligating the primary probe pairs across the whole tissue sample, all at the same time, which would include capture of entire probes. *See supra*, II.C.

On the record before us, solely for purposes of institution, we find that the 487 application does not describe the use of whole/intact probes that

are collected and extended as recited in the challenged claims. Rather, paragraphs 252 and 261 of the 487 application describe whole/intact probes floating in the in situ histochemistry milieu, and not bound to target analytes as the claims require. Ex. 1009 ¶¶ 252, 261. We conclude that, on this record, the disclosure of the 487 application describes whole probes only in the context of removing unbound whole probes to reduce signal noise. *Id.* As described above, all references to "collecting probes" refer only to cleaved off identifier oligonucleotides, not release of entire probes. Thus, for purposes of institution, we find that the 487 application does not provide written description support for the full scope of the claims, and that Chell is prior art. We invite the parties to further develop this issue as well as the issue of whether the 487 application provides written description support for "on-analyte" ligation as recited in the claims during trial. We now turn to the question of whether Chell anticipates the challenged claims.

*5. Anticipation*

Petitioner alleges that Chell discloses all limitations of challenged claims 1–30. Pet. 52–75. Patent Owner, for purposes of institution, does proffer any evidence to support its stated argument that Chell does not anticipate claims 1–30. *See, generally*, Prelim. Resp.

We have reviewed the evidence of record and determine, for the purposes of institution, that Petitioner has demonstrated that there is a reasonable likelihood that at least one of the challenged claims is unpatentable. In particular, we are persuaded by the evidence provided by Dr. Spellman regarding Chell's disclosure of each claim limitation of claims 1 and 16. *See* Ex. 1002 ¶¶ 294–349; Ex. 1006, Figures 6, 13. Nevertheless, we recognize that the issues in dispute are highly fact-intensive and implicate genuine issues of fact more appropriately resolved on a fully

developed record. In the absence of any argument on this ground from Patent Owner, we will evaluate this ground on the record that is developed during trial.

## III. CONCLUSION

For the reasons expressed above, we determine that Petitioner has demonstrated a reasonable likelihood of showing that at least one claim of the '689 patent is unpatentable. As set forth in the Order below, we institute a trial on all challenged claims and all asserted grounds of unpatentability. *See* 37 C.F.R. § 42.108(a) ("When instituting *inter partes* review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.").

Our factual findings and determinations at this stage of the proceeding are preliminary, and based on the evidentiary record developed thus far. This is not a final decision as to the patentability of claims for which *inter partes* review is instituted. Our final decision will be based on the record as fully developed during trial. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that "there is a significant difference between a petitioner's burden to establish a 'reasonable likelihood of success' at institution, and actually proving invalidity by a preponderance of the evidence at trial"). Any final decision in this proceeding will be based on the full trial record.

The Board will deem forfeited any issue not raised by Patent Owner in a timely response to the Petition, or as permitted in another manner during trial, even if asserted in the Preliminary Response or discussed in this Decision.

Nothing in this Decision authorizes Petitioner, in a manner not otherwise permitted by the Board's rules, to supplement the information pertaining to any ground advanced in the Petition.

## IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, an *inter partes* review is instituted as to all challenged claims on all the grounds raised in the Petition; and

FURTHER ORDERED that *inter partes* review is instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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**Exhibit F**

142 IPR Proceeding Petition

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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10X GENOMICS, INC.,
Petitioner

v.

NANOSTRING TECHNOLOGIES, INC.,
Patent Owner

---

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

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**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,473,142**

***Mail Stop "PATENT BOARD"***
Patent Trial and Appeal Board
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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# EXHIBIT LIST

| Exhibit No. | Description |
|---|---|
| 1001 | *Intentionally Left Blank* |
| 1002 | *Intentionally Left Blank* |
| 1003 | *Curriculum Vitae* of Paul Spellman, Ph.D. |
| 1004 | File History of U.S. Patent No. 11,377,689 |
| 1005 | International Patent Application Publication No. WO 2017/019456 A2 to So *et al.*, published February 2, 2017 ("So-456") |
| 1006 | International Patent Application Publication No. WO 2021/133849 A1 to Chell *et al.*, published July 1, 2021 |
| 1007 | "Explore Illumina sequencing technology," Illumina, Inc., accessible at https://www.illumina.com/science/technology/next-generation-sequencing/plan-experiments/paired-end-vs-single-read.html |
| 1008 | *Intentionally Left Blank* |
| 1009 | U.S. Patent Application No. 16/272,487, filed February 11, 2019 |
| 1010 | *Intentionally Left Blank* |
| 1011 | *Intentionally Left Blank* |
| 1012 | File History of U.S. Patent Application No. 16/272,487 |
| 1013 | Merritt, *et al*., "Multiplex digital spatial profiling of proteins and RNA in fixed tissue," *Nature Biotechnology* 38:586-599 (May 2020) |
| 1014 | File History of U.S. Patent No. 11,473,142 |
| 1015 | "Visium Spatial Gene Expression Reagent Kits," 10x Genomics, Inc., Document No. CG000239, Rev. F, 2021 |
| 1016 | Stahl *et al.*, "Visualization and analysis of gene expression in tissue selections by spatial transcriptomics," *Science* 353(6294):78-82 (July 1, 2016), with attached Supplementary Materials ("Stahl") |
| 1017 | International Patent Application Publication No. WO 2012/140224 A1 to Frisen *et al.*, published October 18, 2012 ("Frisen") |

| Exhibit No. | Description |
|---|---|
| 1018 | Spatial Transcriptomics Workflow, accessible at https://spatialtranscriptomics.com/workflow/ |
| 1019 | Kivioja *et al.*, "Counting absolute numbers of molecules using unique molecular identifiers," *Nature Methods* 9(1):72-76 (January 2012), with attached Supplementary Information |
| 1020 | *Intentionally Left Blank* |
| 1021 | *Intentionally Left Blank* |
| 1022 | NanoString Technologies, Inc.'s Initial Infringement Contentions with Attachment A and Exhibit 1, *10x Genomics, Inc. et al. v. NanoString Technologies, Inc.*, Case No. 1:22-cv-01375 (D. Del.), filed November 23, 2022 |
| 1023 | Scheduling Order, *NanoString Technologies, Inc. v. 10x Genomics, Inc.*, Case No. 1:22-cv-01375 (D. Del.), filed April 13, 2023 |
| 1024 | Joint Claim Construction Statement with Exhibits A through C, *NanoString Technologies, Inc. v. 10x Genomics, Inc.*, Case No. 1:22-cv-01375 (D. Del.), filed August 4, 2023 |
| 1025 | Duncan *et al.*, "A method for detecting single mRNA molecules in Arabidopsis thaliana," *Plant Methods* 12:13 (2016) |
| 1026 | Lieben, L., "Spatial transcriptomics in plants," *Nature Reviews Genetics* 18:394 (2017) |
| 1027 | Jemt *et al.*, "An automated approach to prepare tissue-derived spatially barcoded RNA-sequencing libraries," *Scientific Reports* 6:37137 (2016) |
| 1028 | Asp *et al.*, "Spatial detection of fetal marker genes expressed at low level in adult human heart tissue," *Scientific Reports* 7:12941 (2017) |
| 1029 | "Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation," United States Patent and Trademark Office Memorandum, June 21, 2022 |
| 1030 | Fantini et al., "Assessment of antibody library diversity through next generation sequencing and technical error compensation," *PLOS One* 12(5):e0177574 (2017) |
| 1031-1037 | *Intentionally Left Blank* |
| 1038 | Complaint, *NanoString Technologies, Inc. v. 10x Genomics, Inc.*, Case No. 1:22-cv-01375 (D. Del.), filed October 20, 2022 |
| 1039 | 5' Amino Modifier C6, Integrated DNA Technologies |

| Exhibit No. | Description |
|---|---|
| 1040 | Devor *et al.*, "Strategies for Attaching Oligonucleotides to Solid Supports," Integrated DNA Technologies, 2005 |
| 1041 | Ambardar *et al*., "High Throughput Sequencing: An Overview of Sequencing Chemistry," *Indian Journal of Microbiology*, 56(4):394-404 (October-December 2016) |
| 1042 | U.S. Patent No. 10,329,600 to Fu *et al*., issued June 25, 2019 |
| 1043 | U.S. Patent No. 11,473,142 to Beechem *et al*., issued October 18, 2022 ("142 patent") |
| 1044 | Declaration of Paul Spellman, Ph.D. |
| 1045 | Onodera, K., "Selection for 3'-End Triplets for Polymerase Chain Reaction Primers," *Methods in Molecular Biology*, 402:61-74 (2007) |
| 1046 | Tian *et al.*, "A large-scale analysis of mRNA polyadenylation of human and mouse genes," *Nucleic Acids Research*, 33(1):201-212 (2012) |
| 1047 | CodeLink Activated Slides User Guide, SurModics, Inc., |
| 1048 | Khodakov *et al.*, "Recent developments in nucleic acid identification using solid-phase enzymatic assays," *Microchem Acta*, 181(13-14):1633-1646 (2014) |
| 1049 | European Patent Application Publication No. EP 1114859 A1 to Ota *et al.*, published July 11, 2001 |
| 1050 | Mercier *et al.*, "Solid Phase DNA Amplication: A Simple Monte Carlo Lattice Model," Biophysical Journal, 85:2075-2086 (October 2003) |

# I. INTRODUCTION

Petitioner 10x Genomics, Inc. requests review of claims 1-13 of U.S. Patent No. 11,473,142[1], which is assigned to NanoString Technologies, Inc. The challenged claims of the 142 patent relate to spatially detecting oligonucleotides (*e.g.*, mRNAs) in tissue samples using spatially barcoded arrays.

NanoString has accused 10x's spatial gene expression products (Visium) of infringing the 142 patent in related litigation. However, the broad claims of the 142 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 predates the 142 patent's claimed February 2018 priority date. By this time, numerous publications of spatially detecting target oligonucleotides with arrays of spatial barcodes existed, including the Stahl, Frisen, and So-456 references relied on herein.

This Petition demonstrates that claims 1-13 of the 142 patent should be canceled for at least the following reasons:

[1] The 142 patent is a sibling of U.S. Patent No. 11,377,689, which is the subject of *10x Genomics, Inc. v. NanoString Technologies, Inc.*, IPR2023-01298, filed on August 16, 2023.

***First***, claims 1-13 as interpreted by NanoString are anticipated and/or rendered obvious by Stahl *et al.*—a 2016 publication in *Science* by the founders of a company called Spatial Transcriptomics. Stahl describes the fundamental Spatial Transcriptomics technology of collecting mRNAs onto spatially barcoded arrays, performing cDNA synthesis reactions to incorporate spatial barcodes into the cDNA products, collecting the cDNA products, processing the cDNA products, and analyzing them by sequencing. EX1016, 78-79, FIGs. 1-2. 10x acquired Spatial Transcriptomics in 2018 and then used this same technology to develop the accused Visium products.

Stahl's arrays contain immobilized probes comprising a "spatial barcode," which corresponds to the probe's location on the array (and thus the location of the target mRNAs within the tissue sample), and a "unique molecular identifier" (UMI) sequence to track amplified products in the workflow. *Id.* Stahl teaches that, after overlaying a tissue sample on the barcoded array, the target mRNAs in the sample are captured on the array via hybridization to the "mRNA capture region" on the probes. *Id.*, 79-80. Once the mRNAs are hybridized to the probes on the arrays, the probes are extended via a reverse transcription reaction to synthesize cDNA products that are complementary to the captured mRNAs. *Id.* Stahl's cDNA products thus comprise the complementary DNA sequence of the target mRNAs and the spatial barcode and UMI sequences of the probes. *Id.* The cDNA products

are then cleaved off the array and used to generate a sequencing library for next-generation sequencing. *Id.* Stahl's methods describe all of the claimed methods of the 142 patent. Additionally, Frisen—a 2012 patent publication by the same Spatial Transcriptomics founders who co-authored Stahl—further described the well-known technique of solid-phase amplification on spatially barcoded arrays. Stahl's teachings in view of Frisen further render obvious certain 142 patent claims.

***Second***, claims 1-13 of the 142 patent as interpreted by NanoString are also anticipated and/or rendered obvious by So *et al.* ("So-456"), a patent publication by Illumina. So-456 discloses a spatial analysis method that, similar to Stahl, uses arrays of immobilized "capture probes" that each occupies a distinct position on the array. EX1005, ¶[0085]. Each probe includes a nucleic acid sequence, called a "spatial address," that corresponds to the position of the probe on the array and a UMI sequence to track amplified products in the workflow. *Id.*, ¶¶[0085], [0089], [00302], [00314]. After overlaying a tissue sample onto the array, target mRNAs from the tissue sample are captured on the array via capture probes and labeled with the spatial address of the capture probes via a reverse transcription reaction that synthesizes cDNA products comprising the sequence complementary to the target mRNAs and the spatial address sequence. These spatially addressed cDNA molecules are processed and subsequently 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's methods include all of the steps of the 142 patent's claimed methods.

Accordingly, the Board should cancel claims 1-13 of the 142 patent.

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

10x certifies that the 142 patent (EX1043) is IPR-eligible and 10x is not barred or estopped from requesting IPR of any 142 patent claim.

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

10x petitions for IPR, requesting cancelation of claims 1-13 of the 142 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. (EX1044), Professor of Medicine and Human Genetics and an expert in genetics and genomics approaches for detecting and monitoring human diseases. *Id.*, ¶¶12-23.

## 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 | 1-4, 6-13 | Stahl |
| 2 | § 103 | 1-13 | Stahl |
| 3 | § 103 | 5 | Stahl and Frisen |
| 4 | § 102 | 1-13 | So-456 |
| 5 | § 103 | 1-13 | So-456 |

The asserted references are prior art for at least the following reasons. Stahl *et al.*, *Science* 353(6294):78-82 (2016) ("Stahl"; EX1016) published on July 1, 2016, which is before the 142 patent's February 12, 2018, earliest claimed priority date. Stahl is prior art under AIA 35 U.S.C. § 102(a)(1).

WO 2012/140224 ("Frisen"; EX1017) was filed on April 13, 2012, and published on October 18, 2012, which are both before the 142 patent's February 12, 2018, earliest claimed priority date. Frisen is prior art under AIA 35 U.S.C. §§ 102(a)(1) and 102(a)(2).

WO 2017/019456 ("So-456"; EX1005) was filed on July 21, 2016, and published on February 2, 2017, which are both before the 142 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).

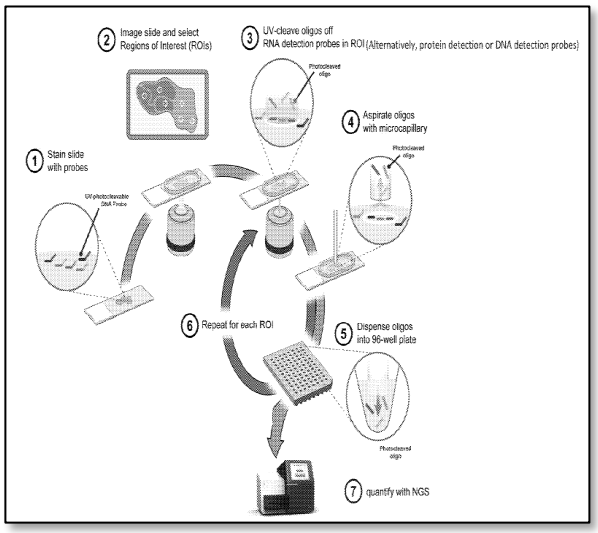
All five Grounds in this Petition are presented under NanoString's

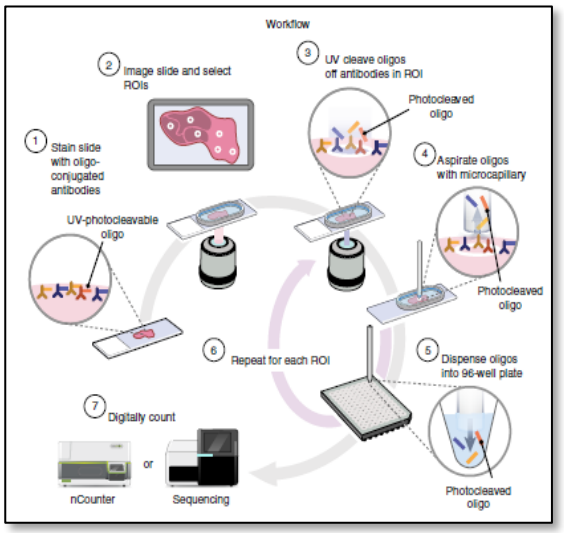
interpretation of the challenged claims in district court.

## V. THE 142 PATENT

The 142 patent issued on October 18, 2022, from U.S. Appl. No. 17/476,712 ("712 application"), filed September 16, 2021. The 712 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, filed November 26, 2018, and 62/629,180, filed February 12, 2018. EX1043, 1-2.

The 142 patent relates to spatially detecting and quantifying proteins or nucleic acids in tissues and cells. EX1043, Abstract; EX1044, ¶¶39-60. As evident from its disclosures throughout, the 142 patent specification is tailored towards NanoString's product, "GeoMx":




*Compare* EX1043, FIG. 20 *with* EX1013 (GeoMx publication), FIG. 1A; EX1044, ¶49.

The 142 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. EX1043, 37:19-25, FIGs. 11, 19, 20; EX1044, ¶¶50-60.

Independent claim 1 of the 142 patent recites a method comprising "collecting a plurality of oligonucleotides" from a first and second location of a tissue sample, "synthesizing" a first and second plurality of DNA products that incorporates "at least one nucleic acid sequence that identifies the first [and second] location of the tissue sample," and "sequencing" the first and second plurality of DNA products to spatially detect the collected oligonucleotides. EX1043, 147:33-61; EX1044, ¶¶61-62.

Claims 2-13 depend from claim 1, and further narrow the independent claim with, *e.g.*, sequencing method and library amplification steps. EX1043, 147:62-148:62; EX1044, ¶63.

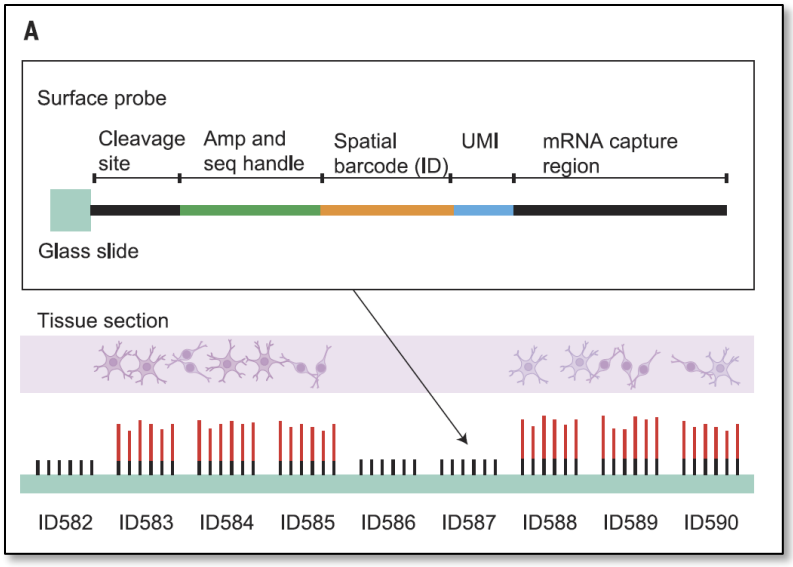
During prosecution, the examiner issued a single Office action, rejecting the pending claims for indefiniteness. EX1014, 226-227. No prior art rejections were raised. *Id.* NanoString subsequently interviewed the examiner, amended the claims, and the Office issued a Notice of Allowance. *Id.*, 249, 458-467. The examiner never considered Stahl or So-456. *Id.*

## VI. STATE OF THE ART PRE-DATING THE 142 PATENT

Spatial array barcoding originated from Spatial Transcriptomics ("ST") in 2011. EX1016; EX1017; EX1044, ¶65. Soon thereafter, others applied the ST workflow in various spatial detection methods. EX1005, ¶¶[00140]-[00144], [00150]-[00164], [00307]-[00320]; *see also* EX1006; EX1025; EX1026; EX1027; EX1028; EX1044, ¶65.

### A. Stahl disclosed spatially detecting nucleic acids using barcoded arrays

Stahl, ST's 2016 *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 target molecules. EX1016, Abstract; EX1044, ¶¶66-67. Stahl's methods incorporated these spatial barcodes into arrays of oligonucleotide "surface probes" immobilized in clusters ("spots") on a glass slide. EX1016, 78, FIG. 2A; EX1044, ¶¶66-67. Stahl's barcoded array approach is shown below:



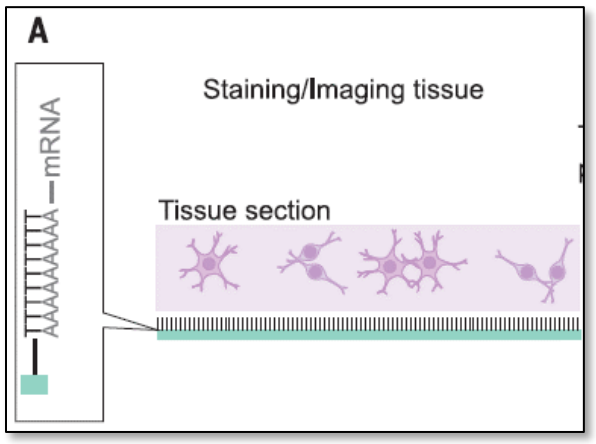

EX1016, FIG. 2A.

Each spot on the array (ID583, ID584, etc.) contained a cluster of capture probes having a unique spatial barcode, as well as a unique molecular identifier ("UMI") sequence to identify duplicate post-amplification molecules. EX1016, Abstract, 78, FIG. 2A; EX1018, 3; EX1044, ¶¶67-70. The capture 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.* Stahl discloses that its capture probes comprise an "AmC6" (amino modifier C6) conjugate, which is used to immobilize the capture probes on the glass slides. EX1016, Suppl. Materials, 2-3; EX1039, 1; EX1044, ¶¶67-70; EX1028, 9. Stahl depicts its capture probes immobilized on their 5'-ends. EX1016, FIG. 2A, Suppl. Materials, 3; EX1044, ¶¶67-70.

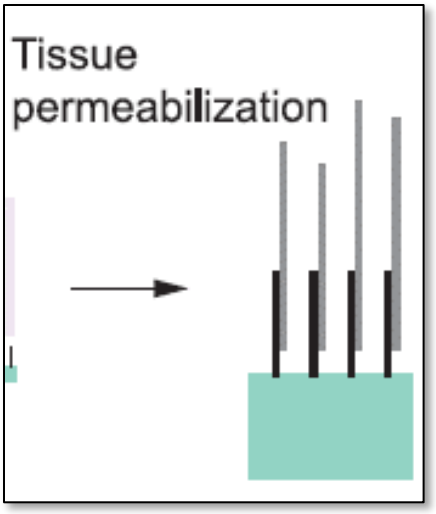
Stahl taught that the spatial barcodes serve as tags for locations of their corresponding capture probes on the solid substrate. *Id.* This allowed

differentiation of biological molecules based on their spatial location within the sample. EX1016, Abstract, 78, FIG. 2A; EX1044, ¶68.

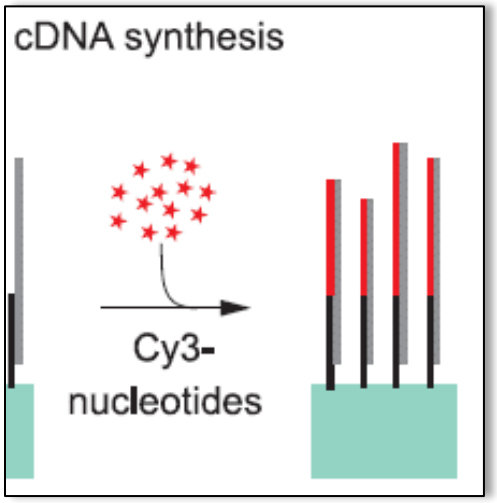
In Stahl's method, a tissue section selected for analysis is overlaid on an array of immobilized capture probes. EX1016, 78, FIGs. 1A, 2A; EX1044, ¶¶71-73. The probes are immobilized on a glass slide, depicted as a green bar on Stahl's Figure 1A, excerpted below:




EX1016, FIG. 1A; EX1044, ¶¶71-74. After overlaying the tissue on the array, Stahl taught that the tissue is permeabilized, such that the mRNAs in the tissue section diffuse from the tissue down onto the array in the same spatial vicinity as their location in the tissue. *Id.* The mRNAs are captured on the array spots via hybridization to the mRNA capture region in the capture probes. *Id.* Stahl depicts the captured mRNA on the array as grey bars in Figure 1A, excerpted below:



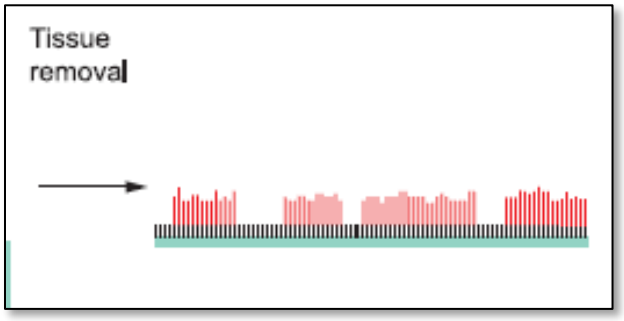

EX1016, FIG. 1A; EX1044, ¶74. After capture, Stahl discloses performing a reverse transcription reaction on the captured mRNAs to synthesize cDNAs (a 3'-extension of the capture probe). EX1016, FIG. 1A; EX1044, ¶¶75-76. The cDNA extension products are shown in red in Stahl's Figure 1A:




EX1016, FIG. 1A; EX1044, ¶¶75-76. After cDNA synthesis, the resulting cDNA extension product comprises a sequence complementary to the captured mRNA, as

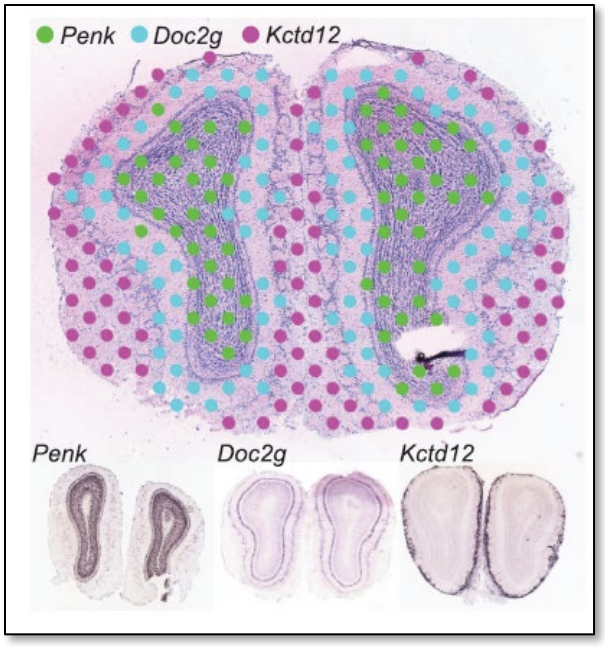
well as the sequences of the probe's spatial barcode and UMI. EX1016, FIG. 2A; EX1044, ¶76.

After cDNA synthesis, Stahl discloses removing the tissue sample by enzymatic digestion (proteinase K), leaving the array probe-cDNAs bound to the slide:




EX1016, FIG. 1A, 00011; EX1044, ¶¶77-79. The cDNAs on the slide can then be either imaged for gene expression or amplified to generate sequencing libraries for sequencing on next-generation sequencing (NGS) platforms, such as "Illumina NextSeq." EX1016, Suppl. Materials, 2-3; EX1044, ¶¶77-79.

After sequencing, Stahl's method used the spatial barcodes to identify the locations of the detected sequences. Stahl's workflow "sorted the RNA-seq data to its corresponding array features by using the spatial barcodes and aligned the tissue image with the features of the array, which enabled visualization and analyses." EX1016, 78; EX1044, ¶78. Stahl presented results of its spatial imaging methods in, *e.g.*, Figure 2B, demonstrating visualization of expression of three different genes in a mouse olfactory bulb:




EX1016, FIG. 2B; *see also*, *id.*, 81, FIGs. 3, S4, S10A-10C; EX1044, ¶79.

### B. So-456 disclosed spatially detecting nucleic acids using barcoded arrays

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.

So-456 provided an overview of its spatial barcode methods in Figure 2, depicting the steps of preparing a tissue sample, capturing (transferring) the nucleic acids released from the tissue sample onto an array, and preparing a sequencing library for analysis:

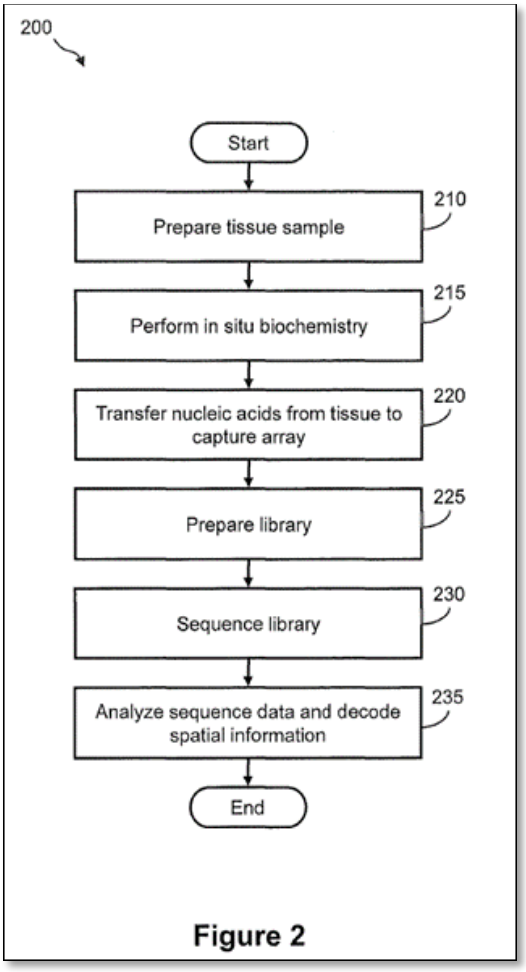



**Figure 2**

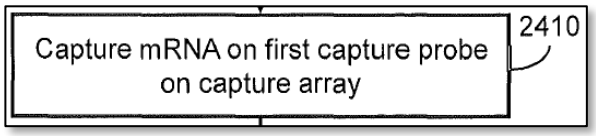
EX1005, FIG. 2, ¶[00151]; EX1044, ¶¶80-81. So-456 provided different embodiments of its spatial barcoding methods, some of which involved analyzing genomic DNA in a tissue sample while others involved analyzing mRNA in a tissue sample.

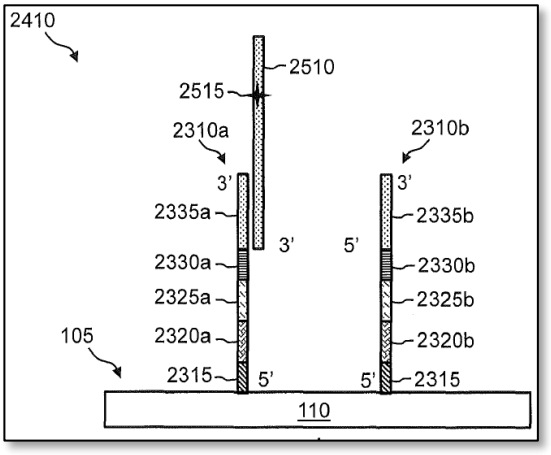
One of So-456's mRNA embodiments is referred to herein as So-456's "mRNA-capture approach." In So-456's mRNA-capture approach, mRNAs ("total mRNA" or "gene-specific mRNA") are released from a tissue sample and captured on the spatially barcoded probes immobilized on an array. EX1005, ¶¶[00152]-

[00154], [00161], [0034]-[0035], [00307]-[00320], FIGs. 2, 24-25; EX1044, ¶¶82-88. So-456 discloses an mRNA-capture embodiment in Figures 24-25. EX1005, ¶¶[0034]-[0035], [00307]-[00320], FIGs. 24-25.

So-456's method depicted in Figures 24-25 begins with contacting a tissue sample with a capture array (*e.g.*, capture array of Figure 1A) comprising immobilized, spatially barcoded capture probes. EX1005, ¶¶[00308]; EX1044, ¶¶88-89. The method uses two capture probes for each gene-specific mRNA. EX1005, ¶[00308]; EX1044, ¶¶88-89.

Next, So-456's method released mRNAs from the tissue sample and captured them onto the array by hybridization of the 3'-end of the mRNAs (2510 in Figure 25A) to the gene-specific regions (2335a in Figure 25A) on the first capture probes (2310a in Figure 25A). *See* step 2410 in Figures 24 and 25A:

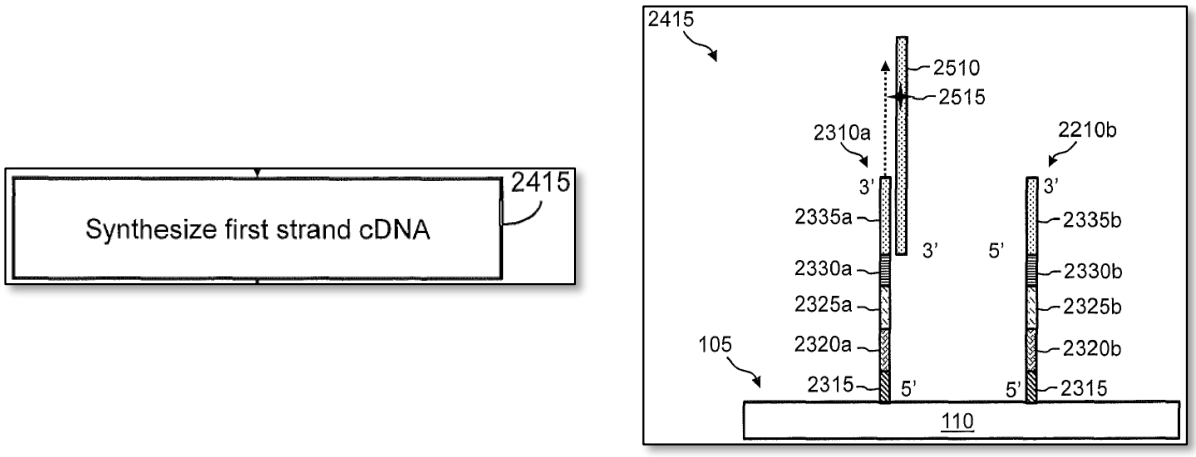



EX1005, FIGs. 24, 25A, ¶¶[00308], [00315]; EX1044, ¶89.

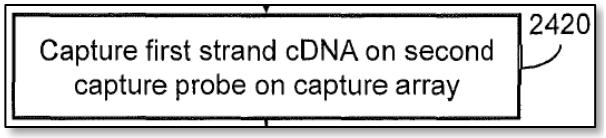
After mRNA capture, So-456's method synthesized the first-strand cDNAs

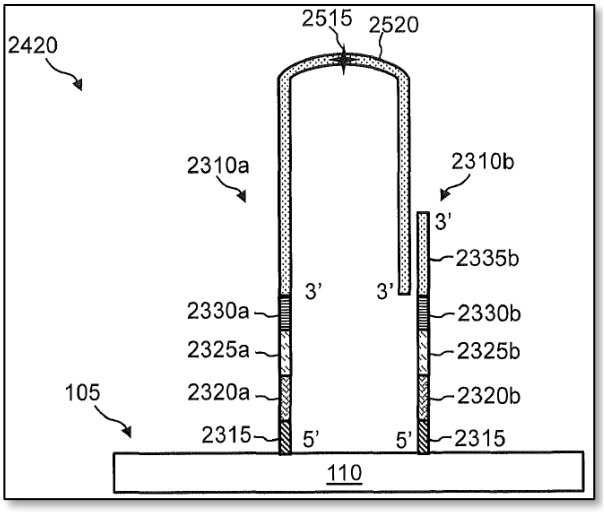
from the captured mRNA molecules by using the capture region (2335a in Figure 25A) of the first capture probe (2310a in Figure 25A) as a reverse transcriptase primer. *See* step 2415 in Figures 24 and 25A, with a dotted arrow depicting first-strand cDNA synthesis:




EX1005, FIGs. 24, 25A, ¶¶[00309]-[00316]; EX1044, ¶89.

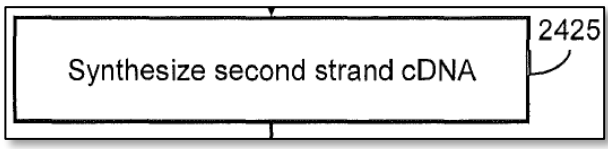
After synthesis of the first-strand cDNA, the 3'-end of the synthesized cDNA product (2520 in Figure 25B) is hybridized to the capture region (2335b in Figure 25B) of the second capture probe (2310b in Figure 25B). *See* step 2420 in Figures 24 and 25B:

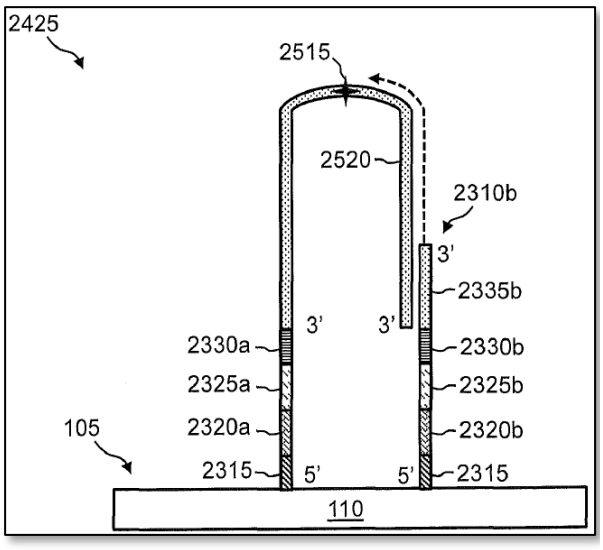



EX1005, FIGs. 24, 25B, ¶¶[00310]-[00317]; EX1044, ¶89.

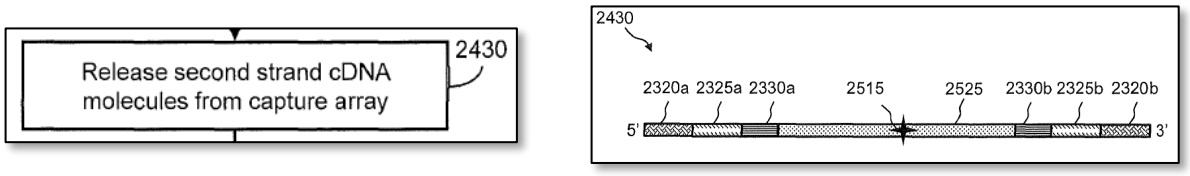
After the first-strand cDNA hybridizes to the second capture probe, So-456's method synthesized second strand cDNAs by using the capture region (2335b in Figure 25B) of the second capture probe (2310b in Figure 25B) as a primer. *See* step 2425 in Figures 24 and 25B, with dotted arrow depicting second strand cDNA synthesis:



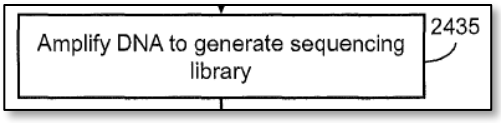
EX1005, FIGs. 24, 25B, ¶¶[00311], [00318]; EX1044, ¶89.

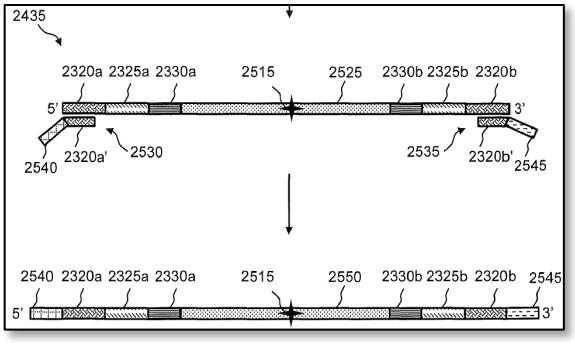
Next, So-456's method released the second strand cDNAs (2525 in Figure 25C) from the capture array by cleavage of the cleavable region (2315 in Figure 25B) of the capture probes. *See* step 2430 in Figures 24 and 25C:




EX1005, FIGs. 24, 25C, ¶¶[00312], [00319]; EX1044, ¶89. The released cDNAs (2525 in Figure 25C) include the SBS ("sequencing-by-synthesis") primer regions (2320a, 2320b), spatial address regions (2325a, 2325b), and UMI regions (2330a, 2330b), along with the sequence of the target mRNA. EX1005, ¶[00319]; EX1044, ¶89.

The released cDNAs are then amplified to generate a sequencing library comprising amplicons (2550 in Figure 25C) by using the SBS primer regions (2320a, 2320b) as binding sites for amplification primers. *See* step 2435 in Figures 24 and 25C:




EX1005, FIGs. 24, 25C, ¶¶[00313], [00320]; EX1044, ¶89. So-456 also disclosed that the amplification and library preparation can take place before releasing the cDNAs – *i.e.*, on the solid substrate. EX1044, ¶¶90-91.

Finally, So-456's method sequenced the library (*e.g.*, by SBS), followed by analyzing the sequencing data and decoding the spatial information based on the spatial barcodes to determine the location of mRNA molecules in the tissue sample (*e.g.*, Steps 230-235 of Figure 2). EX1005, ¶¶[00156]-[00158], FIG. 2; EX1044, ¶90.

### C. Frisen disclosed spatially detecting nucleic acids using barcoded arrays

In April 2012, Jonas Frisen and Patrik Stahl—who co-founded ST and co-authored the Stahl *Science* paper—filed a PCT application (along with co-inventor Joakim Lundeberg) entitled "Method and Product for Localised or Spatial Detection of Nucleic Acid in a Tissue Sample," which published on October 18, 2012, as WO 2012/140224 ("Frisen"). EX1016; EX1017, Face. Stahl (EX1016)

and Frisen (EX1017) list Jonas Frisen, Patrik Stahl, and Joakim Lundeberg as authors and inventors, respectively. EX1016, 78; EX1017, face.

Frisen disclosed methods for "spatial transcriptomics" or "spatial genomics" to spatially detect nucleic acids in a tissue sample using a spatially barcoded array. EX1017, Abstract, 1:12-33; EX1044, ¶¶92-93. Like Stahl, Frisen uses the ST array technique, which is an array comprised of immobilized capture probes containing a spatial barcode, called "positional domain," and a "capture domain" (that hybridized to the target nucleic acids). EX1017, Abstract, 8:21-28; EX1044, ¶¶92-93. Frisen's capture probes were immobilized such that their 3'-ends were free to enable the probes to function as primers for primer extension reactions. *Id.*

Frisen's method comprised contacting the array with a tissue sample to allow the position of a capture probe to be correlated with a position in the tissue sample, hybridizing the RNAs (*e.g.*, mRNAs) of the tissue sample to the capture domain of the capture probes, "generating cDNA molecules from the captured RNA molecules" using the capture probes as RT (reverse transcription) primers such that the cDNA molecules are tagged with the capture probe's positional domain, releasing the tagged DNA molecules from the surface of the array, sequencing the released molecules, and analyzing the sequence to determine the spatial location of the target nucleic acids. EX1017, 8:18-10:5; EX1044, ¶94.

Frisen also disclosed generating a complementary strand of tagged DNA (*i.e.*, second strand cDNA) and/or amplifying the tagged DNA before releasing molecules from the array surface. EX1017, 7:32-8:3, 8:33-9:4, 12:4-11; EX1044, ¶95. Frisen elaborated that "it will be necessary to enhance, i.e., amplify the amount of secured nucleic acid, e.g. synthesized cDNA[,] to yield quantities that are sufficient for DNA sequencing." EX1017, 39:9-11, 42:32-33 ("Thus in a preferred embodiment, the method of the invention may comprise a step of amplifying the DNA, e.g. cDNA molecules."); EX1044, ¶95.

Frisen specified that the second strand cDNA synthesis may occur on the array, either as a discrete step of second strand synthesis or as the initial step of an amplification reaction. EX1017, 12:9-10, 38:20-23, 42:28-43:7; EX1044, ¶96. Frisen's Example 11 exemplified a method for generating a second strand cDNA together with the first-strand cDNA on a solid surface (chip). EX1017, 103:12-19; EX1044, ¶96.

## 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. EX1044, ¶¶25-36; *see also* EX1004, 268 (NanoString admitting during prosecution of sibling U.S. Patent No. 11,377,689 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 142 patent claims from the concurrent litigation. *See* EX1022 (infringement contentions); EX1038 (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 claim 1. EX1043, 147:34-41. According to NanoString, the claimed collecting steps are broad enough to encompass diffusion and capture of mRNAs across the *whole* tissue sample, all at the same time. EX1022, 11-14, 18; EX1044, ¶¶97, 100-101, 199-200.

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

Stahl anticipates claims 1-4 and 6-13 under NanoString's interpretation of these claims. EX1044, ¶¶98-159. Stahl is presumed enabled.

### A. Claim 1

#### 1. "A method comprising:

**a) [and (b)] collecting a plurality of oligonucleotides from a first location [and second location] of a tissue sample …"**

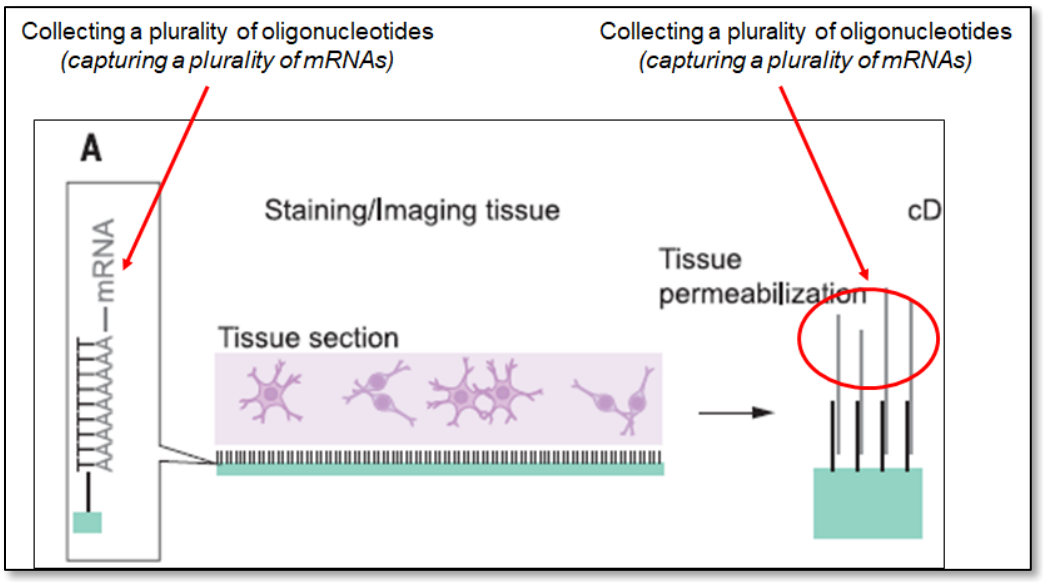
Stahl discloses claim 1's collecting steps (a) and (b) under NanoString's interpretation. EX1044, ¶¶99-104. In concurrent litigation, NanoString alleged that these collecting steps encompass diffusion and capture of mRNAs across the *whole* tissue sample, all at the same time. EX1022, 11-14, 18; EX1015, 16-17; EX1044, ¶¶100-101.

Stahl discloses a method called "spatial transcriptomics" that "allows visualization and quantitative analysis of the transcriptome with spatial resolution in individual tissue sections." EX1016, Abstract, Suppl. Materials, 1 ("[t]he *Spatial Transcriptomics method* follows the following workflow….")[2]; EX1044, ¶102.

Stahl discloses that its method collects a plurality of oligonucleotides under NanoString's interpretation because in Stahl's method, mRNAs (oligonucleotides) from a tissue sample are "captured" (collected) onto arrays of immobilized capture

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

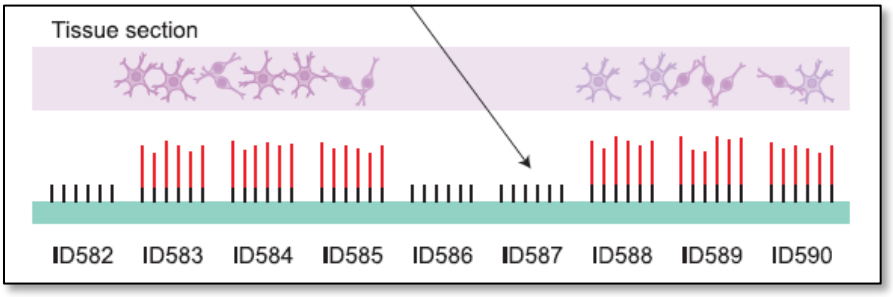
probes. EX1016, 78, FIG. 1A; EX1044, ¶103. Stahl teaches that "it is possible to *capture mRNA* in tissue sections," and further describes generating sequencing libraries "[a]fter *capturing* and reverse-transcribing mRNA…." EX1016, 78, 80 ("cDNA … is generated from *captured mRNA* by reverse transcription."); EX1044, ¶103. Stahl depicts collecting the mRNAs onto the array in Figure 1A, as shown in Dr. Spellman's annotation below:



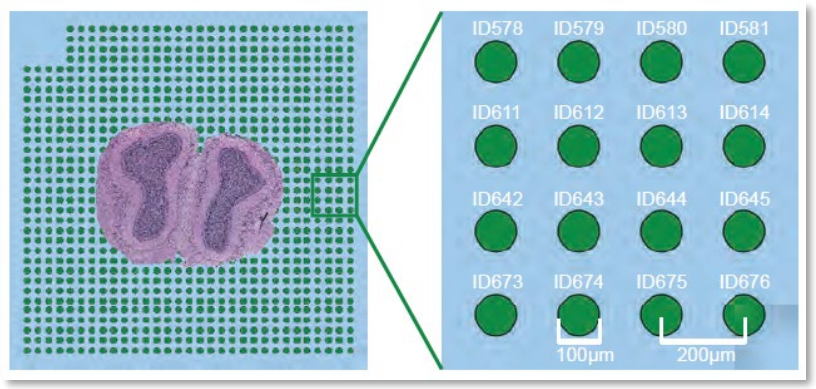

EX1016, FIG. 1A (annotated); EX1044, ¶103.

Stahl's method also collects mRNAs (oligonucleotides) from a first and second location, according to NanoString's interpretation. EX1022, 11-14, 18; EX1015, 16-17. Stahl discloses that capturing the mRNAs onto the array is achieved with "minimal diffusion" while "maintain[ing] positional representation" from within the tissue. EX1016, 78; EX1044, ¶104. That is, mRNAs from one position (a first location) in the tissue are collected in one spot on the array, while

mRNAs from another position (a second location) are collected in a different spot on the array, all while maintaining positional representation. *Id.* Stahl depicts the first and second locations in, *e.g.*, Figure 2A and S2, shown below:




EX1016, FIG. 2A;




EX1016, FIG. S2; EX1044, ¶104. In each figure, Stahl depicts different locations ("spots"), labeled as ID583, ID584, etc. (FIG. 2) or ID578, ID579, etc. (FIG. S2). *Id.*

**"under conditions that release the plurality of oligonucleotides from the first location [and second location] of the tissue sample"**

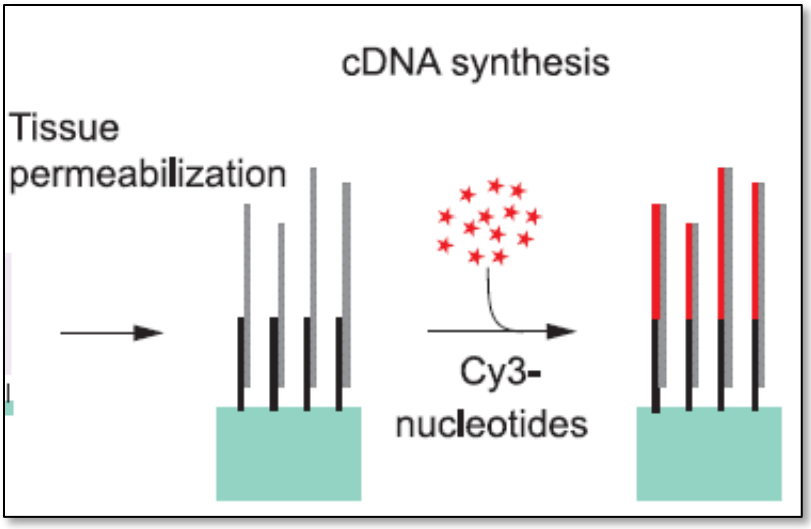
Stahl discloses collecting the mRNAs under conditions that release the mRNAs from their locations in the tissue sample under NanoString's interpretation

of the claims. EX1022, 11-14, 18; EX1015, 16-17; EX1044, ¶¶105-106. Stahl discloses a process of tissue "permeabilization," in which the tissue sample was treated with "0.01% pepsin … dissolved in 0.1M HCl," to release the mRNAs from the tissue so they diffuse onto the array. EX1016, 78, Suppl. Materials, 4-5, FIG. 1A; EX1044, ¶¶105-106.

Accordingly, Stahl discloses claim 1's steps (a) and (b).

**2. "c) [and (d)] synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction…"**

Stahl discloses the synthesis steps (c) and (d) because Stahl's method uses a reverse transcription reaction to "synthesize" cDNA products using the captured mRNAs as templates. EX1044, ¶¶107-108. Stahl provides a figure depicting "[s]patially localized *cDNA synthesis*," which shows "*cDNA synthesis* with Cy3-labeled nucleotides." EX1016, 79, FIG. 1, 78 ("[w]e used fluorescently labeled nucleotides to visualize the *synthesized cDNA*."), Suppl. Materials, 4-5; EX1044, ¶¶107-108. Stahl's Figure 1A depicts cDNA synthesis as red bars:




EX1016, FIG. 1A; EX1044, ¶107.

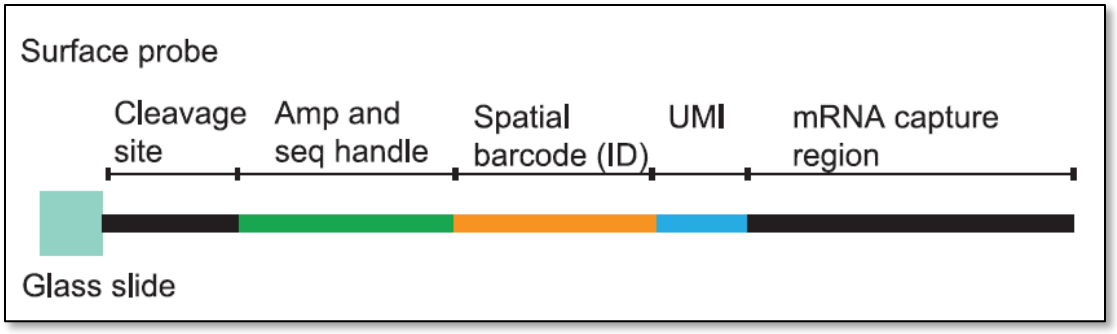
**"that uses the plurality of oligonucleotides collected in step (a) [and step (b)] as templates…"**

Stahl's synthesis reactions use the first and second plurality of oligonucleotides (mRNAs) collected in steps (a) and (b) (respectively) as templates, because Stahl uses reverse transcription to synthesize a "complementary" DNA, *i.e.*, cDNA, strand using the captured mRNA as a template. EX1016, 78-79, Suppl. Materials, 4-5; EX1044, ¶¶109-110. For example, Stahl discloses: "We asked whether it would be possible to introduce positional molecular barcodes in the *complementary DNA (cDNA) synthesis reaction* within the context of an intact tissue section." EX1016, 78. This is also depicted in Stahl's Figure 1A (reproduced above), which shows the captured mRNAs (collected first and second plurality of oligonucleotides) as grey bars serving as templates for the cDNA synthesis, shown as red bars. *Id.*, FIG. 1A;

EX1044, ¶¶109-110. Because Stahl's synthesis reactions take place simultaneously in different spots on the array (*see, e.g.*, EX1016, FIGs. 2A, S2), Stahl's method synthesizes a first and second plurality of DNA products, as claimed. EX1044, ¶¶109-110.

**"and incorporates at least one nucleic acid sequence that identifies the first location [and second location] of the tissue sample into each of the first plurality [and second plurality] of DNA products; and…"**

Stahl's synthesis reactions also incorporate at least one nucleic acid sequence that identifies the first (and second) location of the tissue sample into the first (and second) plurality of DNA products, as claimed. EX1044, ¶¶111-115. Stahl discloses that each capture probe on its array comprises a "spatial barcode," which is used to "sort[] the RNA-seq data to its corresponding array features." EX1016, 78; EX1044, ¶112. As Stahl explains, "Each array feature contains unique *DNA-barcoded probes* containing a cleavage site, a T7 amplification and sequencing handle, *a spatial barcode*, a unique molecular identifier (UMI), and an oligo(dT) VN-capture region." EX1016, 80, FIG. 2A. Stahl provides a diagram of its spatially barcoded capture probe in Figure 2A:




EX1016, FIG. 2A; *see also id.*, Suppl. Materials, 3 ("surface *spatially barcoded* oligonucleotides … 18MER_*SPATIALBARCODE*"); EX1044, ¶¶112-113.

Stahl's synthesis reaction produces cDNA products comprising the spatial barcode of the capture probe, thus incorporating the spatial barcode (*i.e.*, sequence that identifies a location on the array) into the cDNA products. EX1016, FIGs. 1-2, Suppl. Materials, 8 (referring to "*barcoded cDNA*"); EX1044, ¶¶114-115.

Accordingly, Stahl discloses claim 1's step (c) and (d).

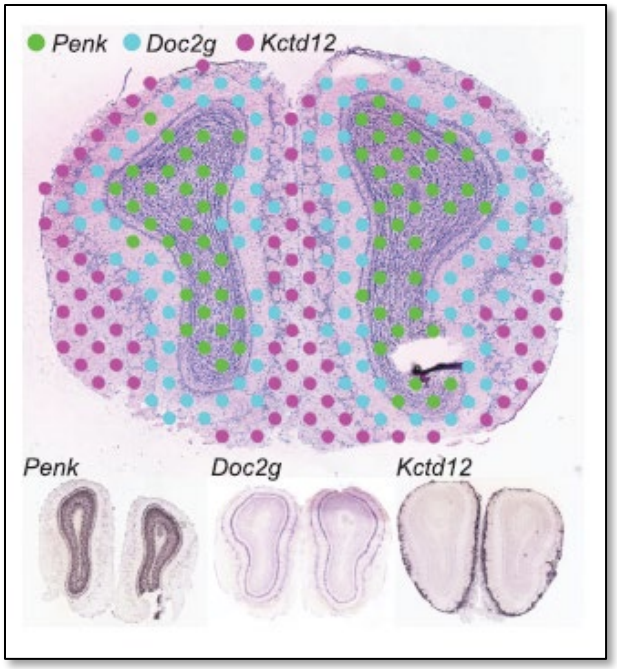
**3. "e) identifying the first plurality of DNA products and the second plurality of DNA products synthesized in step (c) and step (d) by sequencing the first plurality of DNA products and the second plurality of DNA products,**

**thereby spatially detecting the plurality of oligonucleotides collected from the first location of the tissue sample and the plurality of oligonucleotides collected from the second location of the tissue sample."**

Stahl discloses claim 1's sequencing step under NanoString's interpretation. EX1022, 11-14, 18; EX1015, 18; EX1044, ¶¶116-121. 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; EX1044, ¶116.

After synthesizing the cDNA products (first and second plurality of DNA products) on the array, Stahl discloses generating "sequencing libraries" by collecting the spatially barcoded cDNA synthesis products, amplifying them, and sequencing the amplified library "on the Illumina NextSeq platform using paired-end sequencing according to the manufacturer's protocol." EX1016, Suppl. Materials, 6-7; EX1044, ¶¶117-118. Stahl further discloses "identifying" the cDNA synthesis products by sequencing them because Stahl explains that the sequencing ("RNA-seq") data was "sorted … to its corresponding array features by *using the spatial barcodes*," which "enabled visualization and analyses." EX1016, 78; EX1044, ¶¶117-118.

Stahl's method "spatially detected" the first and second plurality of oligonucleotides (mRNAs) collected from the tissue sample, because Stahl's method uses the spatial barcodes to identify the spatial origin of the corresponding mRNA sequence in the tissue. EX1016, 78; EX1044, ¶¶119-120. For example, Stahl presents results of its spatial detection methods in Figures 2 and S4. Figure 2B is shown below, depicting visualization and expression of three genes in mouse olfactory bulb tissue (upper), which Stahl confirmed with in situ hybridization (bottom):



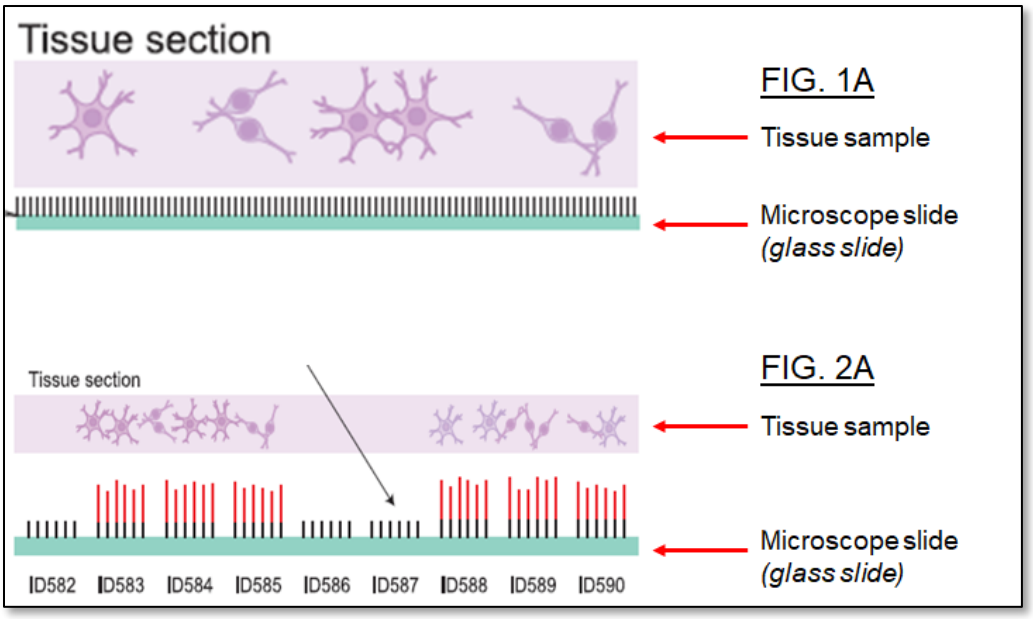

EX1016, FIG. 2B, 78; *see also id.*, 81, FIGs. 3, S4, S10A-10C; EX1044, ¶¶119-120. Accordingly, Stahl discloses claim 1's sequencing step (e).

In sum, Stahl teaches every limitation of claim 1 under NanoString's interpretation, arranged as claimed. Stahl's methods are presumed enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1290-91 (Fed. Cir. 2012); *Apple Inc. v. Corephotonics, Ltd.*, 861 F. App'x 443, 450 (Fed. Cir. 2021); *Activision Blizzard, Inc. et al. v. Acceleration Bay, LLC*, IPR2015-01996, Paper 101 at 19 (P.T.A.B. Mar. 29, 2017). Thus, Stahl anticipates claim 1.

### B. Claim 2

Claim 2 depends from claim 1, and requires that "the tissue sample is immobilized onto a microscope slide." EX1043, 147:62-63. Stahl discloses this limitation. EX1044, ¶¶123-126.

Stahl "immobilized reverse-transcription oligo(dT) primers *on glass slides* and *placed on the slides* sections of adult *mouse olfactory bulb*." EX1016, 78; EX1044, ¶124. Stahl also discloses using "Codelink Activated *microscope glass slides*," and that, "for Spatial Transcriptomics experiments, dried [tissue] *sections were mounted* … and covered with a coverslip." EX1016, Suppl. Materials, 2, 4; EX1044, ¶124. Stahl depicts the tissue sample immobilized on a glass slide in, *e.g.*, Figures 1A and 2A, shown in Dr. Spellman's annotations below:




EX1016, FIGs. 1A, 2A (annotated); EX1044, ¶124.

Stahl further discloses that its glass slides are "microscope slides" as claimed, because Stahl discloses that, after immobilizing the tissue on the glass slide and covering it "with a coverslip," "[b]right field imaging was carried out using the Metafer Slide Scanning Platform" (*i.e.*, a microscope). EX1016, Suppl.

Materials, 4; *id.*, 79 (the "tissue is sectioned, placed onto oligo(dT) primers, stained, and imaged."); EX1044, ¶¶125-126.

Accordingly, Stahl anticipates claim 2.

### C. Claim 3

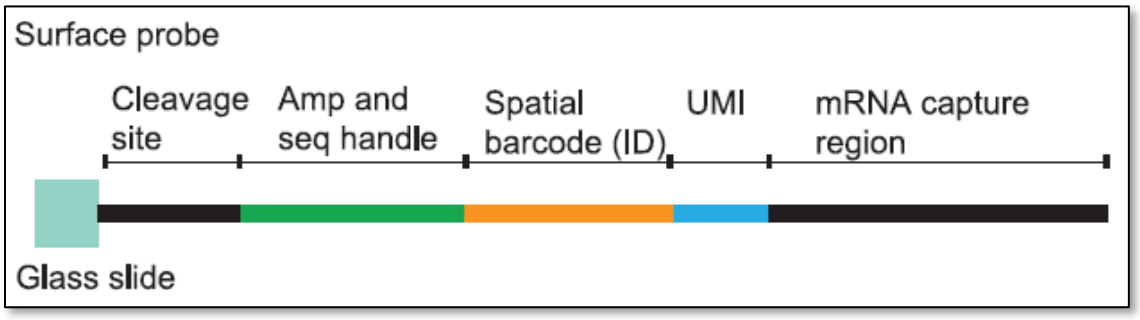
Claim 3 depends from claim 2, and requires that the "microscope slide comprises a plurality of primers immobilized on the microscope slide." EX1043, 148:32-34. Stahl discloses this limitation. EX1044, ¶¶127-128.

Stahl discloses that its workflow uses "*immobilized* reverse-transcription oligo(dT) *primers on glass slides*." EX1016, 78; EX1044, ¶128. Stahl further teaches that "poly-20TVN capture oligonucleotides (IDT)" were "*immobilized*" "on the surface of Codelink Activated *microscope glass slides*." EX1016, Suppl. Materials, 2; EX1044, ¶128. Stahl also discloses that its array of "1007 capture oligonucleotides with 18-mer unique barcodes, a 9-mer semi-randomized UMI and a poly-20TVN capture region" were immobilized on the same "*Codelink Activated Slides*." *Id.* Thus, Stahl anticipates claim 3.

### D. Claim 4

Claim 4 depends from claim 3, and requires that the "plurality of primers is immobilized on the microscope slide at their 5' ends." EX1043, 148:35-36. Stahl discloses this limitation. EX1044, ¶¶129-137.

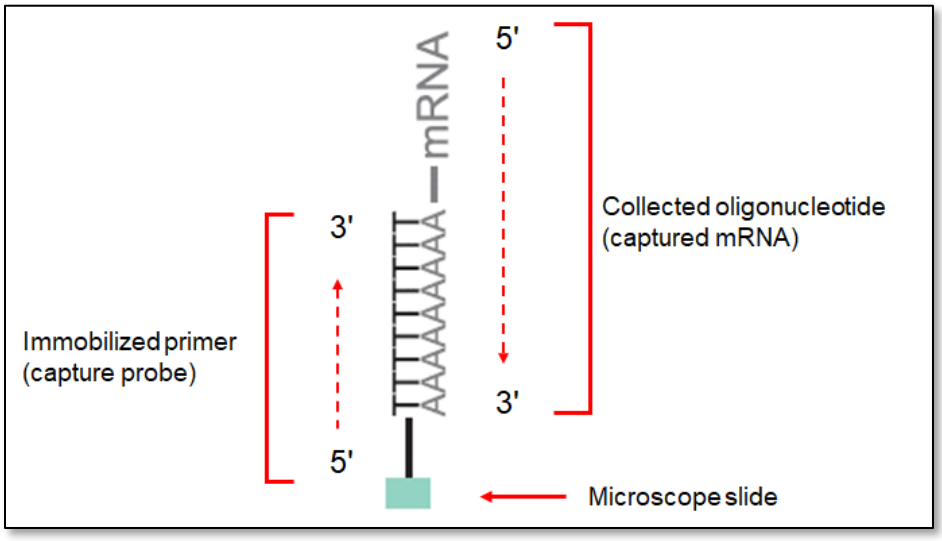
Stahl also discloses that the primers are immobilized on their 5'-ends, as claimed. Stahl's schematic of its immobilized capture probe shows the probe immobilized on a glass slide with the "Cleavage site" at the base, followed by the "Amp and seq handle," spatial barcode, UMI, and mRNA capture region:




EX1016, FIG. 2A. As discussed above for claim 1, Stahl discloses synthesizing cDNA products using the captured mRNAs as templates and extending the capture probes. *See* Section IX.A.2. As Dr. Spellman explains, nucleic acid molecules can only be extended at their 3'-end. EX1044, ¶¶130-131. Thus, to permit 3'-extension of the capture probes for cDNA synthesis, the probes must be immobilized at their other end, *i.e.*, 5'-ends. *Id.*.

Moreover, as shown above, the mRNA capture region of the capture probes (polyT), which hybridizes to its complementary polyA region of the mRNA, is at the free-end of the probe. EX1016, FIG. 2A; EX1044, ¶¶132-133. As Dr. Spellman explains, the polyA region is at the 3'-end of an mRNA. EX1044, ¶132. For the mRNA capture region of the probes to hybridize with the complementary polyA region at the 5'-end of the mRNAs, the mRNA capture region must be at the 3'-

end of the capture probe. *Id.*, ¶133. This is shown in Dr. Spellman's annotation of Stahl's Figure 1A below:




EX1016, FIG. 1A (annotated); EX1044, ¶133. Accordingly, the free-end of the capture probes, where the mRNA capture region is located, is the 3'-end of the probe—further confirming that Stahl's capture probes (primers) are immobilized at the other end, *i.e.*, the 5'-end. EX1044, ¶133.

Stahl further confirms the 5' immobilization of its capture probes by including an "AmC6" (amino modifier C6) conjugate at the 5'-end of the probe:

> Surface spatially barcoded oligonucleotides:
>
> [AmC6]UUUUUGACTCGTAATACGACTCACTATAGGGACACGACGCTCTTCCGATCT[18
>
> MER_SPATIALBARCODE]WSNNWSNNVTTTTTTTTTTTTTTTTTTTVN

EX1016, Suppl. Materials, 3; EX1044, ¶134. As Stahl shows, the sequence of its capture probes begins with the AmC6 conjugate, indicating that the AmC6

conjugate is at the 5'-end of the probe. EX1044, ¶135. The AmC6 conjugate is used for immobilizing nucleotides on glass substrates. *See, e.g.,* EX1040, 5; EX1044, ¶¶135-137. Thus, Stahl's capture probes are immobilized using an AmC6 conjugate at their 5'-end. EX1044, ¶¶135-137.

Accordingly, Stahl anticipates claim 4.

**E. Claim 6**

Claim 6 depends from claim 1, and requires that the "sequencing step is performed using a next generation sequencing reaction." EX1043, 148:42-43. Stahl discloses this limitation. EX1044, ¶¶138-140.

Stahl discloses generating "*sequencing* libraries" and provides a detailed description of methods for "cDNA library *preparation for sequencing*." EX1016, 78, Suppl. Materials, 6-8; EX1044, ¶139. Stahl further discloses sequencing the libraries on "the *Illumina NextSeq platform* using paired-end sequencing according to the manufacturer's protocol." EX1016, Suppl. Materials, 7; EX1044, ¶¶139. The Illumina NextSeq platform performs "next generation sequencing reaction[s]," as claimed. *Id.*; EX1007, 1-2; *see also* EX1041, Table 1 (listing "Illumina NextSeq" as one of several "different NGS technologies").

Accordingly, Stahl anticipates claim 6.

**F. Claim 7**

Claim 7 depends from claim 1, and "further comprises amplifying a library using the first plurality of DNA products and the second plurality of DNA products as templates." EX1043, 148:44-46. Stahl discloses this limitation. EX1044, ¶¶141-142.

Stahl discloses amplifying "a library" when discussing the workflow for "cDNA library preparation for sequencing." EX1016, Suppl. Materials, 6-7; EX1044, ¶142. After performing an initial *in vitro* transcription/amplification to produce amplified RNA molecules, Stahl discloses adding DNA adapters to the ends of the amplified RNA, reverse-transcribing the amplified RNA into cDNA, and then performing PCR to *amplify the cDNA* to add Illumina paired-end (PE) sequencing flow-cell binding sites and index sequences before sequencing. EX1016, Suppl. Materials, 7 ("2µl purified cDNA were *amplified by qPCR* … the samples *were amplified* in a total reaction volume of 25µl."); EX1044, ¶142. Stahl's PCR amplification reactions amplified "a library" using the cDNA synthesis products as templates. *Id.*

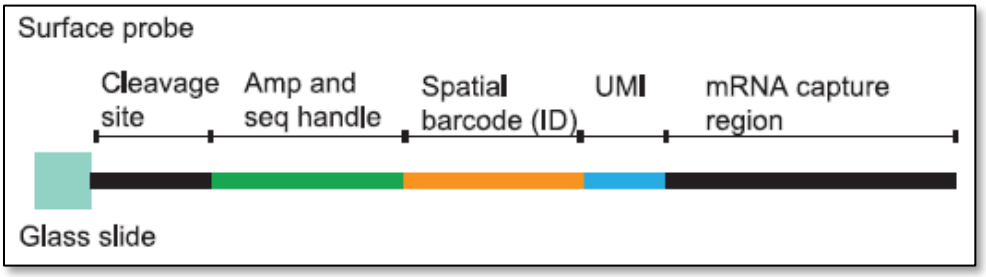
Accordingly, Stahl anticipates claim 7.

**G. Claims 8 and 9**

Claims 8 and 9 each depend from claim 1 and require that the "at least one nucleic acid sequence that identifies the [first (claim 8) and second (claim 9)]

location of the tissue sample comprise at least one unique molecular identifier." EX1043, 148:47-52. Stahl discloses these limitations. EX1044, ¶¶143-145.

As discussed above for claim 1, the spatial barcode in each of Stahl's capture probes identifies the "first" and "second" locations of the tissue sample. EX1016, 78-80, Suppl. Materials, 8, FIGs. 1-2; EX1044, ¶¶144-145. Stahl's barcoded capture probes also comprise a UMI: "[e]ach array feature contains unique *DNA-barcoded probes* containing a cleavage site, a T7 amplification and sequencing handle, a *spatial barcode*, a *unique molecular identifier (UMI)*, and an oligo(dT) VN-capture region." EX1016, 80; EX1044, ¶144. Stahl provides a diagram of its spatially barcoded and UMI-containing capture probes in Figure 2A:



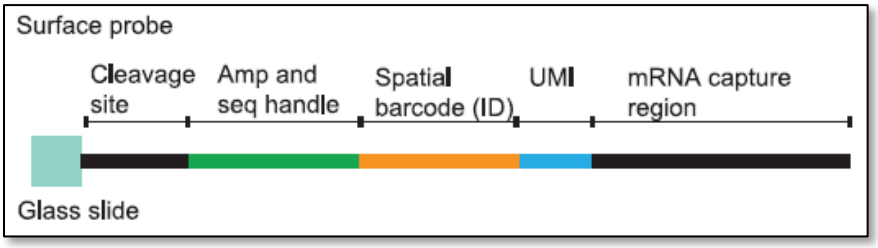

EX1016, FIG. 2A, *see also id.*, FIG. S5 ("UMI-filtered"); EX1044, ¶144. Thus, Stahl teaches a nucleic acid sequence that identifies a location of the tissue sample (*i.e.*, capture probe comprising a spatial barcode) comprising a UMI. Accordingly, Stahl anticipates claims 8 and 9.

### H. Claims 10 and 11

Claims 10 and 11 each depend from claim 1 and require that the "first plurality" (claim 10) and "second plurality" (claim 11) "of DNA products further comprises at least one amplification primer binding site." EX1043, 148:53-58. Stahl discloses these limitations. EX1044, ¶¶146-154.

According to the 142 patent, an "amplification primer binding site" is "a nucleic acid sequence that is complementary to, or at least partially complementary to at least one amplification primer." EX1043, 49:1-7. Stahl discloses that each of the "unique DNA-barcoded probes" on the array (located in a first and second location, as claimed) contains "a T7 amplification and sequencing handle," which Dr. Spellman explains comprises an amplification primer-binding site (PE1 primer-binding site). EX1016, 80, FIG. 2A; EX1044, ¶147.

Stahl provides a diagram of its capture probes comprising the "*Amp* and seq handle" in Figure 2A:




EX1016, FIG. 2A; EX1044, ¶147.

As Dr. Spellman explains, Stahl's "Amp and seq handle" of the capture probe comprises the Illumina "PE1" primer-binding site (highlighted in yellow below):

Surface spatially barcoded oligonucleotides:

[AmC6]UUUUUGACTCGTAATACGACTCACTATAGGGACACGACGCTCTTCCGATCT[18

MER_SPATIALBARCODE]WSNNWSNNVTTTTTTTTTTTTTTTTTTTTVN

EX1016, Suppl. Materials, 3; EX1044, ¶148.

As discussed above for claim 1, Stahl's method synthesizes cDNA products using the captured mRNAs as templates and the capture probes as primers, incorporating the sequence of the capture probes into the cDNA products. EX1044, ¶149. Thus, cDNA products synthesized from the captured mRNAs (first and second plurality of DNA products) comprise the "Amp and seq handle" of the capture probe containing a "PE1" primer-binding site. *Id.*.

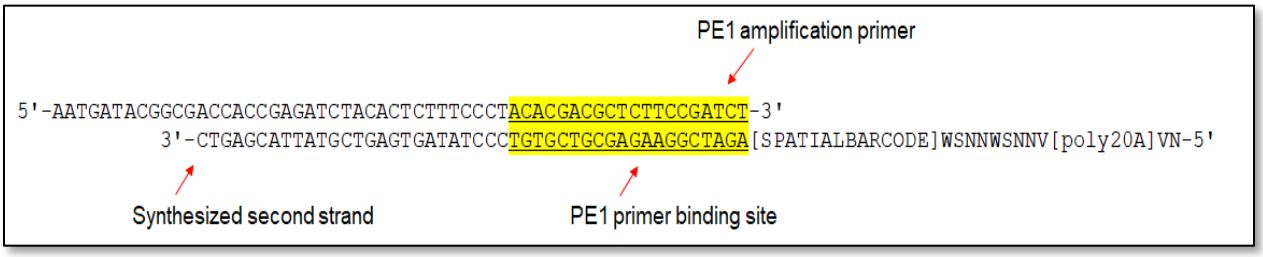
The PE1 primer-binding site is an amplification primer binding site because it is complementary to the amplification primers that are used for preparing the sequencing library. EX1016, Suppl. Materials, 6-8; EX1044 ¶¶ 150-151. Stahl discloses synthesizing second-strand DNA products complementary to the released cDNA products. EX1044, ¶¶150-151; EX1016, Suppl. Materials, 6. These second-strand DNA products therefore comprise a sequence complementary to the capture probe sequence, including the PE1 primer-binding site sequence. This is depicted

in Dr. Spellman's figure below, with the PE1 primer-binding site highlighted in yellow:




EX1044, ¶151.

The second-strand DNA products are PCR-amplified using PE1 amplification primers (PCR primers InPE1.0 and InPE2.0). EX1016, Suppl. Materials, 8; EX1044, ¶152. During amplification, the PE1 primer-binding site on the second-strand DNA products binds to its complementary sequence on the PE1 amplification primers (PCR primer InPE1.0) as depicted in Dr. Spellman's figure below:




EX1044, ¶¶152-153; EX1016, Suppl. Materials, 3, 8.

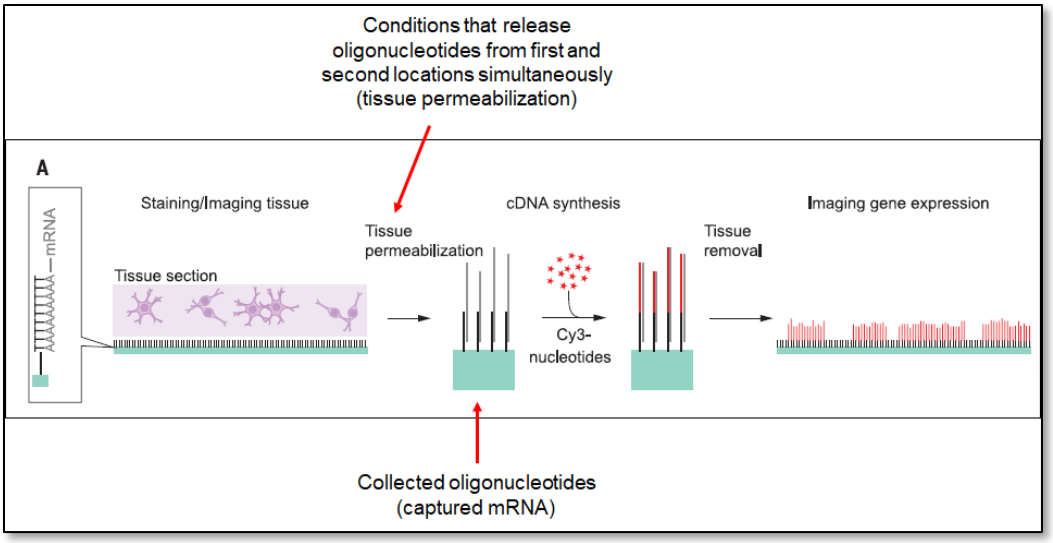
Thus, Stahl's first and second plurality of DNA products (cDNA products synthesized from the captured mRNAs) comprise an amplification primer-binding site (a PE1 primer-binding site contained in the "Amp and seq handle" of the

capture probe). EX1044, ¶¶152-153. Accordingly, Stahl anticipates claims 10 and 11.

### I. Claims 12 and 13

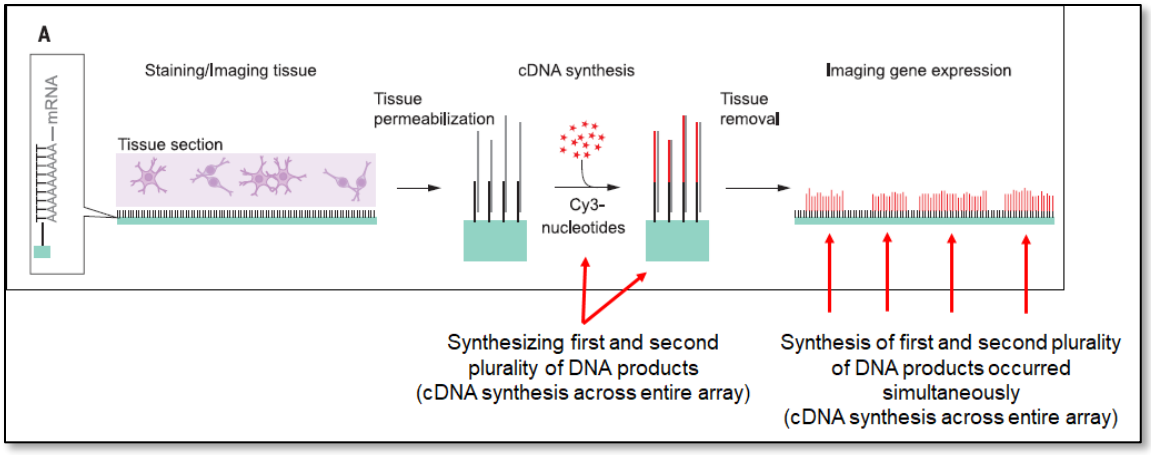
Claims 12 and 13 each depends from claim 1 and requires that the collecting "steps (a) and (b)" (claim 12) and synthesizing "steps (c) and (d)" (claim 13) "are performed simultaneously." EX1043, 148:59-62. Stahl discloses these limitations under NanoString's interpretation. EX1022, 11-14, 18; EX1015, 16-17; EX1044, ¶¶155-159.

Stahl discloses capturing the mRNAs from the whole tissue section, all at the same time, and thus discloses "collecting" the mRNAs from a first and second location "simultaneously," as claimed in claim 12. EX1016, FIGs. 1-2, Suppl. Materials, 4-5; EX1044, ¶156. Specifically, Stahl discloses performing "[p]ermeabilization" "[f]or *each well,* corresponding to *each sub-array* with a section," and that "0.1% pepsin … dissolved in 0.1M HCl … was added to *each well*" to permeabilize the tissue sample. EX1016, Suppl. Materials, 4-5; EX1044, ¶156. Thus, Stahl uniformly performs the permeabilization in each well (*i.e.*, across the whole array) and thus consequently collected the mRNAs from a first and second location of the tissue onto the array simultaneously. *Id.* Stahl depicts simultaneous collection of its mRNAs from a first and second location in Figure 1A, as shown in Dr. Spellman's annotation below:




EX1016, FIG. 1A (annotated); EX1044, ¶156.

Stahl also discloses performing its cDNA synthesis reactions across the entire array, all at the same time, and thus discloses synthesizing the first and second plurality of DNA products "simultaneously," as claimed in claim 13. EX1016, FIGs. 1-2, Suppl. Materials, 5; EX1044, ¶157. After permeabilizing the entire tissue section, Stahl discloses performing "cDNA synthesis" (reverse transcription) across the entire array (*i.e.*, simultaneously), stating that "*[e]ach well* was washed … and 70 µl of reverse transcription mix was *added to each well* and incubated overnight…." EX1016, Suppl. Materials, 5; EX1044, ¶157. Stahl depicts these simultaneous cDNA synthesis reactions in Figure 1A, as shown in Dr. Spellman's annotation below:




EX1016, FIG. 1A (annotated); EX1044, ¶¶157-159.

Accordingly, Stahl anticipates claims 12 and 13.

In sum, Stahl teaches every limitation of claims 1-4 and 6-13 under NanoString's interpretation, arranged as claimed. Accordingly, Stahl anticipates claims 1-4 and 6-13.

## X. GROUND 2: CLAIMS 1-13 WOULD HAVE BEEN OBVIOUS OVER STAHL

### A. Claims 1-4 and 6-13

To the extent NanoString argues that Stahl does not disclose all the elements of claims 1-4 and 6-13, these claims still would have been obvious in view of Stahl, under NanoString's interpretation. EX1044, ¶¶160-164. Even assuming *arguendo* Stahl does not expressly teach the claimed methods, it suggests practicing them according to NanoString's interpretation, and it provided a motivation with a reasonable expectation of success to do so. *Id.*; *Beckson Marine, Inc. v. Nfm, Inc.*, 292 F.3d 718, 727 (Fed. Cir. 2002) ("obviousness does not

require the prior art to reach expressly each limitation exactly. Rather, obviousness may render a claimed invention invalid where the record contains a suggestion or motivation to modify the prior art teaching to obtain the claimed invention.").

A POSA reading Stahl would have been motivated to practice the claimed methods because Stahl teaches that its "spatial transcriptomics" method "provides quantitative gene expression data and visualization of the distribution of mRNAs within tissue sections," "enabl[ing] novel types of bioinformatics analyses." EX1016, Abstract, 82; EX1044, ¶162. A POSA would have had a reasonable expectation of successfully practicing the claimed methods, because Stahl provides detailed descriptions and protocols, with demonstrated success in the form of extensive data and analyses. *See, e.g.,* EX1016, FIGs. 1-4, Suppl. Materials, 1-36; EX1044, ¶163. Moreover, the POSA would have known that Stahl's methods used commercially available materials and reagents, and that the protocol was straightforward, requiring "only a few extra steps compared with RNA-seq analysis of homogenized tissue." EX1016, 82, Suppl. Materials, 1-19. These straightforward methods using routine materials would have further bolstered the expectation of success. EX1044, ¶¶163-164.

**B. Claim 5**

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

solid-phase amplification reaction is carried out on the microscope slide using the plurality of primers immobilized on the microscope slide." EX1043, 148:37-41. Claim 5 uses the open-ended term "comprises," and thus only requires that solid-phase amplification take place as part of claim 1's steps (c) and (d), before the sequencing step (e). *Id.*

According to the 142 patent, "'solid-phase amplification' … refers to *any nucleic acid amplification* reaction carried out on or in association with a solid support such that all or *a portion of the amplified products are immobilized* on the solid support as they are formed." *Id.*, 42:41-45. Moreover, in concurrent litigation, NanoString alleged that claim 5's solid-phase amplification reaction encompasses second-strand cDNA synthesis from the DNA products of steps (c) and (d) while the DNA products remain bound to the primers immobilized on the array slide. EX1022, 32-33; EX1044, ¶¶166-167.

As discussed above for claim 1, Stahl's method performs the synthesis steps (c) and (d) when it synthesizes the cDNA products (first-strand cDNAs) on the array. EX1016, 78-79, FIGs. 1-2, Suppl. Materials, 4-5; EX1044, ¶¶107-115. Stahl's method further involves collecting the first-strand cDNAs and performing second-strand cDNA synthesis in solution prior to performing library amplification (also in solution). EX1016, Suppl. Materials, 6-7; EX1044, ¶¶107-115, 169-170.

A POSA would have generally known that the second-strand cDNA synthesis and library amplification can be performed on Stahl's array, *i.e.*, on the microscope slide. *See*, *e.g.,* EX1017; EX1042. For example, Frisen—which is a PCT publication by Stahl's authors (who co-founded ST)—teaches an array-based workflow including solid-phase second-strand cDNA synthesis and solid-phase amplification steps, which are "solid-phase amplification" according to the 142 patent and NanoString's interpretation. EX1017, 12:9-11, 38:20-23, 39:28-43:18; EX1043, 148:37-41; EX1022, 32-33; EX1044, ¶171. Thus, Stahl in view of the POSA's general knowledge in the art suggests performing claim 5's solid-phase amplification reaction.

A POSA would have been motivated to modify Stahl's method to perform second-strand synthesis and/or library amplification on the array because solid-phase amplification was known to improve "sensitivity and selectivity for nucleic acid identification." EX1048, 1, 2, 11; *see also* EX1050, Abstract, 2075; EX1049, Abstract, ¶¶[0013], [0015], [0101], [0104], FIG. 1; EX1044, ¶¶172-174. POSAs knew that performing enzymatic reactions with molecules immobilized on a solid support provided "additional sensitivity, specificity and scalability of analysis" that are desirable in a "high throughput" molecular bioanalytical method, such as Stahl's array-based method using next generation sequencing. EX1048, 1; EX1016, Abstract, 78, Suppl. Materials, 1-2, 4-8; see also EX1050, Abstract

("solid-phase amplification (SPA)" "allows the easy parallelization of DNA amplification in a single system"); EX1044, ¶¶172-174.

Additionally, POSAs knew that the spatial separation of primers when immobilized on an array for solid-phase amplification "significantly minimizes undesirable primer interactions," thus "reducing the formation of primer dimers, increasing specificity and sensitivity of amplification, and allowing for highly multiplexed analyses." EX1048, 2; see also EX1050, 2075 ("Since [solid-phase amplification] results in a spatially located amplification, it is possible to amplify a large number of different DNA strands in the same experiment (i.e., onto the same solid surface) without mixing them."); EX1044, ¶¶173. Further, solid-phase amplification was desirable for high-throughput methods because it "allows the parallelization of the DNA amplification process without any direct human intervention." EX1050, 2079. Thus, a POSA had ample motivation to modify Stahl's method to perform the second-strand cDNA synthesis and/or library amplification on Stahl's microscope slide on which the tissue sample was overlaid. EX1044, ¶174.

Further, a POSA would have reasonably expected to successfully perform second-strand synthesis and/or library amplification on the array in Stahl's method because performing these steps on a solid surface was known in the art and required only ordinary skill. EX1017, 8:18-10:5, 7:32-8:3, 12:9-10, 38:20-23, 38:9-

43:33, 103:12-19; EX1042, 17:37-18:59, 24:21-25:32; EX1049, ¶¶[0084]-[0086], [0089]-[0093], [0104] EX1044, ¶¶175-177. Stahl's first-strand synthesis is already "solid-phase," and a POSA would have viewed performing second strand synthesis on the substrate as a mere trivial modification. Indeed, the POSA would have known of other successful examples in the art teaching solid-phase second strand synthesis and subsequent solid-phase library amplification — which are solid-phase amplification according to the 142 patent and NanoString's interpretation. *See, e.g.*, EX1005, ¶¶[00109], [00156], [00318], FIGs. 24-25; EX1042, 25:6-18, 25:48-62, 26:19-47; EX1049, ¶¶[0084]-[0086], [0089]-[0093], [0104]; EX1044, ¶¶175-177.

NanoString did not assert any objective indicia during prosecution (EX1014, 249, 467; EX1004, 253-272, 469-477; EX1012, 1550-1564), nor is 10x aware of any objective indicia that share a nexus with the challenged claims. Accordingly, under NanoString's interpretation, claims 1-13 would have been obvious over Stahl. EX1044, ¶¶160-178.

## XI. GROUND 3: CLAIM 5 WOULD HAVE BEEN OBVIOUS OVER STAHL AND FRISEN

As discussed above for Grounds 1 and 2, Stahl discloses all of the elements of claims 1-4 and 6-13 or renders claims 1-13 obvious. Even if claim 5 were not obvious over Stahl alone, it would have been obvious over Stahl in combination with Frisen. EX1044, ¶¶179-196.

Stahl and Frisen together teach or suggest Stahl's method including a solid-phase amplification reaction, wherein the reaction is carried out on the microscope slide using the primers immobilized on the microscope slide, as recited in claim 5. EX1044, ¶180. According to the 142 patent, "'solid-phase amplification' … refers to *any nucleic acid amplification* reaction carried out on or in association with a solid support such that all or *a portion of the amplified products are immobilized* on the solid support as they are formed." EX1043, 42:41-45. Moreover, in concurrent litigation, NanoString alleged that claim 5's solid-phase amplification reaction encompasses second-strand cDNA synthesis from the DNA products of steps (c) and (d) while the DNA products remain bound to the primers immobilized on the array slide. EX1022, 32-33; EX1044, ¶180.

As discussed above for claim 1, Stahl's method performs the synthesis steps (c) and (d) when it synthesizes the cDNA products (first-strand cDNA) on the array. EX1016, 78-79, FIGs. 1-2, Suppl. Materials, 4-5; EX1044, ¶¶181-182. Stahl's method further includes "cDNA library preparation for sequencing" that includes in-solution second-strand cDNA synthesis and amplification. EX1016, Suppl. Materials, 6-8; EX1044, ¶182. Specifically, Stahl's library preparation involves releasing the cDNA products from the array (microscope slide) and performing the following steps in solution: *synthesizing second-strand cDNAs* using the cDNA products as template, performing in vitro transcription to

synthesize amplified RNAs (aRNAs) from cDNAs, re-synthesizing cDNAs from aRNAs by reverse transcription, and *amplifying* the cDNAs to generate a sequencing library. EX1016, Suppl. Materials, 6-8; EX1044, ¶182. Thus, Stahl's method includes performing a second-strand cDNA synthesis step in solution prior to performing library amplification steps (also in solution). EX1044, ¶182.

Frisen, teaches array-based spatial detection methods using solid-phase second-strand cDNA synthesis and solid-phase library amplification steps, both of which are "solid-phase amplification" according to the 142 patent and NanoString's interpretation. EX1017, 12:9-10, 38:20-23, 42:28-43:7; EX1044, ¶183. Specifically, Frisen discloses a method for determining and/or analyzing a transcriptome of a tissue sample comprising "generating cDNA molecules from the captured RNA[s]" that are hybridized to the spatially barcoded probes immobilized on an array and "optionally amplifying said cDNA molecules" on the array before releasing "cDNA molecules and/or optionally their amplicons from the surface of the array," for further processing for sequencing. EX1017, 8:18-9:5; EX1044, ¶183. For an obviousness inquiry, all of Frisen's disclosure must be considered. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004); *Merck & Co. v. Biocraft Labs., Inc*. 874 F.2d 804, 807 (Fed. Cir. 1989).

Frisen explains that in some instances, it "will be necessary to enhance, i.e.[,] amplify, the amount of secured nucleic acid, e.g. synthesized cDNA[,] to

yield quantities that are sufficient for DNA sequencing." EX1017, 39:9-16; *see also id.*, 42:32-33 ("Thus in a preferred embodiment, the method of the invention may comprise a step of amplifying the DNA, e.g. cDNA molecules."). Thus, Frisen discloses methods for spatially detecting mRNAs in a tissue sample comprising amplifying cDNA products synthesized from the mRNAs. Frisen also discloses methods that include performing "amplification … in situ on the array." *Id.*, 55:24-26, 23:18-20; EX1044, ¶184.

Additionally, Frisen discloses that the synthesized cDNA products are treated to comprise double stranded DNA in a "single reaction to generate only a second DNA, e.g. cDNA, strand" or in an "amplification reaction to generate multiple copies of the second strand." *Id.*, 38:9-19; EX1044, ¶185. Frisen specifies that the "step of second strand DNA, e.g. cDNA, synthesis may take place *in situ on the array*, either as a discrete step of second strand synthesis … or in the initial step of an amplification reaction." *Id.*, 38:20-23. Indeed, Frisen's Example 11 exemplified a method that includes generating a second strand cDNA together with the first-strand cDNA on a chip, *i.e.*, solid surface. *Id.*, 103:12-19. Thus, Frisen discloses methods comprising a solid-phase amplification reaction, wherein the solid-phase amplification reaction is carried out on the array onto which the tissue sample was overlaid, using the primers immobilized on the array under the patent's definition and NanoString's interpretation. EX1044, ¶¶185-186.

**Motivation:** A POSA would have been motivated to modify Stahl's method to include second-strand cDNA synthesis and/or library amplification on its array as disclosed in Frisen for several reasons. EX1044, ¶¶187-192. *First*, as Dr. Spellman explains, a POSA would have appreciated that Frisen discloses applications and modifications of Stahl's spatial barcoding array workflow from Spatial Transcriptomics. *Id.*, ¶187. Indeed, both Stahl and Frisen provide methods coined as "spatial transcriptomics," provide overlapping spatial transcriptomics workflows, and further include overlapping authors and inventors (Frisen lists the inventors as Jonas Frisen, Patrik Stahl, and Joakim Lundeberg, each of whom is a co-author on Stahl). EX1016, 78; EX1017, Face, 1:18; EX1044, ¶187.

*Second*, the POSA would have known that performing Frisen's solid-phase second-strand cDNA synthesis and/or solid-phase library amplification offers certain advantages by producing the cDNA products and amplicons on the array in allocated spatial spots prior to collection. EX1044, ¶¶188-189. Solid-phase amplification was known to improve "sensitivity and selectivity for nucleic acid identification." EX1048, 1, 2, 11; *see also* EX1050, Abstract, 2075; EX1049, Abstract, ¶¶[0013], [0015], [0101], [0104], FIG. 1; EX1044, ¶¶188-189. POSAs knew that performing enzymatic reactions with molecules immobilized on a solid support provided "additional sensitivity, specificity and scalability of analysis" that are desirable in a "high throughput" molecular bioanalytical method, such as

Stahl's array-based method using next generation sequencing. EX1048, 1; EX1016, Abstract, 78, Suppl. Materials, 1-2, 4-8; see also EX1050, Abstract ("solid-phase amplification (SPA)" "allows the easy parallelization of DNA amplification in a single system"); EX1044, ¶189.

Additionally, POSAs knew that the spatial separation of primers when immobilized on an array for solid-phase amplification "significantly minimizes undesirable primer interactions," thus "reducing the formation of primer dimers, increasing specificity and sensitivity of amplification, and allowing for highly multiplexed analyses." EX1048, 2; see also EX1050, 2075 ("Since [solid-phase amplification] results in a spatially located amplification, it is possible to amplify a large number of different DNA strands in the same experiment (i.e., onto the same solid surface) without mixing them."); EX1044, ¶¶190-191.

Further, solid-phase amplification was desirable for high-throughput methods because it "allows the parallelization of the DNA amplification process without any direct human intervention." EX1050, 2079; EX1044, ¶¶190-191. Thus, a POSA would have been motivated to modify Stahl 2016's method to perform the second-strand cDNA synthesis and/or library amplification on Stahl 2016's array—i.e., on the microscope slide onto which the tissue sample was overlaid, using the plurality of primers immobilized on the microscope slide. *Finally*, Frisen explicitly suggests implementing such modifications into a

workflow like Stahl's workflow. EX1017, 12:9-11, 38:20-23, 38:27-32, 39:5-6, 42:28-43:7, 103:12-19; EX1044, ¶191.

Thus, a POSA would have been motivated to modify Stahl's method to include second-strand cDNA synthesis and/or library amplification on its array as disclosed in Frisen.

**Reasonable expectation of success:** As Dr. Spellman explains, a POSA would have reasonably expected to successfully modify Stahl's workflow to implement Frisen's solid-phase second-strand cDNA synthesis and/or solid-phase library amplification steps because doing so required only known techniques and ordinary skill. EX1044, ¶¶193-195. A POSA would have known that Stahl's first strand synthesis is already "solid-phase," and would have viewed performing second strand synthesis on the substrate as a mere trivial modification. *Id.*, ¶193. Methods of solid-phase cDNA synthesis and amplification were commonplace in molecular biology laboratories, and reagents such as primers, buffers, nucleotides, polymerase enzymes, and materials were all standard commercial products. EX1017, 8:18-10:5, 7:29-8:3, 12:9-10, 38:9-43:33, 103:12-19; EX1005 ¶¶[0034]-[0035], [00109], [00141]-[00143], [00151]-[00158], [00307]-[00320], FIGs. 1, 2, 24-25; EX1042, 1:61-2:9, 3:11-34, 17:37-18:59, 24:21-25:32, 26:19-47; EX1044, ¶194. Indeed, Frisen detailed "suitable means" for second strand synthesis and

provided an exemplary method in Example 11. EX1017, 12:9-11, 39:28-43:18, 103:12-19.

NanoString did not assert any objective indicia during prosecution (EX1014, 249, 467; EX1004, 253-272, 469-477; EX1012, 1550-1564), nor is 10x aware of any objective indicia that share a nexus with the claim 5. Accordingly, under NanoString's interpretation, claim 5 would have been obvious over Stahl and Frisen. EX1044, ¶¶195-196.

## XII. GROUND 4: SO-456 ANTICIPATES CLAIMS 1-13

So-456 anticipates claims 1-13 under NanoString's interpretation. EX1044, ¶¶197-252. So-456 is presumed enabled.

### A. Claim 1

So-456 in Figure 2 provides an overview of a "*method* … of *spatial detection* and analysis of a *nucleic acid in a tissue sample*" using spatially barcoded arrays. EX1005, ¶¶[00151], [00150], FIG. 2; EX1044, ¶¶81-85, 197-220. So-456 provides specific embodiments of Figure 2's method in, *e.g.*, Figures 24 and 25, comprising each of the collecting, synthesis, and sequencing steps of claim 1 under NanoString's interpretation. EX1005, ¶¶[0034]-[0035], [00307]-[00321]; EX1044, ¶¶197-220.

**1. "A method comprising:**

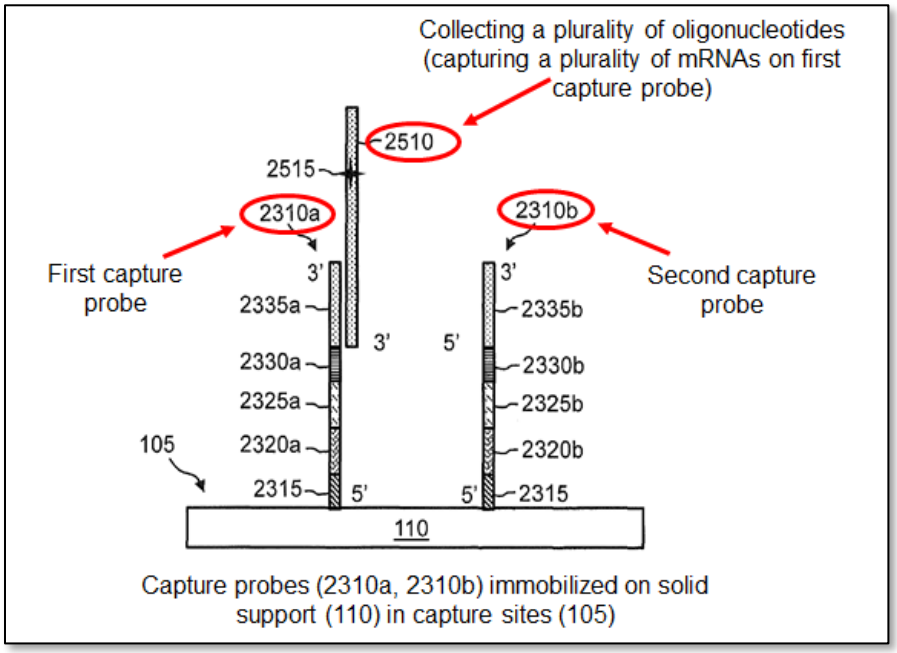
**a) [and (b)] collecting a plurality of oligonucleotides from a first location [and second location] of a tissue sample …"**

So-456 discloses claim 1's collecting steps (a) and (b) under NanoString's interpretation. EX1044, ¶¶199-206. In concurrent litigation, NanoString alleged that the claim's collecting steps encompass diffusion and capture of mRNAs across the *whole* tissue sample, all at the same time. EX1022, 11-14, 18; EX1015, 16-17; EX1044, ¶¶199-200.

So-456's method depicted in Figures 24-25 collects a plurality of oligonucleotides from a "first" and "second" location under NanoString's interpretation. Specifically, So-456's method contacts "a tissue sample … compris[ing] a plurality of mRNA molecules" with a "capture array." EX1005, ¶¶[00308], [00314], FIGs. 24, 25A; EX1044, ¶201. The array comprises for each mRNA molecule (2510) two "capture probes" (2310) that are immobilized in the "5' to 3' direction (i.e., the 5' end of capture probes … are attached to the surface of capture site …)." EX1005, ¶¶[00308], [00314]; EX1044, ¶201. The capture probes used in Figures 24-25's method are the same as the capture probes used in Figure 23's method. EX1005, ¶[00314]; EX1044, ¶201.

So-456's method meets claim 1's collecting step because it captures (collects) the mRNAs (oligonucleotides) from the tissue sample on the first capture probes immobilized on the array. EX1044, ¶202. So-456 discloses that its first

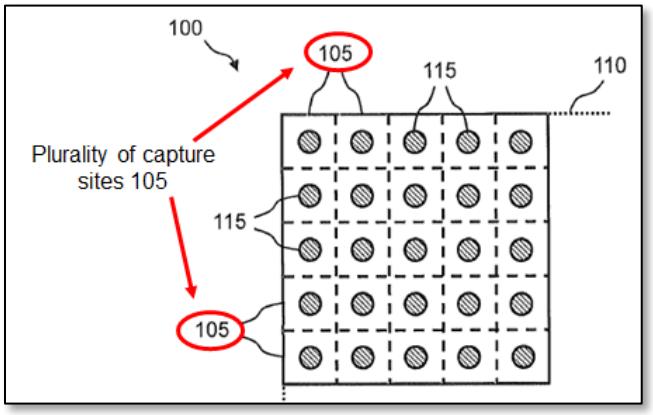
capture probe (2310a) comprises "sequences specific for the 3' end of the mRNA molecule" (2335a) and that the "*mRNA molecules* are *captured* onto the array by hybridization of the 3' end of the mRNA to gene-specific regions [(2335a)] on the first capture probe." EX1005, ¶¶[00308], [00314]-[00315]. This is illustrated in Dr. Spellman's annotations in So-456's Figure 25A.




EX1005, FIG. 25A (annotated); EX1044, ¶¶202-203. Thus, So-456's method collects (captures) a plurality of oligonucleotides (mRNAs).

So-456's method also collects oligonucleotides (mRNAs) from a first and second location of the tissue sample, according to NanoString's interpretation. EX1022, 11-14, 18; EX1015, 16-17; EX1044, ¶204. So-456's method captures mRNAs released from the tissue sample onto capture array (100) comprising "an arrangement (e.g., rows and columns) of capture sites 105 on a solid support 110."

EX1005, ¶¶[00141], [00307], [00314]. The capture probes are immobilized at each of the capture sites. *Id.*, ¶¶[00307], [00314]. This is illustrated in Dr. Spellman's annotations in So-456's Figure 1A.




EX1044, ¶204; EX1005, FIG. 1A (annotated).

So-456 specifies that the "target nucleic acid in the tissue section is transferred onto an array such that the position of a nucleic acid on the array can be correlated with a position in the tissue section." EX1005, ¶¶[00154]; *see also id.*, ¶[0093] ("facilitating the transfer of nucleic acids from a tissue sample onto a capture array"); EX1044, ¶205. So-456 further specifies that its methods "substantially maintain information encoding the spatial orientation of the targets in the sample." EX1005, ¶[00155]; EX1044, ¶205. Thus, So-456's method collects mRNAs from a first location and a second location (different positions) of the tissue sample. *Id.*

So-456's workflow is performed simultaneously at multiple locations of the tissue sample and consequently at multiple capture sites on the array. *Id.*,

¶¶[00141], [00307]-[00308], [00314]-[00315], FIGs. 1A, 24-25; EX1044, ¶206. Thus, So-456's method collects mRNAs from the *whole* tissue sample, all at the same time, as claimed according to NanoString's interpretation. EX1044, ¶206; EX1015, 16-17; EX1022, 11-14, 18.

**"under conditions that release the plurality of oligonucleotides from the first location [and second location] of the tissue sample"**

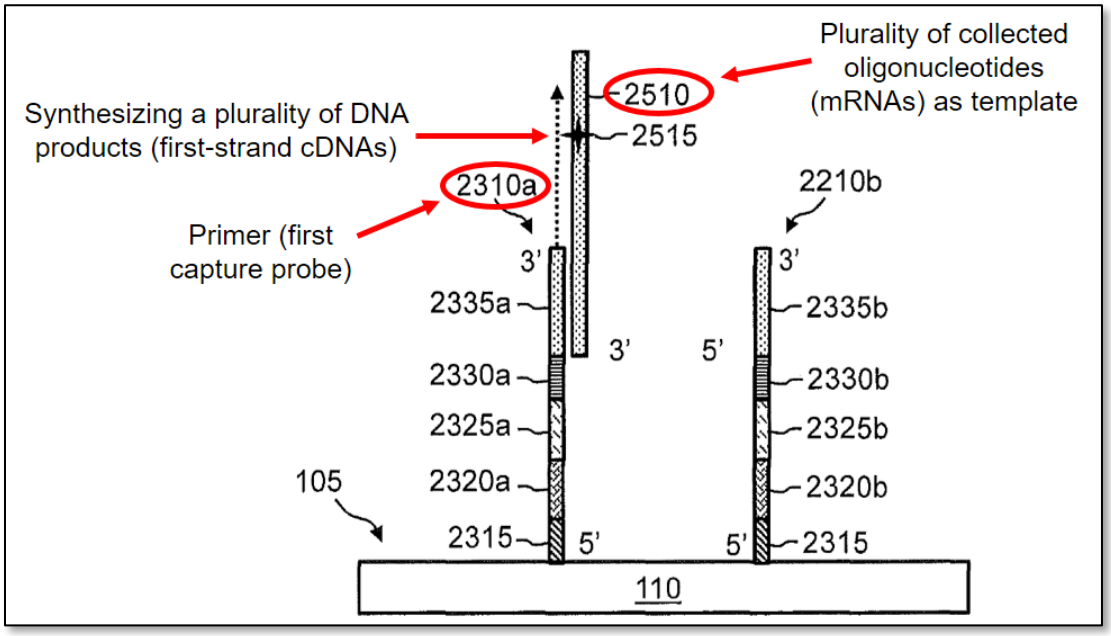
So-456's method collects the oligonucleotides (mRNAs) under conditions that release the oligonucleotides from their locations in the tissue sample under NanoString's interpretation of the claims. EX1022, 11-14, 18; EX1015, 16-17; EX1044, ¶¶207-208. In So-456's method, the "*tissue sample is prepared* for analysis" and the mRNAs from the tissue sample are "captured onto the array," *e.g.*, the "capture array 100 of Figure 1 A." EX1005, ¶¶[00152], [00308], [00315]; *see also id.*, ¶[00154] ("the target nucleic acid [(*e.g.*, mRNA)] in the tissue section is transferred onto an array such that the position of a nucleic acid on the array can be correlated with a position in the tissue section"); EX1044, ¶¶207-208. So-456 also discloses that the "target nucleic acid" (mRNA) "diffuse[s] from the tissue" onto the array, further confirming that the tissue sample was treated to create a condition to "release" the mRNA from the tissue onto the array. EX1005, ¶[00155]; EX1044, ¶¶207-208. Thus, So-456's method collects the

oligonucleotides (mRNAs) under conditions that release the oligonucleotides from their locations of the tissue sample.

Accordingly, So-456 discloses claim 1's collecting steps (a) and (b).

**2. "c) [and (d)] synthesizing a first plurality [and second plurality] of DNA products by performing a synthesis reaction…"**

So-456 discloses the synthesis steps (c) and (d). So-456's method uses the "gene-specific capture regions on the first capture probe" (2310a) as "reverse transcriptase primers" for "synthesis of first strand cDNA from captured mRNA molecules." EX1005, ¶¶[00309], [00316]; EX1044, ¶¶209-210. So-456's Figure 25A depicts this cDNA synthesis as a dotted arrow:



EX1005, FIG. 25A; EX1044, ¶209. So-456's method synthesizes a first and second plurality of DNA products (cDNAs) because it produces the cDNAs from the "captured mRNA *molecules*." EX1005, ¶¶[00309], [00316], FIGs. 24, 25A; EX1044, ¶210. Because So-456's synthesis reactions take place simultaneously in different spots on the array (*see, e.g.*, EX1005, ¶¶[00141], [00307]-[00308], [00314]-[00315], FIGs. 1A, 24-25), So-456's method synthesizes a first and second plurality of DNA products, as claimed. EX1044, ¶¶209-210.

**"that uses the plurality of oligonucleotides collected in step (a) [and step (b)] as templates…"**

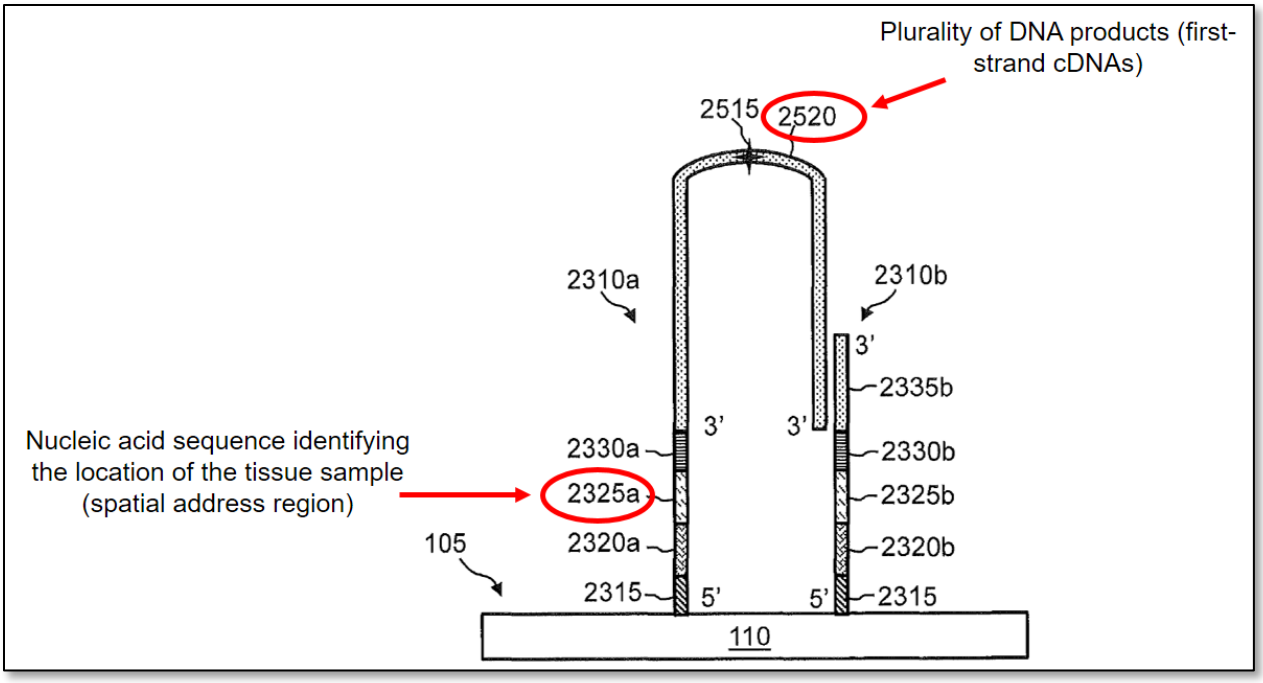
So-456's synthesis reactions use the first and second plurality of oligonucleotides (mRNAs) collected in steps (a) and (b) as templates because So-456 uses reverse transcription to synthesize a cDNA strand using the captured mRNA as a template. EX1005, ¶¶[00309], [00316], FIG. 25A; EX1044, ¶211. This is depicted in So-456's Figure 25A (reproduced above), which shows the captured mRNAs (2510) (collected first and second plurality of oligonucleotides) serving as templates for the cDNA synthesis (dotted arrow). EX1005, FIG. 25A; EX1044, ¶211.

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

So-456's synthesis reactions also incorporate at least one nucleic acid

sequence that identifies the first (and second) location of the tissue sample into the first (and second) plurality of DNA products, as claimed. EX1044, ¶¶212-215. So-456 discloses that the capture probes (2310) in So-456's method of Figures 24-25 are "essentially the same" as the capture probes in So-456's method of Figure 23A. EX1005, ¶[00314]; EX1044, ¶213. So-456 teaches that these capture probes comprise a "spatial address region" that comprises a "unique spatial address sequence." EX1005, ¶¶[00302], [00314]; EX1044, ¶213. So-456 also explains that the spatial address region "corresponds to the position of capture probe 115 in capture array 100." EX1005, ¶[00141].

As Dr. Spellman's annotations of Figure 25B illustrate, the first strand cDNA (2520), which is synthesized using the first capture probe (2310a) as primer and mRNA as template, comprises the spatial address region (2325a):




EX1005, FIG. 25B; EX1044, ¶214.

Thus, So-456's synthesis reaction produces DNA products (first-strand cDNAs) comprising a sequence that identifies a location on the array and the corresponding location of the tissue sample (spatial address region of the capture probe), thus incorporating the sequence into the DNA products. EX1005, FIGs. 25A-B; EX1044, ¶215. Accordingly, So-456 discloses claim 1's synthesizing steps (c) and (d).

**3. "e) identifying the first plurality of DNA products and the second plurality of DNA products synthesized in step (c) and step (d) by sequencing the first plurality of DNA products and the second plurality of DNA products,**

**thereby spatially detecting the plurality of oligonucleotides collected from the first location of the tissue sample and the plurality of oligonucleotides collected from the second location of the tissue sample."**

So-456 discloses claim 1's sequencing step (e) under NanoString's interpretation. EX1044, ¶¶216-220. 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; EX1044, ¶216.

After synthesizing the first-strand cDNA molecules (first and second plurality of DNA products) on the array, So-456's method processes the cDNA molecules to generate a sequencing library. EX1005, ¶¶[00310]-[00313], [00317]-[00320]; EX1044, ¶217. Specifically, So-456's method uses the first-strand cDNA molecules as templates and the second capture probes on the arrays as primers to synthesize the second strand cDNA molecules, and then releases the second strand cDNA molecules from the array by a cleavage reaction. EX1005, ¶¶[00310]-[00312], [00317]-[00319]. The released second strand cDNA molecules comprise the sequence complementary to the first-strand cDNA and the sequence of the second capture probe. EX1044, ¶217. Thus, the released cDNA molecules

comprise spatial address region (2325a) of the first capture probe. EX1005, ¶[00319]; EX1044, ¶217.

So-456 discloses that the released "cDNA molecules are amplified to generate a sequencing library." EX1005, ¶¶[00313], [00320]. So-456 further discloses that "the library is sequenced" and "the sequence data is *analyzed* … and the *spatial information is decoded*." *Id.*, ¶¶[0089], [00157]-[00158]; EX1044, ¶¶218-219. So-456 specifies that 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 the plurality of oligonucleotides collected from the first and second locations of the tissue sample, as claimed). *Id.*, ¶¶[0089], [00158]; EX1044, ¶¶218-219. To achieve this, So-456 discloses that 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]; EX1044, ¶219. So-456 further discloses that its methods "enable the identification of *the location of a cell or a cell cluster* in a tissue" sample. EX1005, ¶¶[0002], [0088]; EX1044, ¶219. Accordingly, So-456 teaches claim 1's sequencing step (e).

In sum, So-456 teaches every limitation of claim 1 under NanoString's interpretation, arranged as claimed. So-456 is presumed enabled. *Antor Media*, 689 F.3d at 1290-91; *Corephotonics*, 861 F. App'x at 450; *Activision Blizzard*,

IPR2015-01996, Paper 101 at 19. Thus, So-456 anticipates claim 1. EX1044, ¶¶198-220.

**B. Claim 2**

Claim 2 depends from claim 1, and requires that "the tissue sample is immobilized onto a microscope slide." EX1043, 147:62-63. So-456 discloses this limitation. EX1044, ¶¶222-224.

So-456 discloses fixing, sectioning, and mounting a "tissue sample" on "a *microscope slide*." EX1005, ¶[00125]; EX1044, ¶223. Moreover, So-456's method in Figure 2 discloses that the tissue sample, *e.g.*, fresh tissue or frozen tissue, is "sectioned onto a *slide*." EX1005, ¶[00152], FIG. 2; EX1044, ¶223. Accordingly, So-456 anticipates claim 2. EX1044, ¶222-224.

**C. Claim 3**

Claim 3 depends from claim 2 and requires that the "microscope slide comprises a plurality of primers immobilized on the microscope slide." EX1043, 148:32-34. So-456 discloses this limitation. EX1044, ¶¶225-227.

In So-456's method, "a tissue sample that comprises a plurality of mRNA molecules is contacted with a capture array," *e.g.*, the "capture array 100 of Figure 1 A." EX1005, ¶¶[00308], [00314]-[00315]; EX1044, ¶226. So-456 discloses that "*any number* of capture probes 115 can be *immobilized on solid support* 110 at each capture site 105" of the array of Figure 1A and that the solid support has "an

*array of capture sites*" that include "*a plurality of capture probes*." EX1005, ¶¶[00141], [00154], FIGs. 1A-1B; EX1044, ¶226.

Accordingly, So-456 discloses that its microscope slide comprises a plurality of primers immobilized on the slide and thus anticipates claim 3. EX1044, ¶¶225-227.

**D. Claim 4**

Claim 4 depends from claim 3 and requires that the "plurality of primers is immobilized on the microscope slide at their 5' ends." EX1043, 148:35-36. So-456 discloses this limitation. EX1044, ¶¶228-229.

So-456's method specifies that "the 5' end of capture probes 2310a and 2310b are attached to the surface of capture site 105." EX1005, ¶[00314]; *see also id.*, ¶[00109] ("[o]ligonucleotides to be used as capture primers … can be immobilized such that a *3'-end is available for enzymatic extension*"); EX1044, ¶229. Accordingly, So-456 discloses that its microscope slide comprises a plurality of primers immobilized at their 5'-ends and thus anticipates claim 4. EX1044, ¶¶228-229.

**E. Claim 5**

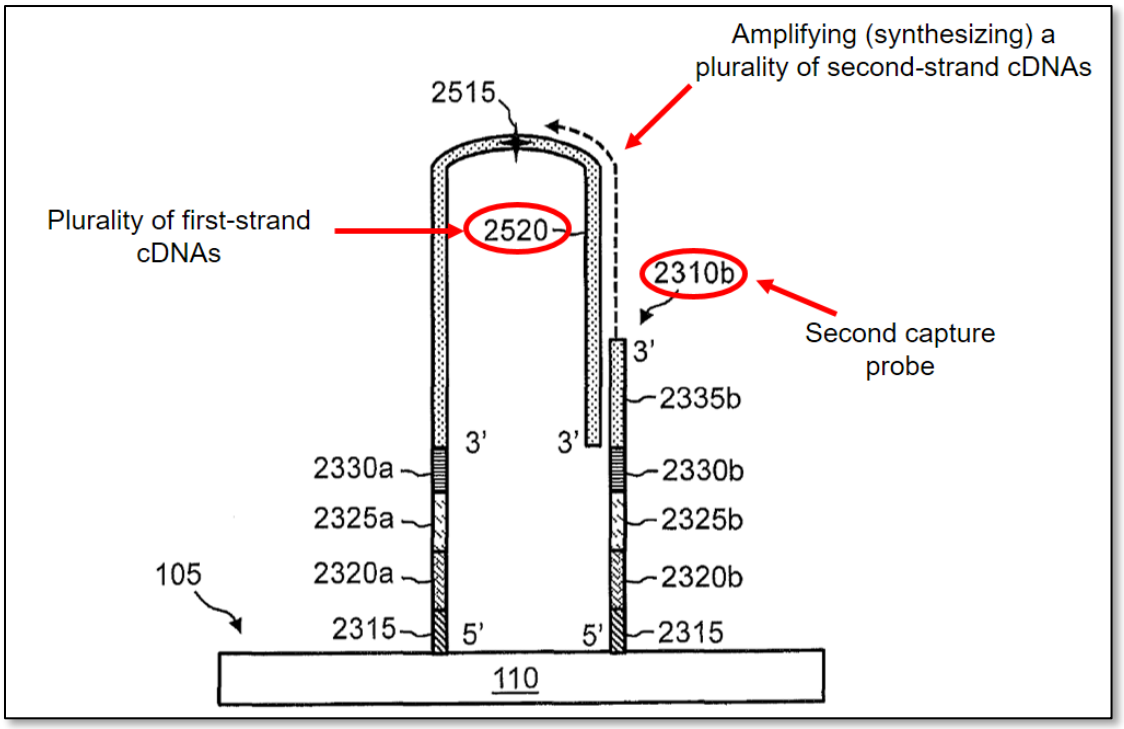
Claim 5 depends from claim 4, and requires that each synthesis step (c) and (d) "comprises performing a solid-phase amplification reaction, wherein the solid-phase amplification reaction is carried out on the microscope slide using the

plurality of primers immobilized on the microscope slide." EX1043, 148:37-41. As discussed above, claim 5 uses the open-ended term "comprises," and thus only requires that solid-phase amplification take place as part of claim 1's steps (c) and (d), before step (e). *Id.* So-456 discloses this limitation. EX1044, ¶¶230-235.

According to the 142 patent, "'solid-phase amplification' … refers to *any nucleic acid amplification* reaction carried out on or in association with a solid support such that all or *a portion of the amplified products are immobilized* on the solid support as they are formed." EX1043, 42:41-45. Moreover, in concurrent litigation, NanoString alleged that claim 5's solid-phase amplification reaction encompasses second-strand cDNA synthesis from the DNA products of steps (c) and (d) while the DNA products remain bound to the primers immobilized on the array slide. EX1022, 32-33; EX1044, ¶231.

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]; EX1044, ¶232. So-456 further specifies that the "[l]ibrary preparation may be accomplished *on the capture array substrate*." EX1005, ¶[00156]. Thus, So-456 method includes solid-phase amplification as required by claim 5 under the 142 patent's definition and NanoString's interpretation. EX1044, ¶232.

Additionally, So-456's second-strand cDNA synthesis step depicted in Figures 24-25 also constitutes a solid-phase amplification reaction under the 142 patent's definition and NanoString's interpretation. EX1044, ¶233. This is illustrated in Dr. Spellman's annotations of So-456's Figure 25B below.




EX1005, FIG. 25B; EX1044, ¶¶233-234.

As shown in Figure 25B above, the first-strand cDNAs are captured on the second capture probes (2310b) that serve as primers and copied (amplified) by a synthesis reaction into the second strand cDNAs (dotted arrow). EX1005, ¶¶[00310], [00317]-[00318], FIGs. 24, 25B; EX1044, ¶233-235.

Thus, So-456's cDNA synthesis reaction is a solid-phase amplification according to the 142 patent's definition and NanoString's interpretation, and it is carried out on the microscope slide (110) using the plurality of primers (capture probes) that are immobilized on the microscope slide, all as claimed. EX1005, FIG. 1; EX1044, ¶235. Accordingly, So-456 anticipates claim 5 under NanoString's interpretation. EX1044, ¶¶230-235.

**F. Claim 6**

Claim 6 depends from claim 1, and requires that the "sequencing step is performed using a next generation sequencing reaction." EX1043, 148:42-43. So-456 discloses this limitation. EX1044, ¶¶236-237.

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]; EX1044, ¶237; *see also* EX1005, ¶¶[00156], [00595]. Accordingly, So-456 anticipates claim 6. EX1044, ¶¶236-237.

**G. Claim 7**

Claim 7 depends from claim 1, and "further comprises amplifying a library using the first plurality of DNA products and the second plurality of DNA products as templates." EX1043, 148:44-46. So-456 discloses this limitation. EX1044, ¶¶238-239.

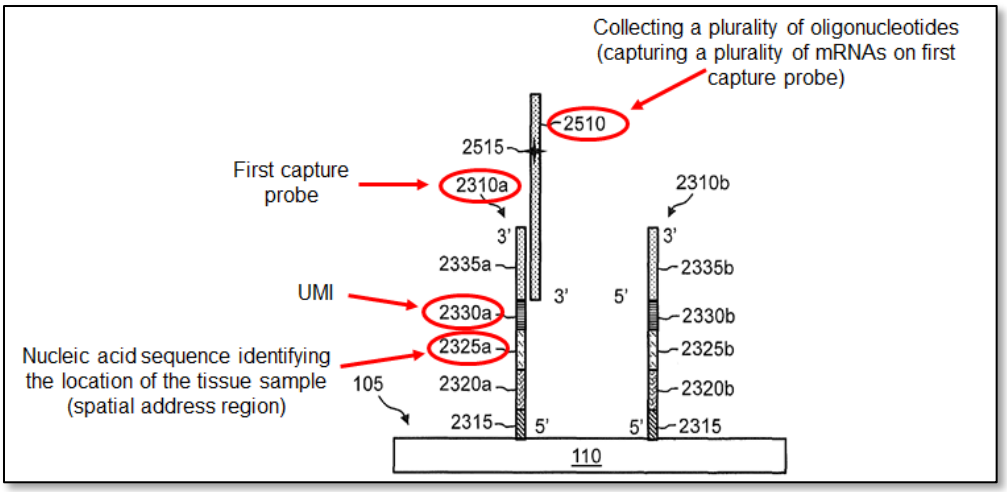
As discussed above under claim 5, So-456's method copies (amplifies) the first-strand cDNAs (DNA products) synthesized from the captured mRNAs into the second strand cDNAs by using the first-strand cDNAs as templates and second capture probes as primers. EX1005, ¶¶[00310], [00317]-[00318], FIGs. 24, 25B; EX1044, ¶¶230-235, 239. Next, the second strand cDNAs (2525) are released from the array and "*amplified* to generate a sequencing library." EX1005, ¶¶[00312]-[00313], [00319]-[00320]; EX1044, ¶239. So-456 specifies that "cDNA molecule 2525 is *amplified* using an SBS primer 2530 and a second SBS primer 2535" to generate a "library *amplicon* 2550." EX1005, ¶[00320]; *see also id.*, ¶¶[00141]-[00142], [00182]; EX1044, ¶239. Accordingly, So-456 discloses amplifying a library using the cDNAs (*i.e.*, first and second plurality of DNA products) as templates and thus anticipates claim 7.

### H. Claims 8 and 9

Claims 8 and 9 each depend from claim 1 and require that the "at least one nucleic acid sequence that identifies the [first (claim 8) and second (claim 9)] location of the tissue sample comprise at least one unique molecular identifier." EX1043, 148:47-52. So-456 discloses these limitations. EX1044, ¶¶240-242.

As discussed above for claim 1, the "spatial address region" in each of So-456's capture probes identifies the first and second locations of the tissue sample. EX1005, ¶¶[00302], [00314]; EX1044, ¶241. So-456's capture probes also

comprise a UMI: "Capture probes 2310 include … a *spatial address region 2325*, a *unique molecular identifier (UMI) 2330*, and a capture region 2335." EX1005, ¶[00302]; EX1044, ¶241. For example, capture probe 2310a comprises "*spatial address region 2325a*, which comprises a unique spatial address sequence …; *UMI region 2330a*, which comprises a unique sequence for capture probe 2310a." EX1005, ¶[00302]; EX1044, ¶241. This is depicted in Dr. Spellman's annotated Figure 25B below:



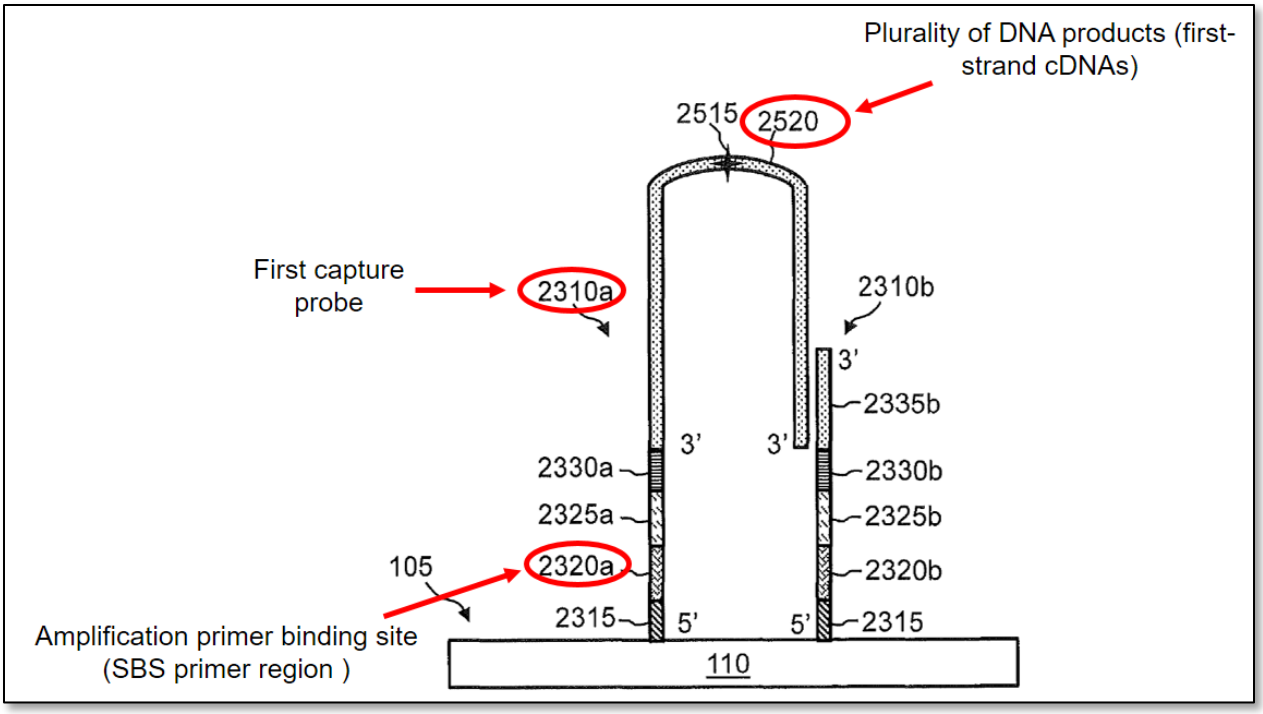

EX1005, FIG. 25B; EX1044, ¶241. Thus, So-456 teaches a nucleic acid sequence that identifies a location of the tissue sample (*i.e.*, capture probe comprising a spatial address region) comprising a UMI and anticipates claims 8 and 9. EX1044, ¶¶240-242.

## I. Claims 10 and 11

Claims 10 and 11 each depend from claim 1 and require that the "first plurality" (claim 10) and "second plurality" (claim 11) "of DNA products further

comprises at least one amplification primer binding site." EX1043, 148:53-58. So-456 discloses these limitations. EX1044, ¶¶243-247.

According to the 142 patent, an "amplification primer binding site" is "a nucleic acid sequence that is complementary to, or at least partially complementary to at least one amplification primer." EX1043, 49:1-7; EX1044, ¶244. As discussed above for claim 1, So-456's method synthesizes a first and second plurality of DNA products (first-strand cDNAs) using the collected oligonucleotides (captured mRNAs) as templates and capture probes as primers. *See* Section XII.A.2. So-456's capture probes comprise an "SBS [sequencing-by-synthesis] *primer region 2320.*" EX1005, ¶[00302]; *see also id.*, ¶[00141]; EX1044, ¶245. For example, capture probe 2310a comprises "SBS primer region 2320a." EX1005, ¶[00302]; EX1044, ¶245. Thus, So-456's first-strand cDNAs (2520) synthesized from captured mRNAs comprise SBS primer region (2320). EX1044, ¶245. This is depicted in Dr. Spellman's annotated Figure 25B below:




EX1005, FIG. 25B (annotated); EX1044, ¶245.

As discussed above for claim 1, So-456's method synthesizes second-strand cDNAs using the first-strand cDNAs as templates and the second capture probes on the arrays as primers. EX1005, ¶¶[00310]-[00312], [00317]-[00319]; EX1044, ¶246. So-456's released second-strand cDNAs (2525) comprise the sequence complementary to the first-strand cDNAs (which includes SBS primer region 2320a). EX1005, ¶[00319]; EX1044, ¶246 Thus, the released cDNAs (2525) include SBS primer region (2320a). *Id.*

So-456 also teaches that "cDNA molecule 2525 is amplified using an SBS primer 2530" that are "complementary to *SBS primer region 2320a*." EX1005, ¶[00320]; *see also id.*, ¶[00141]; EX1044, ¶247.

Thus, So-456's first and second plurality of DNA products (first-strand cDNAs) comprise at least one amplification primer binding site (SBS primer region). Accordingly, So-456 anticipates claims 10 and 11. EX1044, ¶¶243-247.

**J. Claim 12**

Claim 12 depends from claim 1 and requires that collecting "steps (a) and (b)" "are performed simultaneously." EX1043, 148:59-60. So-456 discloses this limitation under NanoString's interpretation. EX1022, 11-14, 18; EX1015, 16-17; EX1044, ¶¶248-249.

So-456 discloses capturing the mRNAs from the whole tissue section, all at the same time, and thus discloses "collecting" the mRNAs from a first and second location "simultaneously," as claimed in claim 12. EX1005, ¶[00144]; EX1044, ¶249. 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 mRNAs when the "mRNA molecules are *captured onto the array* by hybridization of the 3'-end of the mRNA to gene-specific regions on the first capture probe." EX1005, ¶[00308]; EX1044, ¶249; *see also* EX1005, ¶[00315] ("mRNA molecule 2510 is captured at capture site 105 by hybridization of the 3' end of mRNA molecule 2510 to capture region 2335a."). Accordingly, So-456 anticipates claim 12.

### K. Claim 13

Claim 13 depends from claim 1 and requires that synthesizing "steps (c) and (d)" "are performed simultaneously." EX1043, 148:61-62. So-456 discloses this limitation. EX1044, ¶¶250-251.

So-456 specifies simultaneously synthesizing by disclosing that the capture probes are used as primers for "synthesis of first strand cDNA *from captured mRNA molecules*" that are "captured onto the array." EX1005, ¶¶[00308]-[00309]; *see also id.*, ¶[00109]; EX1044, ¶251. So-456 further specifies that the spatial address region "can be *encoded in the nucleic acid* in the process of preparing the nucleic acid for sequencing." EX1005, ¶[0089]; EX1044, ¶251. Thus, So-456's method performs the synthesizing steps (c) and (d) at multiple capture sites on the array. Accordingly, So-456 anticipates claim 13.

In sum, So-456 teaches every limitation of claims 1-13 under NanoString's interpretation, arranged as claimed. Accordingly, So-456 anticipates claims 1-13.

## XIII. GROUND 5: CLAIMS 1-13 WOULD HAVE BEEN OBVIOUS OVER SO-456

To the extent NanoString argues that So-456 does not expressly teach all the elements of claims 1-13, So-456 indisputably suggests practicing the claimed methods according to NanoString's interpretation for the reasons discussed in Ground 4, and it provides a motivation with a reasonable expectation of success in so doing. EX1044, ¶¶253-256; *Beckson Marine*, 292 F.3d at 727; *See* Section XII.

A POSA reading So-456 would have been motivated to practice the claimed methods because, e.g., So-456 teaches a "*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], [00307]-[00320], FIGs. 2, 24-25; EX1044, ¶254. So-456 discloses that its methods "enable the characterization of transcriptomes and/or genomic variations in tissues while preserving spatial information about the tissue." EX1005, Abstract; see also EX1005, ¶¶[0002], [0085], [0088]; EX1044, ¶254. A POSA would have had a reasonable expectation of successfully practicing the claimed methods, because So-456 provides detailed descriptions and protocols. *See, e.g.,* EX1005, ¶¶[0034]-[0035], [00109], [00141]-[00143], [00151]-[00158], [00307]-[00320], FIGs. 1, 2, 24-25; EX1044, ¶255. Moreover, a POSA reading So-456 would have known that they could practice So-456's methods using standard laboratory materials and reagents, needing only ordinary skill, which would have further bolstered the expectation of success. *Id*., *see also* EX1042, 1:61-2:9, 3:11-34, 17:37-18:59, 24:21-25:32, 25:48-62, 26:19-47; EX1049, Abstract, ¶¶[0013], [0015], [0084]-[0086], [0089]-[0093], [0101], [0104], FIG. 1.

NanoString did not assert any objective indicia during prosecution (EX1014, 249, 467; EX1004, 253-272, 469-477; EX1012, 1550-1554), nor is 10x aware of any objective indicia that share a nexus with the challenged claims. Accordingly,

under NanoString's interpretation, claims 1-13 would have been obvious over So-456. EX1044, ¶¶253-256.

## XIV. 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. Neither Stahl nor So-456 were previously presented to the Office by the Applicant or ever considered by the Examiner. EX1014, 205-213, 217, 224-229, 237-245, 250, 259, 458-466, 472, 485, 494-500, 506-507; 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, although Frisen was cited in an Information Disclosure Statement during prosecution, the Examiner never considered the Stahl and Frisen combination, as applied in the Petition. EX1014, 224-229, 458-466, 494-500; EX1004, 222-235, 493-503; EX1012, 1517-1532, 2436-2456. In fact, the Office did not raise any prior art rejections during prosecution of the 142 patent or its parent or sibling application. *Id.* 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 142 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 142 patent is currently projected to be December 9, 2024—approximately four months before a Final Written Decision would be reached in this IPR. *See* EX1023. Thus, much of the substantive briefing and discovery 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.

## XV. 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 142 patent was asserted in *NanoString Technologies, Inc. v. 10x Genomics, Inc.*, Case No. 1:22-cv-01375 (D. Del.).

U.S. Patent No. 11,377,689, a sibling to the 142 patent, is the subject of the same district court litigation (Case No. 1:22-cv-01375) after it was severed from Case No. 1:22-cv-00261. The 689 patent is also the subject of pending *inter partes* review, *10x Genomics, Inc. v. NanoString Technologies, Inc.*, IPR2023-01298, filed on August 16, 2023.

**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).

## XVI. CONCLUSION

Claims 1-13 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 13,202 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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Case IPR2023-01300
U.S. Patent No. 11,473,142

**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. 11,473,142** and associated Exhibits 1003-1007, 1009, 1012-1019, 1022-1030, and 1038-1050 were served in their entireties upon the Patent Owner on September 25, 2023, via FedEx® Express at the following address:

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**Certificate of Service**

I, Sophie Rogers Churchill, certify that I am not less than 18 years of age, and that notice of the foregoing ***Motion of 10x Genomics, Inc. for Entry of an Order (I) Modifying the Automatic Stay with Respect to the 653 Action and the IPR Proceedings and (II) Granting Related Relief*** was caused to be served on February 22, 2024, by email and CM/ECF service where available and first class mail otherwise, on (i) the parties listed on **Exhibit A** and (ii) the parties entitled to notice pursuant to Bankruptcy Rule 2002, as reflected on **Exhibit B**.

Date: February 22, 2024

*/s/ Sophie Rogers Churchill*
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**Exhibit B**

**In re: NanoString Technologies, Inc., *et al.***
Core/2002 Service List
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**In re: NanoString Technologies, Inc., *et al.***
Core/2002 Service List
Case No. 24-10160 (CTG)

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