

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

10X GENOMICS, INC. and PRESIDENT AND
FELLOWS OF HARVARD COLLEGE,

*Plaintiffs, Counterclaim
Defendant,*

v.

NANOSTRING TECHNOLOGIES, INC.,

*Defendant, Counterclaim
Plaintiff.*

C.A. No. 22-261-MFK

NANOSTRING TECHNOLOGIES, INC.,

*Plaintiff, Counterclaim
Defendant,*

v.

10X GENOMICS, INC.,

*Defendant, Counterclaim
Plaintiff.*

C.A. No. 22-1375-MFK

10X GENOMICS, INC. and PRESIDENT AND
FELLOWS OF HARVARD COLLEGE,

*Plaintiffs, Counterclaim
Defendant as to certain claims,*

v.

VIZGEN, INC.,

*Defendant, Counterclaim
Plaintiff.*

C.A. No. 22-595-MFK

JOINT CLAIM CONSTRUCTION BRIEF

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X3	U.S. Patent No. 11,473,142 ("142 Patent")	A0165-A0282
X4	Merritt, C.R., Ong, G.T., Church, S.E. et al. "Multiplex digital spatial profiling of proteins and RNA in fixed tissue," <i>Nat Biotechnol</i> 38, 586–599 (2020). https://doi.org/10.1038/s41587-020-0472-9	A0283-A0305
X5	Beechem, J.M. (2020). "High-Plex Spatially Resolved RNA and Protein Detection Using Digital Spatial Profiling: A Technology Designed for Immuno-oncology Biomarker Discovery and Translational Research," In: Thurin, M., Cesano, A., Marincola, F. (eds) <i>Biomarkers for Immunotherapy of Cancer. Methods in Molecular Biology</i> , vol 2055. Humana, New York, NY. https://doi.org/10.1007/978-1-4939-9773-2_25	A0306-A0327
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X15	Ji et al., "Single Molecule Fluorescent in Situ Hybridization (smFISH) of <i>C. Elegans</i> Worms and Embryos," <i>WormBook</i> (2012):1-16, available at https://www.ncbi.nlm.nih.gov/books/NBK126649/ .	A0702-A0723

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X20	U.S. Patent No. 11,293,052 (052 Patent)	A0903- A0971
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X25	U.S. Patent No. 11,078,520	A1167- A1196
X26	Raj, A., van den Bogaard, P., Rifkin, S. et al. Imaging individual mRNA molecules using multiple singly labeled probes. <i>Nat Methods</i> 5, 877–879 (2008). https://doi.org/10.1038/nmeth.1253 (10X595-00014775-10X595-00014777)	A1197- A1200
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X28	John Eid et al., Real-Time DNA Sequencing from Single Polymerase Molecules. <i>Science</i> 323,133-138(2009). DOI:10.1126/science.1162986	A1207- A1214
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X30	Microsoft Computer Dictionary (5th Ed. 2002) excerpt. https://burmasterrecords.files.wordpress.com/2009/12/microsoft_computer_dictionary_fifth_edition1.pdf	A1228- A1231
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N1	Goransson et al., “A single molecule array for digital targeted molecular analyses,” <i>Nucleic Acids Research</i> , 2009, Vol. 37, No. 1 e7, doi:10.1093/mar/gkn921	A1232- A1241
N2	’054 Patent file history	A1242- A1310

Exhibit	Description	Appx Pages
V1	Shalek and Satija, “MERFISHing for spatial context,” <i>Trends in Immunology</i> , July 2015, Vol. 36, No. 7	A1311- A1313
V2	Excerpt of <i>Merriam-Webster’s Collegiate Dictionary</i> , 11 th Ed. 2003.	A1314- A1317
V3	Excerpt of <i>Dictionary of Science and Technology</i> , 2 nd Ed. 2007.	A1318- A1321
V4	Declaration of Dr. Michael Metzker in Support of Vizgen’s Claim Construction Response Brief	A1322- A1361
V5	U.S. Patent No. 6,391,544	A1362- A1371

I. 10X AND HARVARD ASSERTED PATENTS (261 AND 595 CASES)¹

A. INTRODUCTION

1. Defendants NanoString's and Vizgen's Introduction

Defendants' constructions for the disputed terms in Plaintiffs' asserted patents help explain complex DNA detection technology to a jury and resolve ambiguities in the specifications. NanoString and Vizgen respectfully request that the Court enter the claim constructions below.

a. TOSS Patents

U.S. Patent Nos. 10,227,639 ("639 Patent"), 11,021,737 ("737 Patent"), 11,293,051 ("051 Patent"), 11,293,052 ("052 Patent"), 11,293,054 ("054 Patent"), and 11,549,136 ("136 Patent") are directed to methods for biological analysis using a temporal order of signal signatures ("TOSS"). Accordingly, these patents are referred to as the TOSS Patents.

Many biological molecules such as RNAs and proteins are enriched in regions where they function. Hence, their locations in a tissue section or in cells provide insights into their functions. One traditional approach to investigate the spatial localization of these molecules is to tag each different type of a molecule with a chemical compound that imparts a unique color and then detect the positions of the molecules by imaging the tissue section or the cells. Under this method, each color observed in the image indicates the presence of a specific molecule at that spot. Due to the limited number of distinct color labels, however, the number of molecule species detectable in each assay is limited.

As set forth in Defendants' accompanying technology tutorial, the TOSS Patents purport to overcome this limitation by tagging each molecule species with a unique nucleic acid label,

¹ The parties each complied with their respective page limits (40 cumulative pages for 10x and Harvard's combined briefing and 40 cumulative pages for Vizgen and NanoString's combined briefing). The overall joint brief exceeds 80 pages due to the inclusion of the agreed-upon terms and additional formatting that was necessary when combining the briefs for each of the three cases.

which can then be decoded in a temporally-sequential manner. *E.g.*, '737 patent at 19:49-20:5 (A0800); '639 Patent at 10:27-50 (A0530).² Instead of tagging each molecule directly with a color label, the TOSS Patents purport to tag the molecule with an intermediate nucleic acid label, which can then be decoded by detecting a series of color labels (or “signal signatures”) in a sequence of ordered steps. The temporal series of steps generates a sequential order of signal signatures, which allegedly allows more nucleic acid labels to be decoded (and thus more molecules to be detected) using the same number of color labels.

For example, a traditional assay using 4 color labels (*e.g.*, red (R), green (G), blue (B), yellow (Y)) can only detect 4 different molecules at a time. The TOSS Patents, however, contemplate an assay using 4 color labels and 3 temporal steps that can theoretically detect $4 \times 4 \times 4 = 64$ different molecules in each assay. That is because the combination of color labels and temporal steps gives rise to a larger number of distinct color codes:

GRR, RGR, RRG, ... , RBY, BBY, GBY, YBY, ...

The temporal order of signal signatures as disclosed in the TOSS patents is obtained with the use of a “detection reagent” comprising the unique nucleic acid label and a probe that specifically “binds to said analyte.” *E.g.*, '737 Patent cl. 1 (A0832); '639 Patent cl. 1 (A0577). The distinct color codes are obtained when the predetermined subsequences of the detection reagent’s nucleic acid label are detected in a sequence of ordered steps. For example, the detection reagent of Figure 15 illustrates a detection reagent with a probe that binds to an analyte (such as *C. albicans*) and three pre-determined subsequences that when read (imaged) from 5’ to 3’ give a distinct color code to identify the analyte (*C. albicans*). '737 Patent (Fig. 15) (A0790, 796, 810).

² The '737, '051, '052, and '136 Patents share an identical or substantially identical specification with each other. Further, the '639 and '054 Patents share an identical or substantially identical specification with each other. Defendants cite the '737 patent specification and '639 patent specification for ease.

Though the temporal order of signal signatures lies at the heart of the TOSS Patents, the concept of using a string of symbols to encode a large amount of information is well known in the scientific field. For example, the binary code implemented in nearly all computer systems uses 2 numbers—1 and 0—to encode practically indefinite information. This was also used specifically in the nucleic acid field. For instance, a reference published in 2008 discloses the same scheme as the TOSS Patents wherein a nucleic acid label is decoded using the order of colored labels. *See Ex. N1* at A1239 (Fig. 3). More specifically, the decoding scheme (Fig. 3C) relies on the order of four colors—green (G), red (R), blue (B), and dark (D)—to identify different genomic fragments. *See id.* (as an example, genomic fragment #2 CCNA1 is coded by DBBD whereas genomic fragment #3 DACH is coded by DBDB). Additionally, as acknowledged by the TOSS Patents, methods of decoding the nucleic acid labels by the temporal order of signal signatures are also well known—such as nucleic acid sequencing. *See* '737 Patent at 23:25-55 (A0802); '639 Patent at 14:3-33 (A0532).

b. 767 patent

U.S. Patent No 11,299,767 (“’767 patent”) allegedly covers a “Method for Generating a Three Dimensional Nucleic Acid Containing Matrix,” and discusses creating a “three dimensional matrix” to help detect the locations of nucleic acids. ’767 Patent at 1:51-60 (A1131). The inventors explained that the invention involves amplifying (or copying) nucleic acids into “amplicons” to make many duplicates of each nucleic acid for detection with 3D fluorescence imaging: “[t]he present invention relates to methods of making a three-dimensional matrix of nucleic acids and amplifying, detecting and sequencing such nucleic acids within the matrix.” *Id.* at 1:28-31 (A1131). The inventors further explained that the amplicons “can then be covalently attached to the matrix, for example, by copolymerization or cross-linking. This results in a structurally stable and chemically stable three dimensional matrix of nucleic acids,” wherein

during amplification a functional group is introduced that covalently bonds with the matrix. *Id.* at 2:41-44 (A1131). After this amplification, “[t]he three dimensional nucleic acid amplicon matrix can be repeatedly interrogated using standard probe hybridization and/or fluorescence based sequencing.” *Id.* at 10:64-66 (A1135). In other words, the amplicons allow an observer to visualize nucleic acids within the sample, which are otherwise invisible to the naked eye, and create a mechanism to immobilize the nucleic acids to the matrix.

2. Plaintiffs 10x’s and Harvard’s Introduction³

The asserted Church patents are directed to *in situ* genetic analysis of biological samples (i.e., in cells or tissues).⁴ Dr. Church’s lab at Harvard solved critical problems preventing scientists from performing *in situ* experiments on large numbers of genes simultaneously. One problem was a fundamental limit on the number of distinct targets one could visualize in a tissue sample using fluorescent dyes attached to probes. 639 Patent (**Ex. X13**), 1:51-60 (A0526). It was well known that one could target specific proteins or bits of DNA or RNA in a tissue and see colored spots under a microscope within cells to show the presence of a given gene—but these assays were capped by the number of distinct, detectable colors one could use, and the “blur” from having many colored spots lit up in the same place at the same time. **Ex. X13**, 1:60-67 (A0526).

Dr. Church’s team came up with an ingenious solution. Instead of binding fluorescent probes directly to the targets, the invention used sets of target-specific probes that assigned a multi-part nucleic acid code to each target, where the multi-part code itself was a landing spot for a series

³ Emphasis added, and internal quotes and citations omitted in 10x’s briefs unless otherwise noted.

⁴U.S. Patent Nos. 10,227,639 (639 Patent, **Ex. X13** (A0511-A0579)); 11,021,737 (737 Patent, **Ex. X18** (A0770-A0833)); 11,293,051 (051 Patent, **Ex. X19** (A0834-A0902)); 11,293,052 (052 Patent, **Ex. X20** (A0903-A0971)); 11,293,054 (054 Patent, **Ex. X21** (A0972-A1044)); and 11,549,136 (136 Patent, **Ex. X22** (A1045-A1111)) share a common or substantially similar specification and 11,299,767 (767 Patent, **Ex. X23** (A1112-A1141)) contains a portion of the specification.

of fluorescently-labeled decoder probes. In a given imaging cycle each subsequence could be targeted (or not). By spacing out imaging cycles, and knowing which subsequences corresponded to which colors in a given cycle (including dark when no decoder probe/subsequence binding) the invention constructed a *temporal* sequence of lights at the location of a target that would identify the target in that location. That invention dramatically expanded the number of targets for each assay without requiring more colors—a code using one of several colors or the absence of signal in multiple rounds exponentially increases the number of addressable targets. And looking at only certain subsequences at a time (leaving others dark) minimized the blurring problem.

The first set of patents implements this idea of a temporal order of signals. The claim construction dispute arises because Defendants, in an attempt to create a non-infringement argument, seek to add limitations to the claims that are not necessary or even related to the temporal-order innovation, such as requiring only a single probe “molecule” rather than multiple probes per target, or requiring each probe molecule to contain every piece of the target’s code.

The 767 Patent solved a problem with securing in place the genetic material within a tissue that exists in 3D space. Old methods typically extracted nucleic acids from their native environment or risked moving targets in tissue samples during processing. 767 Patent, 1:41-47 (**Ex. X23**, A1131). The 767 Patent created a way to fix the nucleic acids in place with a 3D matrix of nucleic-acid-binding polymers. With this innovative 3D-matrix approach, the door was opened to using sequencing or imaging approaches to detect cellular nucleic acids. Vizgen seeks to limit the claims to a single type of detection—detecting “amplicons”—that is not required by the specification.

B. AGREED UPON CONSTRUCTIONS IN THE 261 CASE⁵

Claim Terms	Agreed Construction
“temporal order of signal signatures” 737 Patent, claims 1 and 24; 051 Patent, claims 1, 26, and 96; 052 Patent, claims 1 and 26	“a sequence of signal signatures determined in a temporally-sequential manner, i.e., the sequence of signal signatures is progressed through by a number of active operations performed in a temporally-sequential manner”
“decoder probe” 639 Patent, claim 1; 051 Patent, claims 26, 66, 90, 96; 052 Patent, claims 26 and 65; 054 Patent, claims 1 and 17	“an oligonucleotide with a sequence complementary to a pre-determined sequence of the nucleic acid label”
“signal signature” 639 Patent, claim 1; 737 Patent, claims 1, 8, and 24; 051 Patent, claims 1, 26, 66, and 96; 052 Patent, claims 1 and 26; 054 Patent, claims 1, 17, and 18	“a change in, or occurrence of, a response or indicator that is detectable either by observation or instrumentally”

C. DISPUTED CONSTRUCTIONS (Terms Proposed by NanoString and Vizgen in the 261 and 595 Cases)**1. Whether the steps of the method claims must be performed in the order written**

Claim Term⁶	Defendants’ Construction	Plaintiffs’ Construction
Whether the steps of the method claims must be performed in the order written	Claim steps must be performed in the order written	Not all of the claimed method steps must be performed in the order written
TOSS patents method claims		

a. Defendants NanoString’s and Vizgen’s Opening Position

The parties dispute whether the steps of the method claims must be performed in the order written (Defendants’ position) or whether only some of the claimed method steps must be

⁵ D.I. 164-1 at 8-10 (261 Case); D.I. 55-1 (1375 Case); D.I. 203-1 (595 Case).

⁶ D.I. 164-1 at 6-8 (261 Case); D.I. 55-1 (1375 Case); D.I. 203-1 (595 Case).

performed in the order written (Plaintiffs' position). Notably, Plaintiffs do not identify which specific steps must be performed in the order written and which need not be.

Method claims must be construed to require that the steps be performed in the order written where "the claim language, as a matter of logic or grammar, requires that the steps be performed in the order written, or the specification directly or implicitly requires the order of steps." *Mformation Techs., Inc. v. Research In Motion Ltd.*, 764 F.3d 1392, 1398 (Fed. Cir. 2014) (quoting *TALtech Ltd. v. Esquel Apparel, Inc.*, 279 F. App'x 974, 978 (Fed. Cir. 2008)). Order may also be required where the claim implicitly requires order, such as when "a claimed step refers to the completed results of the prior step." *Kaneka Corp. v. Xiamen Kingdomway Group Co.*, 790 F.3d 1298, 1306 (Fed. Cir. 2015); *see also E-Pass Techs., Inc. v. 3Com Corp.*, 473 F.3d 1213, 1222 (Fed. Cir. 2007) ("Substantively, because the language of most of the steps of its method claim refer to the completed results of the prior step, [the plaintiff] must show that all of those steps were performed in order."). As documented below, the claims, specification, and file history all uniformly confirm that the claim steps must be performed in the order written.

The Claim Language. First, and most important, the method claims of the TOSS Patents all require, as a matter of logic or grammar, that the steps be performed in the order written. For example, claim 1 of the '639 patent (upon which asserted claim 20 depends), requires, in step (b), that an analyte is immobilized in the sample and a probe is coupled to said analyte, wherein the probe targeting the analyte, as part of the detection reagent, contacts the sample in step (a). *See* '639 Patent cl. 1 (A0577). Furthermore, in step (b), hybridizing a first decoder probe, and detecting a first signal signature, followed by hybridizing a second decoder probe and detecting a second signal signature, results in "provid[ing] a set of signal signatures." *Id.* Then, in step (c), the "set of signal signatures" is compared to identify the analyte. *Id.*

Thus, as written, step (c) requires the results of step (b), and step (b) requires the results of step (a). Critically, all of the asserted claims include a parallel structure wherein the results of previous steps are prerequisites for later claim steps. *See, e.g.*, '737 Patent cls. 1, 24 (A0832-833); '051 Patent cls. 1, 26 (A0898-899); '052 Patent cls. 1, 26 (A0967-969); '054 Patent cl. 1 (A1043); '136 Patent cls. 1, 24 (A1110-1111). When the steps of a method claim refer to the completed results of prior steps, this establishes that claim steps must be performed in the order written. *See, e.g., E-Pass*, 473 F.3d at 1222; *see also Mantech Envtl. v. Hudson Envtl. Servs.*, 152 F.3d 1368, 1376 (Fed. Cir. 1998) (“the sequential nature of the claim steps is apparent from the plain meaning of the claim language”).

Yet additional evidence in the claims confirms that the steps must be performed in the order written. For instance, claim 17 of the '054 patent (from which asserted claim 18 depends), requires “prior to coupling said second decoder probe to said second subsequence, removing said first signal signature,” making clear that the order of the “first” and “second” coupling and detecting steps are important. '054 Patent cl. 17 (A1043). As another example, claim 1 of the '737 patent specifies that the detecting step is “detecting a temporal order of the signal signatures,” wherein “said temporal order of signal signatures is associated with said one or more pre-determined subsequences” and wherein the “temporal order of signal signatures” is used to identify the analyte. '737 Patent cl. 1 (A0832). Numerous other claims include the express “temporal order” requirement. *See* '737 Patent cl. 24 (A0833); '051 Patent cls. 1, 26 (A0898-899); '052 Patent cls. 1, 26 (A0967-969); '136 Patent cl. 24 (A1111).

As yet another example, claim 1 of the '639 patent uses the terms “first” and “second” to describe decoder probes and signal signatures in steps (b)(i) to (b)(iv), further confirming that the claim steps must be performed in the order required. Consistent with this, claim 4 of the '639

patent, which depends from claim 1, requires that “prior to hybridizing said second decoder probe with said second subsequence, removing said first signal signature,” a limitation that makes no sense unless the steps are considered to be in order and the first signal signature of step (b)(ii) is formed prior to hybridizing said second decoder probe of step b(iii). As explained below, the specification further teaches that *temporal* ordering is the key distinction of the alleged inventions over the prior art, leaving no doubt that the terms “first” and “second” in claim 1 of the ’639 patent are intended to impose a temporal order requirement.

The Specification. While the logic and grammar of the claims alone establishes that the method steps be performed in the claimed order, the specifications cement this by emphasizing throughout that detecting in a “temporally sequential manner” and the “temporal order of the signal signatures” is key to the invention. *See, e.g.*, ’639 patent at 2:58-3:5; 3:41-43; 3:60-63 (A0526-527); ’737 patent at 4:31-45; 5:12-14, 31-34 (A0792-793). Most important, the specifications single out detection in a temporally sequential manner as the key improvement that distinguishes the alleged inventions over the prior art. Specifically, the patents contrast the alleged inventions with “general nanostring technology,” which is based on the “spatial location of signals” and that “require[s] at least a plurality of optical labels to be detected simultaneously.” ’639 patent at 7:58-8:5 (A0529); ’737 patent at 9:31-43 (A0795). The specifications state that the “previous methods do not involve detection of signatures *in a temporally-sequential manner* as described herein.” ’639 patent at 8:5-7 (A0529); ’737 patent at 9:45-47 (A0795).⁷ The specifications criticize the “previous methods” using spatial detection as opposed to temporal detection as requiring high optical magnification and a thorough control of the amount of probes used in detection. ’639 patent at 8:7-22 (A0529); ’737 patent at 9:47-62 (A0795). The patents further conclude that “because

⁷ All emphasis in Defendants’ sections added unless otherwise noted.

the detection reagents described herein *are detected and/or imaged in a temporal series of steps*, the number of probes (and corresponding analytes) that can be detected in a multiplex assay grows multiplicatively with the number of detection steps in a time series and the number of optical labels being used.” ’639 patent at 10:44-48 (A0530); ’737 patent at 19:64-20:2 (A0800).

The Federal Circuit has repeatedly held that such statements distinguishing the prior art reflect a disclaimer that limits claim scope. *See, e.g., Retractable Technologies, Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011) (limiting the claims to syringes having a one-piece body because in “distinguishing prior art syringes comprised of multiple pieces, the specifications state that the prior art had failed to recognize a retractable syringe that ‘can be molded as one piece outer body’”); *Poly-Am., L.P. v. API Indus., Inc.*, 839 F.3d 1131, 1136 (Fed. Cir. 2016) (“Similarly, an inventor may disavow claims lacking a particular feature when the specification distinguishes or disparages prior art based on the absence of that feature.”); *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1343–44 (Fed. Cir. 2005) (“[I]t would be peculiar for the claims to cover prior art that suffers from precisely the same problems that the specification focuses on solving.”); *Donghee Am., Inc. v. Plastic Omnium Advanced Innovation & Research*, 2020 WL 2214215, at *2-*3 (Fed. Cir. 2020) (approving ordered construction where inventor distinguished prior art that allowed for or required a different order).

It is unsurprising that the patents distinguish the alleged inventions from the prior art on the basis of temporal detection because that is the singular focus of the patents. The specifications of the ’639 and ’737 patents use the term “temporal” or “temporally” *sixty-one* times, explaining over and over that temporal detection is the basis for the alleged inventions function.⁸ The

⁸ *See, e.g.,* ’639 patent at 2:61-63 (A0526) (“*detecting in a temporally-sequential manner* said plurality of the pre-determined subsequences of said detection reagents”), 2:66-3:2 (A0526-527) (“wherein a *temporal order of the signal signatures* corresponding to said plurality of the

examples in the patents likewise confirm the focus on the temporal aspects of the invention. Figure 1 of the '639 Patent, for instance, depicts “the temporal sequence of optical images or spot-readings” obtained in accordance with embodiments of the patents. '639 Patent at Fig. 1, 8:26-37 (A0529); *see also* '737 Patent at Fig. 3, 10:11-23 (A0795). Specifically, the sequencing readouts for anti-*E.coli* and anti-*S. aureus* contain the same three readings. The sole difference between the two readouts is the order (*i.e.*, temporal sequence) of the readings through cycle 1 to cycle 3. To obtain the temporal sequence, it is imperative that the method steps are performed in the claimed order. The importance of temporal order is demonstrated throughout the patent. *See, e.g.*, '639 Patent at Fig. 2, 8:38-50 (A0521, 529) (“the temporal sequence of optical images or spot-readings can then be computationally analyzed to determine the identity of the corresponding probe reagent”); Fig. 8, 9:35-43 (A0521, 530) (“This microarray was then exposed to **a sequence of fluorescently labeled detection probes and displacement oligonucleotides**, as per displacement-hybridization readout. Imaging the array after each readout step demonstrated fluorescence corresponding to the expected pattern (shown next to each image)”); Fig. 9, 9:44-56 (A0522, 530) (“[a]s the readout progresses, fluorescence from prior readout steps needs [to] be removed so as

subsequences of said detection reagent identifies a subpopulation of the detection reagents”), 3:17-20 (A0527) (“**before detection of the pre-determined subsequences in a temporally-sequential manner**”), 3:21-23 (A0527) (“the method can further **comprise comparing the temporal order of the signal signatures** with different identifiers of said at least one probe reagent”), 3:41-43 (A0527) (“**detected in a temporally-sequential manner**”), 3:60-63 (A0527) (“repeating steps (a) through (c) for other subsequences of said detection reagents, thereby **producing a temporal order of the signal signatures** corresponding to said each detection reagent”), 13:13-16 (A0532) (“**detected in a temporally-sequential manner**”), 13:14-20 (A0532) (“The term “temporally-sequential manner” is used in reference to **detecting or decoding in a time series** a plurality of the pre-determined subsequences”), 11:23-29 (A0531) (“As used herein, the term “temporal order of the signal signatures” refers to a sequence of signal signatures **determined in a temporally-sequential manner**, *i.e.*, the sequence of signal signatures is progressed through by a number of active operations **performed in a temporally-sequential manner**, *e.g.*, using a different set of decoding reagents or decoder probes in each active operation.”); '737 patent at 4:34-36, 4:39-41, 4:56-59, 4:60-62, 5:12-14, 5:31-34, 22:35-38, 22:38-42, 20:44-50 (A0792-793, A0801, A0800).

not to obstruct the current step's signal"); '737 Patent at Fig. 4, 10:24-37 (A0780, 795), Fig. 10, 11:21-29, Fig. 11, 11:30-42 (A0786, 796, 787, 796).

Where, as here, a specification teaches only one approach, the claims should be construed accordingly. *Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc.*, 554 F.3d 1010, 1019 (Fed. Cir. 2009) (limiting the term "wound" to "skin wound," rather than allowing it to encompass "pus pockets," where all of the examples in the specification involved skin wounds); *Hologic, Inc. v. SenoRx, Inc.*, 639 F.3d 1329, 1335 (Fed. Cir. 2011); *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1375 (Fed. Cir. 2009).

The File History. The prosecution history further confirms that the claim steps must be performed in the order as written. In an Office Action dated August 3, 2020, the Examiner of the application that became the '054 Patent, for instance, laid out the interpretation of the claim language, stating specifically that the "parts of the second step are interpreted as being performed in the order they are recited in view of the instant specification, which describes an ordered and sequential detection of signals to generate a signature or pattern of signals that can be processed in order to identify the analyte." **Ex. N2** ('054 Patent file history) at 10XH-00003531 (A1250); *see also id.* at 10XH-00003530-3532 (A1249-1251) (providing the Examiner's complete rationale regarding ordering of the claim steps). This characterization was not contested. *Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1096 (Fed. Cir. 2013) (affirming construction where applicants did not "challenge an examiner's characterization").

Consistent with the foregoing, in each Notice of Allowance issued in the '054 patent, the Examiner reiterates the interpretation of the claims that requires the steps to be performed in order. *See, e.g., Ex. N2* ('054 Patent file history) at 10XH-00003666-3668, 3723-3725, 3824-3826, 3882-3885, 3970-3974 (A1262-1264, 1272-1274, 1294-1297, 1305-1309). This further supports

Defendants’ construction. *See Arendi S.A.R.L. v. Google LLC*, 882 F.3d 1132, 1136 (Fed. Cir. 2018) (limiting claims based on prosecution history where “Reasons for Allowance” made clear the scope of the invention).

For these reasons, Defendants’ construction should be adopted.

b. Plaintiffs 10x’s and Harvard’s Answering Position

The parties dispute whether the structure of certain claims permits method steps to be performed in a variety of orders, consistent with the default rule for method claims (Plaintiffs) or whether all claims are limited to performance in a single order (Defendants). “[A]s a general rule the claim is not limited to performance of the steps in the order recited, unless the claim explicitly or implicitly requires a specific order.” *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1345 (Fed. Cir. 2008). “First, we look to the claim language to determine if, as a matter of logic or grammar, they must be performed in the order written.” *Altiris, Inc. v. Symantec Corp.*, 318 F.3d 1363, 1369 (Fed. Cir. 2003). “If not, we next look to the rest of the specification to determine whether it ‘directly or implicitly requires such a narrow construction.’” *Id.* at 1370. Neither grammar, logic, nor the specification impose such a requirement here, and where any ordering is required, it is clear such that a jury could readily discern the order from the claim language.

Instead of applying the test to the specific steps of each claim, Defendants broadly assert that this test compels *every* step in every claim (including 11 independent claims) be performed in the order written because the claims relate to “a temporal order of signal signatures,” and all claims have a “parallel structure.” Br. 7-8. Defendants largely ignore that the claims recite different limitations, and for the specific claim steps they do address, Defendants simply recite claim limitations and state they compel an order without meaningful explanation. Br. 7-9. There is no discussion of the claim language of the 136 Patent (other than an identification of the claims (Br.

7-8)).⁹ Likewise, rather than analyze each claim, Defendants point to certain steps in certain claims of the 639 and 054 Patents and assert that those particular steps lead to the conclusion that every step in every claim of six different patents must be performed in the order stated.

The claim language of the six patents does not compel that result. For instance, the 051, 052, and 136 Patent claims make clear that readout cycles are independent events that do not need to be performed in the order written. A contrary reading is at odds with grammar, logic, and the specification. The 052 patent is illustrative of the problems with Defendants' proposal:

1. (b) performing three or more readout cycles to generate said temporal order of signal signatures, wherein said three or more readout cycles comprise:

(i) **a first readout cycle**, comprising: (1) imaging said biological sample and detecting a *first optical signal* at said location, . . . thereby obtaining **a first** signal signature of said temporal order of signal signatures, . . .

(ii) **a second readout cycle**, comprising imaging said biological sample and detecting an *absence of an optical signal* at said location, thereby obtaining **a second** signal signature of said temporal order of signal signatures

(iii) **a third readout cycle**, comprising imaging said biological sample and detecting a *second optical signal* at said location, . . . thereby obtaining **a third** signal signature of said temporal order of signal signatures. **Ex. X20** (052 Patent), Claim 1 (A0967-968).

These readout cycles are independent cycles that do not need to be performed in the order stated.

The absence of an optical signal (the claimed "second readout cycle") can occur before the detection of a first optical signal or after the detection of a second optical signal. Defendants are attempting to rewrite the claim from "first readout cycle" to "first in time readout cycle." But there is no support for importing those additional limitations into the claim because the performance of the readout cycles *in any order* will still generate a temporal order of signal signatures.

Unlike the cases where an order of steps is required, all the steps of the claims here do not rely upon completion or a product of the former steps. The claimed second readout cycle (which

⁹ Nor did Vizgen previously identify the 136 claims as requiring a specific order (D.I. 164-2 (261 Case); D.I. 55-2 (1375 Case); D.I. 203-2 (595 Case)).

is a cycle that detects an absence of a signal) does not refer back to the first readout cycle, nor does it depend on a product of the first cycle. It can occur before or after the first optical signal is detected. Defendants do not explain how the cases relied upon apply to the method and claim language here. For example, in *E-Pass Techs., Inc. v. 3Com Corp.*, the court relied on logic and grammar that showed each active step was referred to in a subsequent step in past form indicating that the action had been completed (e.g., “transferring a data set” followed by “storing *said transferred* data set”). 473 F.3d 1213, 1222 (Fed. Cir. 2007). Likewise, the court in *Mantech* relied on steps requiring a product of the previous step. *See Mantech Envtl. Corp. v. Hudson Envtl. Servs.*, 152 F.3d 1368, 1376 (Fed. Cir. 1998) (adding acetic acid into water necessarily had to precede step requiring introducing iron “for mixing with *said acidified groundwater*.”). The latter step in these cases relied upon completion or a product of the former, making the latter dependent upon it. Here, the second cycle (and all cycles) are independent sets of events independent of other cycles. Temporal order requires “an order” of signal signatures, but the signal of any subsequence is independent of any signal in another cycle, and different analytes will have different orders.

Further, Defendants also rely on “first” and “second” (Br. 8-9) but do not explain why the claim language here compels a written order when “first” denotes an instance and not an order. Defendants have cited no case supporting the conclusion that the use of the term “first” should be construed as “first in time.” To the contrary, courts have found that the use of “first” “second” and “third” is a commonly used convention to distinguish between repeated instances of an element or limitation. *See 3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1371 (Fed. Cir. 2003) (“The use of the terms ‘first’ and ‘second’ is a common patent-law convention to distinguish between repeated instances of an element or limitation.”); *Hitachi Consumer Elecs. Co. v. Top Victory Elecs. (Taiwan) Co.*, No. 2:10-CV-260-JRG, 2012 U.S. Dist. LEXIS 162106, at *126 (E.D.

Tex. Nov. 13, 2012) (“The use of ‘second’ and ‘third’ in the claim does not refer to an order of steps but rather merely distinguishes between multiple instances of signal processing.”). The use of “first” and “second” indicate that for any one analyte, the steps for that one cycle are happening at a different time than another cycle for that analyte, but that does not require each **cycle** of events be performed in any written order or exclude simultaneous events occurring for other analytes. The claim language (“a” “[first/second] signal signature”) reflects that first/second are used to show instances of readout cycles and not the specific ordering.

The dependent claims of the 052 Patent confirm that an ordering is not required. Claims 25 and 31 specify when the rounds are performed in sequential order (claim 25 (A0968)) or when they are limited to performance in any order (claim 31 (A0969)). Requiring order would render claim 25 superfluous *See Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1380 (Fed. Cir. 2006) (“[R]eading an additional limitation from a dependent claim into an independent claim would not only make that additional limitation superfluous, it might render the dependent claim invalid.”); *Versa Corp. v. Ag-Bag Int’l Ltd.*, 392 F.3d 1325, 1330 (Fed. Cir. 2004) (“The doctrine of claim differentiation ‘creates a presumption that each claim in a patent has a different scope.’”). Claim 31 would also have a broader scope than independent claim 1, contrary to established law. *See Alcon Research, LTD. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) (“It is axiomatic that a dependent claim cannot be broader than the claim from which it depends.”).

Defendants rely heavily on “temporal order,” but this is a red herring.¹⁰ The parties agree “temporal order of signal signatures” means “a sequence of signal signatures determined in a

¹⁰ Defendants also assert that temporal order forecloses “a plurality of optical labels to be detected simultaneously” based on patentee’s distinguishing prior art methods. Br. 9. This is wrong. The specification contrasted prior art methods where detection was based on one resulting color from different ratios of colors bound to a probe that was detected in only **one detection step** with the claimed invention’s multiple rounds of color detection (including mixtures of colors (**Ex. X19**, 44:56-63 (A0878))). Whether the claim steps needed to be performed in order was not at issue.

temporally-sequential manner, i.e., the sequence of signal signatures is progressed through by a number of active operations performed in a temporally-sequential manner” (D.I. 164-1, 261 Case), but this does not require that every step of every claim be performed in the order written. It means that signals are detected in separate imaging cycles (as opposed to one detection step). It does not mean imaging cycles need to be performed in written order. Moreover, that *some* steps of a claim must be performed in a certain order does not mean *all* steps must be performed in the stated order. *Baldwin* 512 F.3d at 1509 (finding only certain claim steps were required to be performed in order).

The specification further confirms that performance of claim steps in the order as written is not required. For purposes of the subsequences, “no-color” is an additional color. *See, e.g., Ex. X19*, 051 Patent, 29:32-34 (A0871) (“Examples of optical signatures can include, without limitations, signatures of fluorescent color, visible light, no-color, and any combinations thereof.”). No-color provides an additional signature that allows for increased multiplexing (increased number of analytes and/or number of readout cycles). The patent is agnostic as to whether each signal signature is color or no-color when describing the relationship between subsequences, color, and detectable probe molecules. 33:45-55; 37:19-67 (A0873, 875). To have a specified signal at a specific cycle would decrease the number of detectable analytes and/or the accuracy of the assay.

Further evidence that “first” and “second” do not compel the 052 steps be performed in the order as written is that these are comprising claims which “indicates that the claim is open-ended and allows for additional steps.” *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003). *See Kaneka*, 790 F.3d at 1306 (“We disagree that the claimed order excludes passive oxidation during other process steps. The claims’ preamble term ‘comprises’ indicates that additional oxidation steps or results are not excluded.”). Comprising allows for additional unrecited steps and cycles, and at a given moment in time, different cycles can occur across

different analytes¹¹. The claim language of the “comprising” claims confirms that additional steps and cycles are contemplated¹². *See, e.g., Ex. X20*, claim 1 (A0967-68) (“three *or more* readout cycles”); claim 4 (A0968) (“*prior to said imaging of (b)(i)(1)*, using a first decoder probe”); claim 54 (A0970) (a fourth readout cycle). The claims are not limited to the number of cycles as written or the number of times *a set* of cycles is repeated. The claims are not limited to the number of times a temporal order is identified (e.g., *Ex. X19*, claims 1(e) and 26(d) (A0898-899)). “Comprising” allows for additional steps, including unidentified steps or repetitions of steps.

Further, because multiple analytes are analyzed simultaneously and decoder probes do not bind every analyte in every cycle, what is characterized as a first or second cycle will happen for different analytes at the same time. Claim 24 of the 136 Patent (*Ex. X22*, A111) includes a first readout cycle with a first decoder probe and a second readout cycle with a second decoder probe. But because not every detection reagent will have a decoder probe bind, a “second” decoder probe may bind to one analyte at the same time that its “first” decoder probe binds to another analyte. The claims as written do not foreclose steps from overlapping in time. *See Kaneka*, 790 F.3d at 1307 (“The claims do not exclude a process in which every claim step is occurring simultaneously.”); *Bio-Rad Labs., Inc. v. 10X Genomics, Inc.*, 496 F. Supp. 3d 563, 574 (D. Mass. 2020) (“But to say the steps must occur in a specific order is not to say that the claim ‘does not permit simultaneous performance.’”).

¹¹ Defendants do not seem to dispute that multiple analytes are analyzed at the same time and rely on examples in the patent that include more than one analyte. *See, e.g., Br. 10-11* (discussing figure 3 and how the temporal order of two analytes differ). Further, the 051 patent states “plurality of [analytes/nucleic acids]” (claims 1 and 26) (*Ex. X19*, A0898-899) and the patent is directed to “a method for detecting a plurality of analytes in a sample.” 4:7-8 (A0858). And “an indefinite article ‘a’ or ‘an’ in patent parlance carries the meaning of ‘one or more’ in open-ended claims.” *Baldwin*, 512 F.3d at 1342.

¹² Defendants do not seem to dispute this as they rely on performance of steps in dependent claims. *See, e.g., Br. 8-9* (relying on the removal step in claim 4 of the 639 patent).

Defendants rely on patentee's silence as to the Examiner's statements about the required ordering of the sub-parts of step 1 (b) of the 054 Patent. Courts are hesitant to place much reliance on silence that occurs during prosecution. *Salazar v. Procter & Gamble Co.*, 414 F.3d 1342, 1345 (Fed. Cir. 2005) (“[A]n applicant's silence regarding statements made by the examiner during prosecution, without more, cannot amount to a ‘clear and unmistakable disavowal’ of claim scope.”). At most, the statement is relevant to certain 054 steps, not every step of every claim.

c. Defendants NanoString's and Vizgen's Reply Position

10x does not dispute that the TOSS Patent claim steps must be performed in the order written. For example, 10x does not dispute that claim 1 of the '052 Patent requires that claim limitations (a)-(c) are performed in the order prescribed in the claim. Br. 13-17. Likewise, 10x admits that temporal order of signal signatures “means that signals are detected in separate imaging cycles (as opposed to one detection step).” *Id.* at 17. 10x thus cannot dispute that the readout cycles must be performed *sequentially*. *Id.* at 13-17. 10x nonetheless argues that the readout cycles need not be performed in the order as written in the claims. 10x's arguments fail for several reasons, including that it does not and cannot explain how a temporal order of signal signatures can be generated without performing the readout cycles in the order as written in the claims.

First, the claim language contradicts 10x's position. 10x emphasizes claim 1(b) of the '052 Patent and its reference to three readout cycles. *Id.* at 14. 10x, however, ignores that those readout cycles are performed to generate a “*temporal order* of signal signatures.” *Id.* The parties have adopted the definition of this term from the specification—“a sequence of signal signatures determined in a *temporally-sequential manner*, i.e., the sequence of signal signatures is progressed through by a number of active operations performed in a *temporally-sequential manner*.” C.A. No. 22-261, D.I. 164, Ex. A. To obtain a temporal order of signal signatures, the readout cycles must be performed in a temporally-sequential manner. Hence, contrary to 10x's

arguments, the “first readout cycle” indeed should mean “first *in time* readout cycle” because the temporal character is an essential element of the claims.

Second, the specification contradicts 10x’s position. As explained in Defendants’ Opening Brief, the TOSS Patent specification characterizes the temporally sequential manner as the key element of the invention. Br. 9-12. Particularly, the specification disparages NanoString’s technology that is “based on detection of spatial location of signals, rather than temporal detection of signals.” ’639 Patent at 8:7-10 (A0529); *see also id.* at 7:58-8:22 (A0529). Accordingly, 10x does not contest that the readout cycles must be performed in separate steps as opposed to one detection step.

10x’s reliance on cases purportedly finding that “the use of ‘first’ ‘second’ and ‘third’ is a commonly used convention to distinguish between repeated instances of an element or limitation” is misplaced. Br. 17-18. In contrast to the claims at issue that expressly recite the temporal order as an essential element, the *3M Innovative* and *Hitachi* opinions involve claims directed to “the structural relationship between the embossing patterns” and “multiple instances of signal processing,” respectively. *3M Innovative Properties Co.*, 350 F.3d at 1371; *Hitachi Consumer Elecs. Co.*, 2012 WL 5494087, at *47. Hence, the use of “first,” “second,” and “third” in the TOSS Patent claims refers to the order of the readout cycles.

Third, the file history contradicts 10x’s position. For example, as explained in Defendants’ Opening Brief, the Examiner specifically found in each of its Office Actions issued in the ’054 Patent that the “parts of the second step are interpreted as being performed in the order they are recited in view of the instant specification, which describes an ordered and sequential detection of signals to generate a signature or pattern of signals that can be processed in order to identify the analyte.” **Ex. N2** at 10XH-00003531, 10XH-00003667 (A1250, 1263). 10x argues that “the

statement is relevant to certain 054 steps, not every step of every claim.” Br. 19. But there is no dispute that Claim 1(b) of the ’054 Patent has the *exact same structure* as, and is representative of, the other TOSS Patent claims.

Moreover, 10x argues dependent claims 25 and 31 of the ’052 Patent confirm that an ordering is not required by invoking claim differentiation. Br. 16. “Claim differentiation, however, ‘is not a hard and fast rule, and the presumption can be overcome by a contrary construction required by the specification or prosecution history.’” *Sprint Commc’ns Co. LP v. Charter Commc’ns, Inc.*, 2019 WL 7037656, at *3 (D. Del. Dec. 20, 2019) (citation omitted). 10x’s arguments with regard to “no-color” and “comprising” are also merely a red herring. Br. 17-18. Defendants did not contend one way or the other that “no-color” is excluded from the claims at issue. Nor did Defendants argue the readout cycles are limited to those expressly recited in the claim language despite the use of “comprising” claims.

2. “detection reagent”

Claim Term ¹³	Defendants’ Construction	Plaintiffs’ Construction
“detection reagent” ’639 patent claim 1 ’737 patent claims 1, 23, 24, 48 ’051 patent claims 1, 26, 43, 48, 80, 85, 89, 90, 96 ’052 patent claims 1, 16, 26 ’054 patent claim 1 ’136 patent claims 1, 24, 27, 28	“a molecule comprising a probe conjugated to a nucleic acid label comprising one or more pre-determined subsequences such that each nucleic acid label identifies said probe and its corresponding analyte”	No construction necessary – plain and ordinary meaning

a. Defendants NanoString’s and Vizgen’s Opening Position

Plaintiff offers no construction for this term, whereas Defendants’ construction accurately captures what the inventors purport to have invented, and what the TOSS Patents claim and disclose. *See, e.g., Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (“The

¹³ D.I. 164-1 at 4-6; 164-2 at 1-3 (261 Case); D.I. 55-1 (1375 Case); D.I. 203-1 (595 Case)

construction that stays true to the claim language and most naturally aligns with the patents' description of the invention will be, in the end, the correct construction."'). In particular, the patents teach that the nucleic acid label of each detection reagent must be sufficient to identify the detection reagent's probe and corresponding analyte, just as Defendants propose.

The TOSS Patents are directed to methods of "detecting and sequencing [] nucleic acids." *E.g.*, '737 Patent at 1:38-41 (A0791). The alleged invention purports to surpass prior methods that required extracting the nucleic acids from their environment, "making it impossible to identify the cellular origin of individual nucleic acids." *Id.* at 1:55-57 (A0791). As an alleged solution to this problem, the TOSS Patents' detection reagent allows identification of nucleic acids in the sample itself: "After the detection reagents bind to the target analytes in a sample, ***the nucleic acid labels of the detection reagents*** carrying nucleic-acid information ***can be decoded to allow identification of respective probe reagent(s)*** conjugated to them." *Id.* at 22:29-35 (A0801); *see also* '639 Patent at 13:7-13 (A0532). The way in which the detection reagents' nucleic acid labels are utilized in the invention is therefore critical for the alleged improvement over the prior art.

Defendants' proposed construction is supported by, and consistent with, the TOSS Patents' specification, which explains that each probe has a corresponding analyte, in a one-to-one relationship. The TOSS Patents define a specific type of detection reagent to achieve the aim of the invention, and Defendants' proposed construction correctly captures this definition. Claims "must be read in view of the specification [*i.e.*, written description]," which is "always highly relevant to the claim construction analysis." *Phillips*, 415 F.3d at 1315 (quotation omitted); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "Usually, [the specification] is dispositive; it is the single best guide to the meaning of a disputed term." *Vitronics*, 90 F.3d at 1582. Here, the TOSS Patents describe the "Detection Reagents (or Detection

Molecules as Used Interchangeably Herein)” as follows:

The detection reagent comprises at least one probe reagent and at least one nucleic acid label, wherein said at least one nucleic acid label comprises at least one pre-determined subsequence to be detected in a temporally-sequential manner; wherein said at least one pre-determined subsequence forms an identifier of said at least one probe reagent; and wherein said at least one probe reagent and said at least one nucleic acid label are conjugated together.

’737 Patent at 29:33-45 (A0805); *see also id.* at 6:50-59 (A0793) (same); *see also* ’639 Patent at 20:16-24, 5:14-21 (A0535, 528).

Defendants’ proposed construction fully comports with this description. **First**, the specification’s description and the claims state that the detection reagent comprises both a probe and a nucleic acid label comprising one or more pre-determined subsequences. *See* ’737 Patent at 29:37-41, 6:52-55, cl. 1 (A0805, 793, 832) (requiring “a probe that binds to said analyte” and a “nucleic acid label comprising one or more pre-determined subsequences”), cl. 24 (A0833) (same); *see also* ’639 Patent at 5:14-21, 20:16-24, cl. 1 (A0528, 535, 577). **Second**, the definition reflects the invention’s clear intent that the “probe is conjugated to a nucleic acid label” in the detection reagent. ’737 Patent at 22:29-35 (A0801); *see also id.* at 47:33-39 (A0814) (“wherein the probe reagent and the nucleic acid label can be conjugated together by any methods known in the art”), 53:21-25 (A0817), 8:58-9:3 (A0794-795) (describing kits according to the alleged invention providing “at least one coupling agent that allows the user to conjugate at least one nucleic acid label to the user’s probe reagents of interest”); *see also* ’639 Patent at 13:7-13, 39:6-12, 44:60-65, 7:19-31 (A0532, 545, 547, 529). **Third**, the definition of “detection reagent” makes clear that the alleged invention requires that the nucleic acid label, through its one or more pre-determined subsequences, “forms an identifier of said at least one probe reagent.” ’737 Patent at 29:41-43 (A0805); *see also id.* at 6:56-57 (A0793); *see also* ’639 Patent at 20:20-22, 5:18-19 (A0535, 528). This identifier is unique to, and therefore uniquely identifies, one specific probe. ’737 Patent at

77:60-67 (A0829) (“An ‘identifier’ as used [in the patents] refers to association of a unique pre-determined subsequence to a specific probe reagent, thus conferring the presence and identity of the probe reagent when the predetermined subsequence is detected.”); *see also* ’639 Patent at 69:46-48 (A0560); *infra* § I.D.1.

Defendants’ construction should also be adopted because it aligns with the “actual invention” where the one or more predetermined subsequences (when detected) identify the probe to which they are conjugated *and* the probe’s corresponding analyte. *See Retractable*, 653 F.3d at 1305 (“In reviewing the intrinsic record to construe the claims, we strive to capture the scope of the actual invention . . .”). The specification defines the detection reagent’s nucleic acid label as “used to identify an analyte or a target.” ’737 Patent at 37:15-19 (A0809); ’639 Patent at 27:63-67 (A0539); *see also Vitronics*, 90 F.3d at 1582. The TOSS Patents define a “probe” as corresponding to “the target or the analyte.” *See* ’737 Patent at 30:61-66 (A0805) (“[T]he term ‘probe,’ ‘probe reagent,’ or ‘probe molecule’ refers to an entity . . . that interacts with or binds to a target molecule or an analyte for the analysis of the target or the analyte.”); ’639 Patent at 21:41-46 (A0536) (same).

The TOSS Patents’ specification shows that the alleged invention operates by having a specific probe that corresponds to a specific analyte. In fact, the totality of the intrinsic evidence demonstrates that the TOSS Patents purport to use probes and analytes that have a one-to-one relationship—each probe has a corresponding analyte. *E.g.*, ’737 Patent at 4:60-65 (A0792) (“agreement between the temporal order of the signal signatures and a particular identifier of said at least one probe reagent identifies the analyte in the sample”), 19:58-59 (A0800) (“different probes (and corresponding analytes)”), 19:65-66, 28:54-61, 53:24-25 (A0800, 804, 817) (“the probe reagents being more accessible by the corresponding analytes in a sample”); ’639 Patent at

3:21-26, 10:36-37, 10:44-45, 19:33-40, 44:64-65 (A0527, 0530, 535, 547). The Figures and singular Example in the specification further provide that the probe is conjugated to a nucleic acid label and used to identify the analyte corresponding to the specific probe. *See, e.g.*, '737 Patent, FIGS. 7 & 15, 10:47-49 (describing FIG. 7 as including "Pathogen-specific antibodies (e.g., anti-*C. albicans*) are individually conjugated to a nanoparticle comprising at least one nucleic acid label as described herein"), 81:20-29 (A0783, 790, 795, 831); '639 Patent at FIGS. 5 & 13, 8:60-62, 73:8-18 (A0518, 525, 529, 562). Thus, by identifying the probe through the nucleic acid label attached to the probe, the nucleic acid label also identifies the analyte to which the probe is bound. The TOSS Patents do not provide, and 10x cannot point to, any description that broadens this understanding.

10x's proposal that no construction is necessary and "detection reagent"—an amalgamation of two generic terms—should be given its plain and ordinary meaning is inappropriate and will not help the jury. A lay jury could not determine any supposed plain and ordinary meaning of "detection reagent" given the complexity and abstract nature of the specific disclosures in the TOSS Patents. The claim construction that "most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Phillips*, 415 F.3d at 1315-16. Here, Defendants' proposed construction aligns with the TOSS Patents' description of the "detection reagent," clarifies the invention, and reflects the "actual invention." *Retractable*, 653 F.3d at 1305.

b. Plaintiffs 10x's and Harvard's Answering Position

The parties dispute whether "detection reagent" should be given its plain and ordinary meaning (Plaintiffs) or rewritten to include multiple narrowing limitations: "a molecule comprising a probe conjugated to a nucleic acid label comprising one or more pre-determined subsequences such that each nucleic acid label identifies said probe and its corresponding analyte"

(Defendants). Defendants’ construction does not “align[] with the patents’ description of the invention.” Br. 21-22 (quoting *Phillips*, 415 F.3d 1303 at 1316).

“Detection reagent” is not ambiguous and does not require a construction because its ordinary meaning is clear, including in light of the surrounding claim language. *Walker Dig., LLC v. Google Inc.*, No. 11-318-LPS, 2013 U.S. Dist. LEXIS 104157, at *3 (D. Del. July 25, 2013) (“While the claims themselves provide substantial guidance as to the meaning of particular claim terms, the context of the surrounding words of the claim also must be considered”). A POSA would understand the meaning in the context of the body of the claim. For example, Claim 1 of the 737 Patent states: “(a) contacting a cell or tissue sample comprising said analyte with a **detection reagent**, wherein said **detection reagent comprises** (i) **a probe** that binds to said analyte and (ii) **a nucleic acid label comprising one or more pre-determined subsequences**.” The claim already specifies what a detection reagent is (i.e., a certain probe and a nucleic acid label) and these few requirements, in combination with the clear meaning of “detection” and “reagent” in the context of the claim, provide a complete and sufficient meaning for the term to a POSA. The guidance from the claim language itself eliminates the need for further construction. *See TQ Delta, LLC v. Zyxel Communs., Inc.*, C.A. No. 1:13-cv-02013-RGA, 2018 U.S. Dist. LEXIS 107098, at *12-13 (D. Del. June 27, 2018) (plain meaning for “full power mode” because the claim language provides “ample guidance” and the Court “does not think ‘a state with full data transmission capabilities’ imparts any more meaning than ‘full power mode’”). No construction is needed to aid the jury. *See Walker Dig.*, 2013 U.S. Dist. LEXIS 104157, at *13 (“[t]he meaning of the ‘releasing’ terms to one of ordinary skill in the art will be made clear to the jury from the overall claim language. . .”).

By contrast, to manufacture a non-infringement argument, Defendants assert this term must be narrowly construed in light of a supposed principle—that “each probe has a corresponding

analyte, in a one-to-one relationship”—inconsistent with the intrinsic evidence. Br. 22. There is no meaningful dispute that “reagent” has a broader ordinary meaning than a single probe molecule. **Ex. X17**, ¶¶ 42-53 (A0744-0747). The specification makes clear that a “reagent” is broader than a single “probe” with a single label in the context of the invention. A “reagent” can comprise a collection of different probes and labels; it is the complete set of predetermined sequences that can be detected in a temporal order that permits detection of an analyte. Plaintiffs did not disavow all reagents other than a single-molecule probe with a single label. *See Cont’l Circuits LLC v. Intel Corp.*, 915 F.3d 788, 797 (Fed. Cir. 2019) (“To disavow claim scope, the specification must contain ‘expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope.’”).

Defendants’ showing falls far short of the disavowal standard. Defendants rely upon a portion of the specification that reflects a broader invention at odds with their own proposal:

Defendants’ construction	051 Patent (Ex. X19), 6:55-62 (A0859)
A molecule	The detection <i>reagent</i>
comprising a probe	comprises at least one probe reagent
conjugated to a nucleic acid label	and at least one nucleic acid label
comprising one or more pre-determined subsequences	wherein said at least one nucleic acid label comprises at least one pre-determined subsequence to be detected in a temporally-sequential manner;
such that each nucleic acid label identifies said probe and its corresponding analyte	wherein said at least one pre-determined subsequence forms an identifier of said at least one probe reagent and wherein said at least one probe reagent and said at least one nucleic acid label are conjugated together

This disclosure is sufficient to confirm that the reagent at issue is not limited to a single molecule, but may include multiple probes and multiple labels, and that these labels are used in detection, but need not individually and completely identify each probe and analyte. **Ex. X17**, ¶¶ 44-64 (A0744-751). This broader understanding is reiterated in examples throughout the specification.

First, the specification (including Defendants’ cited disclosure: “at least one probe

reagent”) states that the detection reagent can have more than one probe reagent. *See Ex. X19*, 051 Patent, 8:16-18 (A0860) (“In some embodiments, the detection reagent can comprise a plurality of probe reagents and a plurality of nucleic acid labels.”); 30:40-46 (A0871) (“Each of the detection reagents described herein can comprise any number of probe reagents.”); Fig. 3 (A0845) (showing two antibody probe reagents for each detection reagent). Detection reagents can contain multiple different probe reagents:

In various embodiments, the detection reagent described herein can comprise one kind/species of probe reagents or *different kinds/species of probe reagents*. In some embodiments, the kind/species of the probe reagents present in the detection reagent can be the same. In other embodiments, the detection reagent can include at least one different kind/species of the probe reagents (e.g., 1, 2, 3, 4, 5, or 6 probe reagent species). In such embodiments, the distinct probe reagent species can be different from the others by types (e.g., antibodies vs. DNA aptamers), binding domains, and/or target analytes.

051 Patent, 37:6-16; 21:45-48 (A0875, 867) (“[D]etection reagents described herein can differ in types of probe reagents (e.g., nucleic acids vs. antibodies), target binding domains, and/or target analytes.”).

A POSA reading the patent would understand that a detection reagent can have at least two probe reagents and the probes can differ. A POSA would understand that a detection reagent could include multiple and/or different detection reagents to increase sensitivity and to increase detection specificity. *Ex. X17*, ¶¶ 44-53 (A0744-747). When detection reagents have different binding regions, multiple detection reagents (along with multiple labels) can hybridize to the same analyte. *Ex. X17*, ¶¶ 46-53 (A0745-747). A POSA would understand that multiple binding events would increase signal sensitivity. *Ex. X17*, ¶¶ 48-50 (A0746-747). A POSA would understand that a detection reagent could contain one probe reagent or could contain multiple and/or different probe reagents. *Ex. X17*, ¶¶ 42-46, 56-64 (A0744-745, 748-751).

Second, each “detection reagent” is not limited to a single “nucleic acid label” as the specification contemplates “*at least one* nucleic acid label.” *Ex. X19*, 051 Patent, 6:55-62 (A0859);

see, e.g., 8:16-18 (A0860) (“In some embodiments, the detection reagent can comprise a plurality of probe reagents and a plurality of nucleic acid labels.”); 29:66-30:1 (A0871) (“a plurality of nucleic acid labels present in the detection reagent can range from about 2 to about 100,000”). The specification describes ways to attach multiple nucleic acid labels to detection reagents. *See, e.g.*, 8:59-9:4 (A0860-861) (describing kits that include “at least one coupling agent that allows the user to conjugate at least one nucleic acid label to the user’s probe reagents”); 6:63-7:8 (A0859-860) (describing use of linker molecules that can be “multivalent” such as “a gold particle, a magnetic bead or nanoparticle”). This is also consistent with Figure 6 (showing exemplary configurations of probe reagents and nucleic acid labels on particles) and 30:3-16 (A0871) (describing particle reagent that can act as a hub to allow 100,000 nucleic acid labels).

Further, the specification describes the use of multiple nucleic acid labels for signal amplification. *See, e.g.*, 051 Patent, 29:61-67 (A0871) (“Depending on various applications and/or assay conditions (e.g., sensitivity, sample volume/concentration), a readout signal of a detection reagent can be amplified by increasing the number of nucleic acid labels present in the detection reagent . . . to a plurality of nucleic acid labels.”); 8:9-14 (A0860) (“[A] detection signal of a probe can be amplified by conjugating the probe to a plurality of the nucleic acid labels.”). The specification describes the importance of multiple labels for increased sensitivity. *See* 051 Patent, 64:41-44 (A0888) (“[T]he detection reagents and methods described herein can be used to locate microscopic tumors in a subject, where other conventional methods are not sensitive enough to detect such microscopic tumors.”).

Third, a specific label molecule need not completely and uniquely identify a single probe and analyte. Defendants’ construction (“identifies”) differs from the specification’s statement that “at least one pre-determined subsequence ***forms an identifier*** of said at least one probe reagent.”

Defendants’ construction would read out every embodiment where a detection reagent has more than one type of probe reagent. The specification’s use of “forms an identifier” of a probe reagent is not the same as identifying a probe reagent. **Ex. X17**, ¶¶ 54-64 (A0747-751). A POSA would understand that the nucleic acid label does not necessarily identify a single probe reagent but instead is used to identify **the analyte**. *Id.* The use of a label to identify the analyte is consistent with the patent’s description of nucleic acid labels. *See Ex. X19*, 051 Patent, 37:20-22 (A0875) (“[T]he nucleic acid label or nucleic acid tag comprises at least one pre-determined nucleic acid subsequence, which *is used to identify an analyte or target*.”). It is also consistent with the description that the probe’s role is to bind a target. *See Ex. X19*, 30:65-31:3 (A0871-872) (“‘[P]robe,’ ‘probe reagent’ or ‘probe molecule’ refers to an entity (e.g., but not limited to, a molecule, a particle, a composite entity, or a multi-molecular entity) that *interacts or binds to* a target molecule or an analyte for the analysis of the target or the analyte.”).

A POSA would understand that the role of the identifiers is to associate a set of identifying subsequences with an analyte of interest; an attached identifier does not need to uniquely identify a particular probe in order to enable identification of the analyte.¹⁴ **Ex. X17**, ¶¶ 55-61 (A0748-750). A POSA would understand that a detection reagent containing multiple probe reagents with different binding domains can be used to bind different regions of the same target nucleic acid molecule (*Id.*, 44-47, 56 (A0744-746, 748-749)) and that to increase signal intensity, the same nucleic acid label could be used for different probe reagents targeting different parts of the same analyte. *Id.*, ¶¶ 48-53 (A0746, 747). Additionally, different subsequences from different probes can be used in combination to form a larger code that is detected in a temporal order identifying a

¹⁴ Defendants rely upon the specification (051 Patent, 22:29-35 (A0867)) to assert that how the nucleic acid labels are utilized is “critical for the alleged improvement over the prior art.” Br. at 22. Defendants’ quotation is incomplete, out of context, and does not support a 1:1 probe:analyte relationship.

specific analyte. *Id.*, ¶¶ 44, 62-63 (A0744-745, 750).

The specification is consistent with these concepts. Because a pre-determined subsequence “forms an identifier of said at least one probe reagent,” a given subsequence could apply to multiple different probes that bind the same analyte. A POSA would understand that because the label identifies the analyte and different probe reagents target the same analyte, the identifier would not distinguish probes within the same detection reagent, but could be used to distinguish one reagent (e.g. a set of probes) from another. *Id.*, ¶¶ 44-47, 55-63 (A0744-746, 748-750). A POSA would understand this is consistent with the purpose, “for detection, identification and/or quantification of **target molecules or analytes**” (Ex. X19, 051 Patent, 8:19-22 (A0860)) and advantages over “conventional methods [that] are not sensitive enough” (64:43-44 (A0888)). The examples shows their construction would read out preferred embodiments, and “a claim interpretation that excludes a preferred embodiment from the scope of the claim is rarely, if ever, correct.” *Accent Packaging, Inc. v. Leggett & Platt, Inc.*, 707 F.3d 1318, 1326 (Fed. Cir. 2013). Defendants’ construction “amounts to a substitution of the words the patentee chose without adequate justification.” *TQ Delta*, 2018 U.S. Dist. LEXIS 107098, at *13.

c. Defendants NanoString’s and Vizgen’s Reply Position

This claim construction dispute boils down to whether a “detection reagent” must identify a specific probe and its corresponding analyte. 10x and its expert assert “plain and ordinary meaning,” but never explain what that meaning is. For example, 10x’s expert claims that the standalone term “reagent” had a plain and ordinary meaning with “a common purpose,” but does not opine that “**detection** reagent” had one—because it does not. Ex. X17 ¶ 42 (A0744). Here, “detection” gives the reagent the specific purpose of identifying analytes. *E.g.*, ’737 Patent at Title (A0771) (“Compositions and Methods for Analyte Detection”), cl. 1 (A0832) (“A method for identifying an analyte”). 10x presents no evidence that “detection reagent” had “an ordinary,

established meaning *in the relevant field*,” which is the key inquiry. *Micron Tech., Inc. v. N. Star Innovations, Inc.*, 855 Fed. Appx. 679, 683 (Fed. Cir. 2021). Accordingly, “plain and ordinary meaning” does not resolve the parties’ disputes, and a construction is necessary. *O2 Micro Int’l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1361 (Fed. Cir. 2008).

10x misinterprets Defendants’ construction, further revealing why this term is confusing for a jury. 10x and its expert claim that Defendants’ construction limits a detection reagent to “a single ‘probe’ with a single [nucleic acid] label.” Br. 27; **Ex. X17** ¶ 43 (A0744). That is incorrect. Defendants’ construction allows each detection reagent to comprise more than one probe or nucleic acid label, consistent with the specification. *See, e.g.*, Br. 22-23 (citing ’737 Patent at 29:33-45 (A0805) (detection reagent has “at least one nucleic acid label”)), 23 (citing *id.* at 8:58-9:3 (A0794-795) (conjugating “at least one nucleic acid label” to a probe)); *see also* Figs. 6A, 6B (A0782). Defendants’ construction requires that “*each* nucleic acid label *identifies* said probe and its corresponding analyte.” Br. 21.

10x’s argument about disavowal (Br. 27) is also a red herring, as this dispute is not about disavowal. Defendants never argued that the inventors disavowed detection reagents with more than one probe or nucleic acid label. Moreover, the inventors cannot disavow what they did not invent, and they did not disclose a hypothetical detection reagent comprising multiple detection reagents. *Cf. Poly-America, L.P.*, 839 F.3d at 1136. 10x’s first and second responses (Br. 27-29) and related expert opinions are therefore irrelevant.

10x’s remaining argument that “a specific label molecule need not completely and uniquely identify a single probe and analyte” also fails. *Id.* at 29-30. While 10x admits (as it must) that the specification describes pre-determined subsequences that “form[] an identifier” (*id.*), it contends that “form[ing] an identifier” is “not the same as identifying,” and identifiers only “*associate* a set

of identifying subsequences with an analyte” but do not “*identify*.” *Id.* at 30. This is confusing and nonsensical—an “identifier” identifies by name and by definition. ’737 Patent at 77:60-67 (A0829). The TOSS patents state that each nucleic acid label comprises at least one pre-determined subsequence that “forms an identifier of said at least one probe reagent” (*id.* at 29:41-43 (A0805)), that the nucleic acid labels “can be decoded to allow *identification of respective probe reagent(s) conjugated* to them,” (*id.* at 22:29-35 (A0801)), and that the labels are “used to identify an analyte or target,” (*id.* at 37:15-19 (A0809)). As taught, the identification of the probe, in turn, identifies the analyte. 10x and its expert do not deny that each nucleic acid label identifies an analyte. *See* Br. 30 (“A POSA would understand that the nucleic acid label does not necessarily identify a single probe reagent *but instead is used to identify the analyte.*”); **Ex. X17** ¶ 57 (A0749) (“the label identifies the analyte”).

Contrary to 10x’s arguments, the TOSS patents do not teach splitting the nucleic acid label between multiple detection reagents to identify an analyte, and in fact refer to “subpopulations” of detection reagents for identifying different analytes. ’737 Patent at 4:31-45 (A0792). There is no basis for 10x’s circular, illogical position that a single “*detection reagent* could include multiple and/or different *detection reagents.*” Br. 28. On the contrary, the specification and all examples show each detection reagent is a single entity that identifies at least one analyte (through identification of its one or more probes). *See* Br. 22-23; ’737 Patent at 29:33-45, 6:50-59 (A0805, 793).

Finally, 10x’s remaining assertions about probes and probe reagents are unsupported. 10x’s expert asserts that a person of ordinary skill “would understand that the specification’s disclosure is not limited to the use of a single probe reagent for a given target analyte,” but does not tie this to the patents. **Ex. X17** ¶ 56 (A0748-749). His contention that “multiple detection

reagents . . . can hybridize to the same analyte” cites no intrinsic or extrinsic evidence and does not change the fact that each detection reagent must identify an analyte. *Id.* ¶¶ 47-51 (A0745-747). The Court should disregard this impermissible expert gap-filling. *See Phillips*, 415 F.3d at 1318 (“conclusory, unsupported assertions by experts . . . are not useful to a court.”); *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1210 (Fed. Cir. 2013) (rejecting “conclusory and incomplete” expert opinion). While 10x notes (and Vizgen agrees) that probes can take various forms (Br. 28-29), they must identify analytes. “Plain and ordinary meaning” does not explain these concepts for the jury. For these reasons, Defendants’ construction should be adopted.

3. “decoding reagent”

Claim Term ¹⁵	Defendants’ Construction	Plaintiffs’ Construction
“decoding reagent” '051 Patent, claims 1, 90, 96	“any reagent that can yield a signal signature”	No construction necessary — plain and ordinary meaning

a. Defendants NanoString’s and Vizgen’s Opening Position

The parties’ dispute whether “decoding reagents” should be interpreted consistently with the specification (Defendants’ position) or instead be left unconstrued (Plaintiffs’ position). Plaintiffs’ suggestion that a technical term such as “decoding reagent” that would be unfamiliar to a lay person has a plain and ordinary meaning is misplaced.

The patent claim prescribes:

- “***detecting*** a [first/second] plurality of ***signal signatures from*** said [first/second] plurality of ***decoding reagents***”

'051 Patent, claim 1 (A0898). Other than specifying that a “decoding reagent” must yield a “signal signature,” the claims include no further requirement on the scope of “decoding reagent.” Hence, “decoding reagents” should be construed to mean “any reagent that can yield a signal

¹⁵ D.I. 164-1 at 4 (261 Case); D.I. 55-1 (1375 Case); D.I. 203-1 (595 Case).

signature.”

The unasserted dependent claim language confirms Defendants’ construction. For instance, claim 6 prescribes:

- “said [first/second] plurality of *decoding reagents comprises* a [first/second] plurality of decoder probes and a [first/second] plurality of *detectable labels*, and...detecting said [first/second] plurality of *detectable labels* to detect said [first/second] plurality of *signal signatures*”

’051 Patent, claim 6 (A0898). Hence, a decoding reagent yields a signal signature by, for instance, its detectable label.

The specification also confirms Defendants’ construction. The phrase “decoding reagents” only appears once in the specification. That sole reference describes forming a temporal order of signal signatures by using decoding reagents:

As used herein, the term “temporal order of the signal signatures” refers to a sequence of signal signatures determined in a temporally-sequential manner, i.e., the sequence of signal signatures is progressed through by a number of active operations performed in a temporally-sequential manner, e.g., using a different set of *decoding reagents* or decoder probes in each active operation. In some embodiments, using a set of decoder probes in each active operation can yield one signal signature corresponding to one subsequence of the detection reagents.

’051 Patent at 20:44-53 (A0866). The specification describes the coding reagent as the reagent that yields a signal signature. For these reasons, Defendants’ construction should be adopted.

b. Plaintiffs 10x’s and Harvard’s Answering Position

The parties dispute whether “decoding reagents” should be given its plain meaning (Plaintiffs) or should be rewritten to “any reagent that can yield a signal signature” (Defendants).

A specialized construction is not necessary in light of the surrounding claim language that explains what a decoding reagent is. *See Walker Dig.*, 2013 U.S. Dist. LEXIS 104157, at *13 (no construction because the “meaning of the [] terms to one of ordinary skill in the art will be made clear to the jury from the overall claim language. . .”). Asserted Claim 96 (A0902) states in part:

wherein said third plurality of **decoding reagents comprises** a third plurality of **decoder probes** and a third plurality of **optical labels**; wherein a decoder probe of said third plurality of decoder probes is complementary to and hybridizes with a third predetermined sequence of said plurality of predetermined sequences. (Ex. X19, A0902)

This language defines structural features (decoder probe and optical labels) of the decoding reagents such that a jury could easily understand what is required of the claim, while Defendants seek to impose a construction by function (yield[ing] a signal signature) without explaining why it will be more helpful to the jury, and it would not be. *See TQ Delta*, 2018 U.S. Dist. LEXIS 107098, at *12-13 (plain meaning because the claim language provides “ample guidance” and the Court “does not think ‘a state with full data transmission capabilities’ imparts any more meaning than ‘full power mode’”). Also instructive is the parties’ agreement that the specification defines “decoder probe” to mean “an oligonucleotide with a sequence complementary to a pre-determined sequence of the nucleic acid label”—a definition in easily understandable features that also tracks claim 96’s language. Further, while the patent describes that optical signatures include no-color (*see, e.g.*, 051 Patent, 6:4-16 (A0859)), it is unclear what Defendants mean by “yield” and whether they seek to exclude the absence of color. This construction would confuse, rather than help, the jury.

c. Defendants NanoString’s and Vizgen’s Reply Position

10x asserts that the term should be given its plain meaning but again does not explain what that meaning is. 10x at most points to the language from dependent claim 96, arguing that the “language *defines* structural features (decoder probe and optical labels) of the decoding reagents such that a jury could easily understand what is required of the claim.” Br. 37. Yet, even if “decoding reagent” is limited to a certain structure in claim 96, that is no basis to contend that *every* claim must include the specific features of claim 96. 10x does not dispute that Defendants’ construction accurately describes the function of decoding reagents: yield a signal signature. This

is taken directly from the specification. *See* '051 Patent at 20:44-53 (A0866). Specifically, “yield” means “generate,” a meaning that is consistent with a lay person’s understanding as well as the TOSS Patent claims (*e.g.*, to generate a temporal order of signal signatures). Thus, Defendants’ construction should be adopted.

D. DISPUTED CONSTRUCTIONS (Terms Proposed by NanoString)

1. “identifier”

Claim Term¹⁶	NanoString’s Construction	Plaintiffs’ Construction
“ identifier ” '639 Patent, claim 1	“a unique expression to distinguish variations from one to another among a class of substances, items, or objects”	No construction necessary — plain and ordinary meaning

a. Defendant NanoString’s Opening Position

The parties dispute whether the term should be defined in accordance with the lexicography of the patentee (NanoString’s position) or instead should be left unconstrued (Plaintiffs’ position). The specification supports NanoString’s position. It is well established that when “a patentee explicitly defines a claim term in the patent specification, the patentee’s definition controls.” *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009). Here, the patentee has just done that, teaching that: “As used herein, the term ‘identifier’ generally refers to *a unique expression to distinguish variations from one to another among a class of substances, items, or objects.*” '639 Patent at 69:46-48 (A0560). NanoString’s construction is drawn directly from this definition and should be adopted.

b. Plaintiff 10x’s and Harvard’s Answering Position

Plaintiffs propose “identifier” be given its plain and ordinary meaning. NanoString asserts “identifier” requires a specialized construction based on purported lexicography: “As used herein,

¹⁶ D.I. 164-1 at 1-2 (261 Case); D.I. 55-1 (1375 Case); D.I. 203-1 (595 Case)

the term ‘identifier’ *generally refers* to a unique expression to distinguish variations from one to another among a class of substances, items, or objects.” 639 Patent, 69:46-48 (Ex. X13, A0560). NanoString is wrong.

That statement falls short of the “exacting” standard for lexicography, especially here where the specification contradicts definitional intent. *Hill-Rom Servs. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014) (“The standards for finding lexicography and disavowal are exacting.”); *Thorner v. Sony Comput. Entm’t Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012) (cleaned up) (“To act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term” and, “the patentee must clearly express an intent to redefine the term.”).

Here, the inclusion of “generally” confirms the patentee did not wish to restrict the term to a single, narrowing definition. See *Mobile Telecomms., Techs., LLC v. Blackberry Corp.*, No. 3:12-CV-1652-M, 2015 U.S. Dist. LEXIS 177576, at *12 n.2 (N.D. Tex. May 8, 2015) (“[T]his language, specifically the use of *generally*, is not precise enough to serve as a lexicography.”); cf. *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1349 (Fed. Cir. 2020) (“the written description’s use of ‘may also include,’ ‘e.g.,’ ‘such as,’ and ‘etc.’ makes clear the patentee did not intend . . . to define [the term]”); *Abbott Labs. v. Andrx Pharm., Inc.*, 473 F.3d 1196, 1210 (Fed. Cir. 2007) (“is” does not always “unambiguously signify that the description provided is definitional”).

The use of “generally” in describing “identifier” is in stark contrast to the language used to define other terms, showing a clear lack of intent. For example, the parties have agreed to constructions of the terms “temporal order of signal signatures,” “decoder probe,” and “signal signature” based on the definitions provided in the specification. Each term is defined with the same linguistic formula: “[a]s used herein, the term [] refers to” (in contrast with “generally refers to”) signaling that the patentee intended to define certain terms but not “identifier.” See *Meds. Co.*

v. Mylan, Inc., 853 F.3d 1296, 1306 (Fed. Cir. 2017) (“[I]t does not accord with the linguistic formula used by the patentee to signal the designation of other defined terms . . . Because it departs from this format, the statement Medicines relies on lacks the clear expression of intent necessary for a patentee to act as its own lexicographer.”); *Abbott*, 473 F.3d at 1210 (no lexicography for term followed by “is” when “as used herein, means” followed other defined terms)¹⁷.

A POSA would understand that the claimed identifier is used to associate a set of identifying subsequences with an analyte of interest but does not need to uniquely identify a particular probe in order to enable identification of the analyte. **Ex. X17**, ¶¶ 55-64 (A0748-751). NanoString’s construction is also at odds with the identifier’s purpose to identify the analyte, not uniquely identify a particular reagent probe. *See* Section III; **Ex. X17**, ¶¶ 55-64 (A0748-751).

c. Defendant NanoString’s Reply Position

10x contends that the definition of the term from the specification should not be adopted due to the inclusion of “generally.” Br. 38-39. To support its argument, 10x cites a footnote from *Mobile*, but omits the passage from the specification of the disputed patent—“a probe message . . . **is generally** a message generated by a network operations center to locate a mobile unit.” *Mobile Telecomms., Techs., LLC*, 2015 U.S. Dist. LEXIS 177576, at *12 (alteration in original). The use of “is” does not “unambiguously signify that the description provided is definitional.” *Abbott Lab’ys*, 473 F.3d at 1210. In contrast, the TOSS Patents, in the section entitled “Some Selected Definitions,” use “generally refers to” to signal the definition of the term “identifier.” ’639 Patent at 68:65, 69:46-48 (A0560). Courts often find the use of “generally refers to” as definitional. *See, e.g., Uniloc 2017, LLC v. Paychex, Inc.*, 2020 WL 2329474, at *4 (D. Mass. May 11, 2020); *BMC Software, Inc. v. ServiceNow, Inc.*, 2015 WL 4776970, at *13 (E.D. Tex. Aug. 13, 2015); *Opal*

¹⁷ NanoString’s reliance on *Martek Biosciences Corp. v. Nutrinova, Inc.*, is misplaced as the specification included “means,” not “generally refers to.” 579 F.3d 1363, 1380 (Fed. Cir. 2009).

Run, LLC v. C & A Mktg., Inc., 2017 WL 413163, at *7 (E.D. Tex. Jan. 31, 2017). Hence, NanoString’s construction should be adopted.

2. “analyte”

Claim Term ¹⁸	NanoString’s Construction	Plaintiffs’ Construction
“analyte” ’639 Patent, claims 1,20 ’737 Patent, claims 1, 24 ’051 Patent, claims 1, 2, 89, 96 ’052 Patent, claim 1, 16, 34 ’054 Patent, claim 1	“the molecule detected, identified or measured by binding of a detection reagent whose probe reagent(s) recognize (i.e., are specific binding partners) thereto”	“the molecule detected, identified or measured by binding of a detection reagent whose probe reagent(s) recognize it (i.e., are specific binding partners thereto)”

a. Defendant NanoString’s Opening Position

The parties dispute whether the Court should adopt the definition as provided in the specification (NanoString’s position) or effectively amend the specification (Plaintiffs’ position). Plaintiffs’ construction is an improper attempt to bypass the federal regulation on amending the specification.

The patentee expressly defines the term-at-issue: “[t]he terms ‘analyte,’ ‘target analyte,’ and ‘target molecule’, as used interchangeably herein, refer to the molecule detected, identified or measured by binding of a detection reagent described herein *whose probe reagent(s) recognize (i.e., are specific binding partners) thereto.*” ’639 Patent at 51:50-54 (A0551), ’737 Patent at 60:10-14 (A0820). NanoString’s construction is drawn verbatim from this definition.

Plaintiffs do not dispute the specification has defined the term. Instead, Plaintiffs contend the definition is unclear and attempt to modify it. Federal Regulations, however, specify requirements for amending a specification, providing that they “must be made by adding, deleting, or replacing a paragraph; by replacing a section; or by providing a substitute specification, in the

¹⁸ D.I. 164-1 at 2-3 (261 Case); D.I. 55-1 (1375 Case); D.I. 203-1 (595 Case)

manner specified in this section.” 37 C.F.R. § 1.121(b); *see also* 35 U.S.C. § 255. Plaintiffs’ effort to amend the specification during claim construction should not be permitted.

For these reasons, NanoString’s construction should be adopted.

b. Plaintiffs 10x’s and Harvard’s Answering Position

The parties substantially agree as to the construction of analyte based on the lexicography included in the specification. Plaintiffs’ proposal—“the molecule detected, identified or measured by binding of a detection reagent whose probe reagent(s) recognize it (i.e., are specific binding partners *thereto*)”—differs by (1) the inclusion of “it” as the object of the sentence inadvertently omitted and (2) moving the adverb “thereto” to inside the parentheses with the phrase it modifies.

While a POSA would understand the claim term’s meaning based on the definition provided in the specification, the issue is which proposed construction is most helpful to the jury. *See Novartis Pharm., Corp. v. Wockhardt USA LLC*, C.A. No. 12-cv-3967 (SDW) (MCA), 2014 U.S. Dist. LEXIS 85368, at *12 (D.N.J. June 24, 2014) (“A key aspect of claim construction is to assist the jury in understanding complicated language and concepts.”); *Becton, Dickinson & Co. v. Neumodx Molecular, Inc.*, No. 19-1126-LPS, 2021 U.S. Dist. LEXIS 88679, at *15 (D. Del. May 10, 2021) (“[T]he Court’s construction uses descriptors that will be helpful by informing the jury of the term’s meaning within the patent.”). Plaintiffs’ construction is the most helpful to the jury because without the modifications, it is less clear what object is being recognized.

Courts routinely modify proposed constructions, including ones based on lexicography, for grammatical correctness.¹⁹ *See, e.g., Fortinet, Inc. v. Forescout Techs., Inc.*, No. 20-cv-03343-

¹⁹ The cases above show that NanoString is wrong that Federal Regulations prohibit the Court from editing lexicography, Br. 41-42. A court has authority to “correct obvious minor typographical and clerical errors in patents.” *Pavo Sols. LLC v. Kingston Tech. Co.*, 35 F.4th 1367, 1373 (Fed. Cir. 2022); *CBT Flint Partners, LLC v. Return Path, Inc.*, 654 F.3d 1353, 1358 (Fed. Cir. 2011) (“It is well-settled law that . . . a district court may correct an obvious error in a patent claim.”).

EMC, 2022 U.S. Dist. LEXIS 213665, at *73 (N.D. Cal. Nov. 28, 2022) (“the Court’s construction is grammatically correct” and “derives from patentee’s express definition”); *Cloud Farm Assocs., L.P. v. Volkswagen Grp. Of Am.*, No. 10-502-LPS, 2012 U.S. Dist. LEXIS 104980, at *20 (D. Del. July 27, 2012) (“[T]he Court adopts a construction that reflects the parties’ agreement and is grammatically correct.”); *Cascades Comput. Innovation, LLC v. Dell Inc.*, No. 11 C 7264, 2014 U.S. Dist. LEXIS 223, at *57 (N.D. Ill. Jan. 2, 2014) (adding “such that” to definition of “precise” “to make the interpretation grammatically correct; [because] ‘precisely’ is an adverb”).

c. Defendant NanoString’s Reply Position

10x contends that this Court can edit lexicography for grammatical correctness despite the Federal Regulations. Br. 41-42. None of the authority 10x relies on, however, addresses correcting lexicography.²⁰ *See, e.g., Fortinet, Inc.*, 2022 U.S. Dist. LEXIS 213665, at *73 (construing the term “said system is RAD-agnostic” by adopting the definition of a similar term “(vendor)-agnostic”); *Cloud Farm Assocs., L.P.*, 2012 U.S. Dist. LEXIS 104980, at *20 (adopting “a construction that reflects the parties’ agreement” as opposed to correcting lexicography); *Cascades Comput. Innovation, LLC*, 2014 U.S. Dist. LEXIS 223, at *57 (adopting and modifying defendants’ construction as opposed to correcting lexicography). Hence, NanoString’s construction should be adopted.

²⁰ 10x further represents that “[a] court has authority to correct obvious minor typographical and clerical errors in patents.” Br. 41 n.19 (cleaned up). However, the case it relies on addressed correcting claim language in view of the patent specification, not correcting lexicography in the specification. *See, e.g., Pavo Sols. LLC*, 35 F.4th at 1373–74 (“We begin by addressing whether the *claim language* contains an obvious minor typographical or clerical error.”); *CBT Flint Partners, LLC*, 654 F.3d at 1358 (“a district court may correct an obvious error in a patent *claim*”).

E. DISPUTED CONSTRUCTIONS (Term Proposed by Vizgen)**1. “using 3D fluorescence imaging to identify said cellular nucleic acid molecules”**

Claim Term²¹	Vizgen’s Construction	Plaintiffs’ Construction
“using 3D fluorescence imaging to identify said cellular nucleic acid molecules” '767 patent claim 1	“using 3D fluorescence imaging of amplicons to identify said cellular nucleic acid molecules”	No construction necessary – plain and ordinary meaning

a. Defendant Vizgen’s Opening Position

Plaintiff again offers no construction for this term, whereas Vizgen’s construction is fully consistent with what the inventors described as their alleged 3D matrix invention and is strongly supported by the specification. *See Phillips*, 415 F.3d at 1315-16.

According to the specification, the alleged invention—which involves making a 3D matrix of nucleic acids *within* a cell to preserve the spatial orientation of the nucleic acids therein—was an improvement over prior methods that required “extracting nucleic acid molecules from their native environment” which made it “impossible to identify the cellular origin of individual nucleic acids.” ’767 Patent at Abstract, 1:41-47 (A1113, 1131). The intrinsic record teaches unequivocally that the claimed invention involves imaging *amplicons* consisting of multiple copies of the originally-present nucleic acids to detect, and thus identify, those nucleic acids.

As noted above, the ’767 patent specification states, “[t]he *present invention* relates to methods of making a three-dimensional matrix of nucleic acids *and amplifying*, detecting and sequencing such nucleic acids within the matrix.” *Id.* at 1:28-31 (A1131) (emphases added). Because the specification describes amplifying the nucleic acids to produce amplicons and imaging those amplicons as an aspect of “the present invention,” the claims are not entitled to a

²¹ D.I. 164-2 at 3-4 (261 Case); D.I. 55-2 (1375 Case); D.I. 203-2 (595 Case)

broader scope. *See Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1330 (Fed. Cir. 2009) (“[W]hen the preferred embodiment is described in the specification as the invention itself, the claims are not necessarily entitled to a scope broader than that embodiment.”).

The '767 patent further teaches that methods for amplifying the target nucleic acids to produce amplicons (including by “rolling circle amplification” or “RCA”) were well known in the art. *Id.* at 6:33-57, 8:32-59 (A1133-1134); *see also id.* at Fig. 10 (A1130) (showing RCA of a nucleic acid prior to detection by hybridization or sequencing). U.S. Patent No. 6,391,544, which is incorporated by reference “in [its] entirety for all purposes” into the '767 patent specification (at 8:55-59 (A1134)), explains that the amplification enables nucleic acid detection:

Nucleic acid amplification reactions are well known and are employed to increase the concentration of a target nucleic acid in a test sample. The ‘target nucleic acid’ typically is present in a sample in low concentrations and therefore cannot easily be detected without amplifying it to increase the concentration of the target sequence in the sample.

U.S. Pat. No. 6,391,544, 1:13-20 (A1364). Why one would amplify before imaging would be well known to those of ordinary skill: to generate enough copies of the target nucleic acid within the sample so its signal would be sufficiently strong for accurate detection (have a sufficiently high signal-to-noise ratio). *See, e.g.*, '767 Patent at 3:16-20, 10:66-11:3, 11:14-17 (A1132, 1135-1136).

Consistent with this understanding, every Example in the '767 patent that uses fluorescent imaging to identify nucleic acid analytes within a sample first amplifies the nucleic acids to produce amplicons. *See, e.g., id.* at Example I (A1136-1137) (titled “Immobilizing, ***Amplifying*** and Imaging DNA/RNA Molecules within cells”); Example II (A1137) (titled “Immobilizing, ***Amplifying*** and Imaging DNA/RNA Molecules within a Fly Embryo”); Example III (A1137-1138) (titled “Immobilizing, ***Amplifying*** and Imaging DNA/RNA Molecules within Mouse Brain”); Example X (A1139-1140) (titled “DNA ***Amplicons*** Embedded within a Cross-Linked Matrix in a Cell are Imaged”). In fact, the remaining Examples all reference amplicons or amplification as

well. *See id.* at Examples IV-VII, XI-XII (A1138-1140). Similarly, the specification describes Figure 2 as “creating a matrix of nucleic acids within cells . . . followed by amplifying the nucleic acids . . . co-polymerizing the amplicons in situ, covalently attaching the amplicons to the matrix material . . . and ***imaging the amplicons.***”

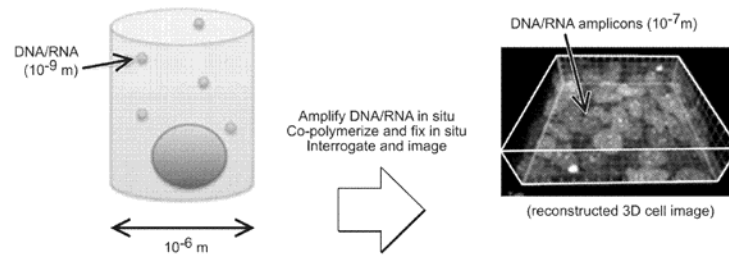


FIG. 2

Id. at FIG. 2, 3:60-67 (A1122, 1132). It also teaches that “sufficient” levels of amplicons are necessary for “three dimensional imaging,” which is the imaging method that the asserted claims recite. *Id.* at 3:16-20 (A1132) (“For example, the nucleic acids are amplified and include a label sufficient for a high level of fluorescence compatible with three dimensional imaging.”). In fact, the ’767 patent does not describe imaging of nucleic acids ***except in relation to amplicons and amplification.*** *See Edwards*, 582 F.3d at 1330.

Vizgen’s proposed construction “using 3D fluorescence imaging of amplicons to identify said cellular nucleic acid molecules” clarifies—consistent with what the inventors described as their alleged invention—that the nucleic acid analytes are amplified, and the resulting amplicons are attached to the matrix via functional groups incorporated during amplification and then imaged. As is clear from the ’767 patent specification, the actual invention requires amplifying the nucleic acids before “3D fluorescence imaging” (as required by all asserted claims). As this understanding reflects what the inventors actually invented—no more, no less—it should be adopted. *See Retractable*, 653 F.3d at 1305. Moreover, it is a “familiar axiom that claims should be [] construed,

if possible, as to sustain their validity,” with the caveat that courts should not rewrite claims to preserve validity. *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 911 (Fed. Cir. 2004) (quoting *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999)). Here the addition of the “of amplicons” clarifies the claims so as to cover what was “actually invented.” If this claim limitation is read to encompass imaging more than just amplicons (such as unamplified nucleic acids), there is no written description support in the ’767 patent specification to support such a reading. Vizgen’s construction appropriately tailors the claims to what the inventors claim they invented.

b. Plaintiffs 10x’s and Harvard’s Answering Position

The parties dispute whether “imaging” in “using 3D fluorescence imaging to identify said cellular nucleic acid molecules” (767 Patent) should be given its ordinary meaning (Plaintiffs) or require reading in the limitation “of amplicons” (Vizgen). The claim language alone resolves that the claim is not limited to “amplicons” and the specification confirms plain meaning should apply.

Claim language. “Fluorescence imaging” is a common term in the art that has an ordinary meaning. **Ex. X17, ¶ 68-69** (A0751-752). It is not an ambiguous phrase that requires consulting the specification to determine its meaning or to clarify it to the jury; nor does Vizgen assert it is ambiguous.

The surrounding claim language does not suggest a specialized meaning apart from the plain meaning. Claim 1 of the 767 Patent (**Ex. X23**, A1141) (below) is a “comprising” claim that describes a method of “analyzing a biological sample” where a 3D matrix is generated that preserves the spatial orientation of nucleic acid molecules in a sample and imaging is used to identify the nucleic acids:

1. A method of analyzing a biological sample, comprising:
 - (a) permeabilizing said biological sample, wherein said biological sample comprises a plurality of cells, wherein a cell of said plurality of cells comprises cellular nucleic acid molecules having a relative three-dimensional (3D) spatial orientation within said cell;

- (b) generating a 3D matrix comprising said cellular nucleic acid molecules attached thereto
- (c) contacting said 3D matrix with reagents to selectively remove a non-nucleic acid component from said biological sample; and
- (d) using ***3D fluorescence imaging to identify said cellular nucleic acid molecules*** and said relative 3D spatial orientation of said cellular nucleic acid molecules within said cell.

The claim language does not require amplifying the nucleic acid molecules to create amplicons.

The “cellular nucleic acid molecules” include the native molecules present in the cell before a 3D matrix is even generated; amplicons are not mentioned in the claim at all. Fluorescence imaging is used for identifying “said cellular nucleic acid molecules.” Vizgen does not even suggest any claim language imposing an amplifying step to depart from the ordinary meaning in the art.

Further, while claim 1(d) of the 767 Patent does not limit the form of nucleic acid (nucleic acid molecules or amplicons) that is being imaged, claim 2 specifically refers to cellular nucleic acids or derivatives of the cellular nucleic acids. *See* claim 2 (A1141) (“The method of claim 1, wherein (d) comprises hybridizing fluorescently labeled oligonucleotides to said cellular nucleic acid molecules or derivatives thereof and imaging said 3D matrix to detect said fluorescently labeled oligonucleotides.”); claim 10 (A1141) (“The method of claim 1, wherein (d) comprises sequencing said cellular nucleic acid molecules or derivatives thereof.”). “It is axiomatic that a dependent claim cannot be broader than the claim from which it depends.” *Alcon Research*, 687 F.3d at 1367.

Further, because this is a “comprising” claim, additional steps—including amplifying nucleic acids prior to imaging—can be performed in the claimed method without requiring such a step in all instances. *See Invitrogen*, 327 F.3d at 1368. Harvard has also obtained the 509 and 520 Patents with the narrower claim scope that requires the step of amplifying prior to imaging:

509 Patent (Ex. X24, A1165)	520 Patent (Ex. X25, A1194)
8. A method of identifying a relative three-dimensional spatial relationship of one or more nucleic	1. A method for analysis, comprising: (a) providing a biological sample comprising a

509 Patent (Ex. X24, A1165)	520 Patent (Ex. X25, A1194)
acids within a cell comprising: contacting a plurality of nucleic acids . . . with a matrix-forming material . . . amplifying the plurality of nucleic acids to produce amplicons within the matrix, . . . labeling the amplicons with a detectable label; and imaging the amplicons to identify the relative three-dimensional spatial relationship of the one or more nucleic acids within the cell.	plurality of cells, wherein a cell of said plurality of cells comprises a plurality of cellular nucleic acids; (b) generating a three-dimensional matrix comprising cellular nucleic acids. . .and (c) detecting signals from said cellular nucleic acids . . . 9. The method of claim 1, further comprising, prior to (b), generating a plurality of amplicons from said cellular nucleic acids. 10. The method of claim 9, . . . 23. The method of claim 10, wherein said amplicons are labelled with detectable labels. . . 25. The method of claim 23, wherein detecting signals from said detectable labels comprises imaging.

A patentee's decision to draft claims with and without a specific limitation is evidence that the limitation should not be read into all claims. *See TQ Delta, LLC v. Zyxel Communs., Inc.*, No. 13-02013-RGA, 2018 U.S. Dist. LEXIS 107098, at *15-16 (D. Del. June 27, 2018) (“[t]he claims of the related ‘268 patent demonstrate that the patentee knew how to draft claims that define ‘low power mode’ in terms of data transmission”); *Personalized Media Communs., LLC v. Apple Inc.*, 952 F.3d 1336, 1342 (Fed. Cir. 2020) (“language from related patent claims can be relevant” “as evidence that [patentee] knew how to exclude [claim scope] when it wanted to”). Amplification is not required but the patentee drafted the claims broadly to include methods of imaging both with and without amplifying, and Plaintiffs are entitled to the full scope. *See Thorner*, 669 F.3d at 1367 (“[P]atentee is free to choose a broad term and expect to obtain the full scope of its plain and ordinary meaning unless the patentee explicitly redefines the term or disavows its full scope.”).

Specification. The specification also supports that “fluorescence imaging” should be given the full scope of its ordinary meaning. The specification describes imaging a 3D matrix that does not first require the step of amplification. The patent describes that “optical properties” (**Ex. X23**,

6:9-13 (A1133)) of the matrix enable common imaging techniques: “the three dimensional matrix material is optically transparent to allow for three dimensional imaging techniques known to those of skill in the art.” 3:11-15; *see* 6:9-11 (A1132-1133) (“[T]he matrix is sufficiently optically transparent . . . for standard Next Generation sequencing chemistries and deep three dimensional imaging.”). As explained, fluorescence imaging was known in the art and a POSA would recognize those methods of imaging that did not first require amplicon generation. **Ex. X17**, ¶¶ 69-83 (A0752-756). This is consistent with the disclosure that “nucleic acids within the matrix can be interrogated using methods known to those of skill in the art including fluorescently labeled oligonucleotide/DNA/RNA hybridization.” 10:49-52. A POSA would recognize that when the patent describes these imaging techniques, amplification is not a necessary aspect.²² **Ex. X17**, ¶¶ 71, 74-75, 83 (A0752, 753-754, 756).

No disavowal or lexicography. Vizgen never expressly states why the Court should depart from plain and ordinary meaning—lexicography or disavowal. *Thorner*, 669 F.3d at 1365 (“There are only two exceptions to this general rule: 1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of a claim term”). Vizgen appears to rely on disavowal,²³ but Vizgen ignores the entirety of the written description, instead relying on one present invention disclosure and the examples described at the end of specification. This does not rise to a “clear and unmistakable disclaimer,” *Thorner*, 669 F.3d at 1365-67, or provide a reason to depart from ordinary meaning. *See Hill-Rom*, 755 F.3d at 1371 (“[W]e do not

²² Vizgen asserts (without support) a POSA would know *why* to amplify before imaging, Br. 44, but does not explain how this supports that the patent *requires* amplicons, and it does not.

²³ If Vizgen is arguing lexicography, the specification distinguishes between nucleic acids and amplicons showing patentee did not intend to equate the terms. *E.g.*, 767 Patent, 2:50-55 (**Ex. X23**, A1131) (“a plurality of nucleic acid molecules, such as DNA or RNA, amplicons or nucleic acid structural units are immobilized”), 7:6-31 (A1134) (definition of definition of “nucleic acid” that omits “amplicons”).

read limitations from the embodiments in the specification into the claims. . . . The standards for finding lexicography and disavowal are exacting.”); *Cont’l Circuits*, 915 F.3d at 797 (“To disavow claim scope, the specification must contain ‘expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope.’”). Vizgen relies on a present invention disclosure that does not recite “imaging of amplicons” (767 Patent, 1:28-30 (A1131)) and Vizgen ignores “present invention” disclosures that omit amplifying completely.²⁴ *See, e.g.*, 767 Patent, 4:34-38 (A1132) (“**The present invention** provides a three dimensional matrix of a plurality of nucleic acids. **The present invention** provides a three dimensional matrix including a plurality of nucleic acids bound thereto.”). Here, where “other portions of the intrinsic evidence do not support applying the limitation to the entire patent. . . . use of the phrase ‘present invention’ . . . is not . . . limiting.” *Absolute Software, Inc. v. Stealth Signal, Inc.*, 659 F.3d 1121, 1136 (Fed. Cir. 2011).

The patent’s examples of imaging amplicons cannot meet Vizgen’s burden to show the patentee disavowed claim scope, in light of the various disclosures described above. *See, e.g. Thorner*, 669 F.3d at 1366-67 (“It is likewise not enough that the only embodiments, or all of the embodiments, contain a particular limitation. We do not read limitations from the specification into claims; we do not redefine words. Only the patentee can do that. To constitute disclaimer, there must be a clear and unmistakable disclaimer.”); *Sisvel Int’l S.A. v. Sierra Wireless, Inc.*, 81 F.4th 1231 (Fed. Cir. 2023) (rejecting construction based on embodiments: “the specification while only expressly disclosing embodiments in a UMTS or GSM network, also broadly teaches: the invention is applicable in many different . . . systems”).

²⁴ Vizgen relies on *Edwards* to claim “present invention” language can limit claim scope, Br. 43-44. But in *Edwards*, unlike here, the surrounding claim language, lexicography, and every example required the importation of the limiting language into the construction of the term “graft.” 582 F.3d 1322 at 1330.

c. Defendant Vizgen’s Reply Position

The sole dispute about this phrase is whether the claimed imaging process applies to amplicons, as opposed to unamplified nucleic acids. But 10x does not explain how the claimed invention could operate without amplification.

10x claims that the ’767 patent includes examples without amplicons, but that is incorrect. All examples require amplicons. *See* Br. 44-45 (discussing Examples I-VII, X-XII, Fig. 2 (A1136-1140)); ’767 Patent at Exs. VIII, IX (A1139) (“A DNA **Amplicon** Matrix”). The specification also explains that “the nucleic acids are amplified to an extent to produce sufficient levels of amplicons for three dimensional imaging.” ’767 Patent at 3:16-20, cl. 1 (A1132, 1141). As Vizgen pointed out, the ’767 patent further incorporates by reference U.S. Patent No. 6,391,544, which confirms that nucleic acids are amplified to enable detection. *See* Br. 44. 10x does not respond to this evidence.

In fact, 10x’s expert opinions contradict this intrinsic evidence in conclusory fashion. Dr. Satija asserts that the ’767 patent “refers to multiple embodiments” without amplification, but tellingly identifies none. **Ex. X17** ¶ 83 (A0756). He discusses techniques like sequencing-by-synthesis (*id.* ¶¶ 75-76 (A0754)), but the patent teaches only performing 3D fluorescence imaging with amplification (e.g., ’767 Patent at 6:30-32 (A1133) (“DNA amplicons”)). Similarly, his discussion of other articles cited in the ’767 patent cannot expand the scope of what the inventors disclosed, as those articles address different applications than the ’767 patent. *See* **Ex. X26** (A1197-1200) (Raj 2008, discussing detection of individual mRNA); **Ex. X27** (A1201-1206) (Harris 2007, discussing amplification-free method for “single-molecule DNA sequencing”); **Ex. X28** (A1207-1214) (Eid 2009, discussing sequencing from “single polymerase molecules”). 10x is not entitled to a broader claim scope than it disclosed. *See Edwards Lifesciences*, 582 F.3d at 1330.

10x's attempts to rely on dependent claims, and claims in other unasserted patents, are misplaced. In '767 patent claims 2 and 10, 10x argues "derivatives" must be amplicons, so "said cellular nucleic acid molecules" are not amplicons, but this is incorrect. Br.47. The specification indicates that "derivatives" can be other entities, such as nucleic acids with "a functional moiety for attachment to the matrix." '767 Patent at 4:48-52 (A1132). Claim 13 recites nucleic acids "attached to said 3D matrix through a non-covalent interaction," further indicating that "derivatives" can be nucleic acids with modifications for covalent bonding. The unasserted patents that 10x cites are not in this case and cannot expand the scope of the '767 patent. *See X2Y Attenuators, LLC v. ITC*, 757 F.3d 1358, 1366 (Fed. Cir. 2014) ("disclosures of related patents may inform the construction of claim terms common across patents, but it is erroneous to assume that the scope of the invention is the same"). Accordingly, claims reciting "amplicons" in other patents do not change the '767 patent.²⁵

Because the only dispute involves amplicons, 10x's remaining arguments are distractions. While "fluorescence imaging" in isolation may have a plain meaning (Br. 46), that is not in dispute. 10x argues there was no lexicography or formal disavowal that restricts the claims to amplicons. *See id.* at 49-50. Vizgen does not argue that, either—rather, Vizgen contends the inventors did not teach or even suggest any method that eschews amplification. Instead, as taught, amplification is explicitly required for the 3D fluorescence imaging methods claimed. 10x has no response to Vizgen's arguments that expanding the claims to encompass imaging without amplicons would render the claim invalid for lack of written description.

²⁵ The cases 10x cites are inapposite. For example, *TQ Delta*, addressed a claim term supported by certain embodiments rather than every embodiment, as is the case here, and did not explain the basis for relying on related patents. 2018 U.S. Dist. LEXIS 107098, at *14-16; *see also Personalized Media*, 952 F.3d at 1342 (finding "language from related patent claims . . . counterbalanced by other claims of the '091 patent itself").

II. VIZGEN ASSERTED PATENT (595 CASE)

A. INTRODUCTION

1. Defendant 10x's Introduction

Fluorescence in situ hybridization (FISH), first developed several decades ago, is a technique that uses fluorescent probes to bind and detect biological targets (such as RNA) “in place” where the target is located in the sample. By 2014, the time of the 303 Patent’s purported invention, major advances in FISH detection techniques to improve the number of targets that can be detected simultaneously had already been developed that included the use of primary probes (probes binding to the target encoding a codeword) and secondary probes (probes that bind to primary probes and detectable by fluorescent signals in multiple steps to mimic a code). These techniques were developed and used, for example, by George Church’s lab at Harvard and described in a provisional application filed in 2011. Other groups also worked on FISH detection before Vizgen, including Long Cai’s lab at California Institute of Technology (SeqFISH), which filed a provisional application in 2013. The detection technique in the 303 Patent is an incremental alleged improvement of earlier multi-probe FISH techniques.

The 303 Patent purports to improve known FISH methods by permitting error correction on the “codes” created while secondary probe signals were either read or not read at the location of a given target in the sample. Vizgen’s technique was simplistic and mathematical instead of technological. Vizgen (1) restricted its signals to correspond strictly to on/off binary values (a “1” for a detected signal and a “0” for the absence of the signal) and (2) to construct codewords by suggesting well-known error detection and correction techniques (e.g., Hamming codes) to differentiate the codewords enough to detect and correct potential errors without applying any further intelligence. 10x’s proposed constructions clarify, consistent with the 303 Patent’s specification and file history, how to match the constructed binary codewords to valid codewords

in a codebook, what functions the “error detection or correction system” perform, and what structures the “error detection or correction system” corresponds to.

2. Plaintiff Vizgen’s Introduction

The ’303 patent is directed to novel ways of studying gene expression in biological systems, claiming methods that provide high-resolution, sub-cellular insight to determine both the precise location and specific identifies of thousands of genes being simultaneously expressed in individual cells. As 10x’s own expert admitted in 2015, the disclosed technology represents “a major advance for spatial transcriptomics, with exciting potential applications in immunology.” **Ex. V1** (A1311-1313). The scientific community recognized the significant contributions of Vizgen’s MERFISH method (cited and discussed in ’303 patent, *see* 43:8-10 (A0401)) and the ’303 patent’s inventors with multiple prestigious and selective awards, including the 2023 Dreyfus Prize in the Chemical Sciences, 2022 Heinrich Wieland Prize, 2021 Lurie Prize in Biomedical Sciences, 2020 Vilcek Prize in Biomedical Sciences, 2019 Pearl Meister Greengard Prize, 2019 NAS Award for Scientific Discovery, 2017 Anne Heidenthal Prize for Fluorescence Research, and Biotech Breakthrough Awards’ “Overall BioTech Company of the Year” (2022).²⁶ 10x improperly tries to restrict the inventions of the ’303 patent by reading portions of the specification into the claims, while overlooking contrary evidence.

²⁶ See <https://www.dreyfus.org/xiaowei-zhuang-2023/>; <https://www.heinrich-wieland-prize.de/laureates/since-2020/articles/id-2022-professor-xiaowei-zhuang-phd.html>; <https://fnih.org/our-programs/powering-science/the-lurie-prize-in-biomedical-sciences/>; <https://vilcek.org/prizes/prize-recipients/xiaowei-zhuang/>; <https://www.rockefeller.edu/greengard-prize/2019-ceremony/>; <https://www.nasonline.org/programs/awards/2019-nas-awards/Zhuang.html>; <https://www.chroma.com/anne-heidenthal-prize>; <https://biotechbreakthroughawards.com/2022-winners/>.

B. DISPUTED TERMS (Terms Proposed by Defendant 10x)**1. “matching the codewords with valid codewords in a codebook by comparing the codewords to the valid codewords in the codebook”**

Claim Term²⁷	Vizgen’s Proposed Construction	10x’s Proposed Construction
“matching the codewords with valid codewords in a codebook by comparing the codewords to the valid codewords in the codebook” 303 Patent, claim 1	Plain and ordinary meaning	“determining that each bit of a produced codeword is the same as each bit in the corresponding position of a valid codeword in the codebook”

a. Defendant 10x’s Opening Position

The 303 Patent claims a particular way to associate readout signals with a valid codeword in the codebook: the readout signals are translated to binary values (1 represents a detected signal and 0 represents the absence of the signal). The binary value codeword is compared bit by bit with codewords in the codebook to determine whether it is exactly the same as a valid codeword in the codebook. If no match is found, then the error detection or correction system determines which bit of the produced codeword has an error and whether the error is correctable. 10x’s proposed construction aligns with the scope of the invention.

The claim language, specification, and prosecution history all support 10x’s proposed construction. “Claim construction focuses on intrinsic evidence—the claims, specification, and prosecution history.” *Sprint Commc’ns Co. v. Cox Commc’ns Inc.*, 302 F.Supp. 3d 597, 607 (D. Del. Nov. 9, 2017). The specification consistently describes that the codeword produced from fluorescent readouts is compared bit by bit to codewords in the codebook to determine whether it is a perfect match with a codeword in the codebook. *See, e.g., Ex. X6* (“303 Patent”) at 36:40-43 (A00397) (“If there are no missed-detection events or false positive signal in the images, this

²⁷ D.I. 164-2 at 5-6 (261 Case); D.I. 55-2 (1375 Case); D.I. 203-2 (595 Case).

codeword will perfectly match one of the expected codewords.”), 36:43-54 (A0397) (showing bit by bit match); 42:41-46 (A0400) (“The SECDED codebook decoded these as either perfect matches to target mRNA codewords, correctable errors which can be unambiguously mapped back to target mRNA, or uncorrectable errors”), Figures 12B-C (A0359) (showing diagrams that vertically align each bit of two codewords for comparison). The error detection or correction operations described in the specification require bit by bit matching, in which any unmatched bit would be detected and corrected (if correctable). *See, e.g., Ex. X6* 20:8-13 (A0389) (“the codewords may be organized such that, if no match is found ... then the match may be identified as an error, and optionally, error correction may be applied [] to determine the correct target for the nucleic acid probes.”), 21:21-25 (A0390) (“If no match is found, then an error in the reading of the codeword may be identified”), 36:54-57 (A0397) (missed-detection or false positive signals are corrected), 42:41-46 (A0400) (using a SECDED codebook, errors need to be corrected to be “unambiguously mapped back to target mRNA”), 35:44-48, 49:50-64, Fig. 12B (A0397, 404, 359) (correcting a single unmatched bit in a Hamming system);²⁸ *Ex. X1 ¶¶* 62-65 (A0025-27). Claims 9 and 10 also specify that when the produced codeword has “one error” or “one or more errors,” the produced codeword is “not matched with one of the valid codewords.” *Ex. X6*, (A0423).

The applicant’s statement during prosecution also confirms 10x’s reading of the claim. “The prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention...” *Phillips*, 415 F.3d at 1317. During prosecution, the examiner rejected the claim because “it is unclear ... in which situation, a codeword matches with

²⁸ While the specification also describes “error-correctable matches” or “matches with one bit errors,” *e.g.* 303 Patent 47:25, 47:49, 49:61 (A0403-404), they are “matches” because they are perfect matches after error correction and correspond to “applying an error detection or correction system, matching the one of the codewords with another of the valid codewords in the codebook.” 303 Patent, claim 1; *e.g., id.* 21:19-29 (A0390) (describing having a match after applying error correction).

a valid codeword and in which situation, a codeword does not match with a valid codeword.”

Ex. X8 at VIZ00002533 (A0449) (October 22, 2020 Rejection).²⁹ In response to this rejection, the applicant stated that “claim 1 has been amended to recite ... identifying the codeword at each location matched to one of the valid codewords associated with the plurality of nucleic acid targets, by **comparing the values at each position of the codeword to the values at each position of the valid codeword.**” **Ex. X7** at VIZ00002552 (A0433) (Applicant’s January 22, 2021 Response); *see also* **Ex. X7** at VIZ00002555 (A0436) (repeating the same amended claim language). 10x’s construction is consistent with the applicant’s statement to the PTO about the scope of the invention, which is part of the intrinsic record. Additionally, in response to the examiner’s 35 U.S.C. § 101 rejection, the applicant argued that “the nucleic acid targets will be identified error-free (due to the codewords associate [sic] with unique combination of read sequences that allow error-detection step),” confirming that the match with valid codewords is a perfect “error-free” match. **Ex. X7** at VIZ00002555 (A0436) (Applicant’s January 22, 2021 Response).

b. Plaintiff Vizgen’s Answering Position

10x’s construction improperly narrows claim 1 to an embodiment where “matching” means “each bit” of a codeword is “the same.” The claims contain no such restrictions, and the ’303 patent discloses various kinds of matching, both exact and inexact. 10x ignores (1) the language of claim 1 and dependent claims, (2) embodiments with a broader application of “matching,” and (3) the plain meaning of “match.” 10x fails to overcome the “‘heavy presumption’ that the terms used in claims mean what they say and have the ordinary meaning that would be attributed to those words by persons skilled in the relevant art.” *SuperGuide Corp. v. DirecTV Enters.*, 358 F.3d 870,

²⁹ At the time of this rejection, the claim language was “matching the codewords to the valid codewords in the codeword space.” **Ex. X9** at VIZ00002524 (A0463) (April 17, 2020 Applicant Response).

874 (Fed. Cir. 2004); Declaration of Dr. Michael Metzker (“Metzker Decl.,” Ex. V4) ¶ 38 (A1334).

First, the language of the claims supports Vizgen’s position. Claim 1 says nothing about matching “each bit” or requiring a perfect match. Moreover, the dependent claims contradict 10x’s view. 10x argues claims 9 and 10 require that “one of the codewords is not matched . . . when the one of the codewords has one or more errors,” or “has one error,” respectively. *See* Br. 56. However, claim 11 expressly provides for no match when there are “**two** errors.” ’303 patent cl. 11 (A0423). Thus, *one* error (less than two) would still permit matching. Claim 12 also recites “comparing the values **at each of the positions** of the codewords,” which indicates that claim 1 does *not* require any bit-by-bit comparison. *Id.* cl. 12 (A0423). This refutes 10x’s view that imperfect matches occur only after error detection or correction. *Cf.* Br. 56 n.28. 10x’s construction improperly renders claims 11 and 12 meaningless by adding a new “each bit” limitation. *See Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022) (“[I]f a dependent claim reads on a particular embodiment of the claimed invention, the corresponding independent claim must cover that embodiment as well.”); Metzker Decl. ¶ 40 (A1334-1335).

Next, 10x’s construction ignores embodiments that allow matching despite differences. The ’303 patent teaches both “exact matches” (’303 patent at 21:64-67 (A0390)) and “matches having one or more one-bit errors” (*id.*) or “error-correctable matches” (*id.* at 47:23-26 (A0403)). The patent discloses use of “confidence levels” calculated from ratios of the “number of **exact matches** to the number of **matches having one or more one-bit errors**.” *Id.* at 21:63-22:17 (A0390). Other Examples show that matching need not be perfect. *See id.* at Ex. 1, 34:50-52 (A0396) (codewords “allow unique identification of each RNA **with some degree of experimental error tolerance**”), Ex. 5, 47:23-26 (A0403) (“If the word **exactly matched** one of the 140 MHD4 code words (exact matches) or **differed by only one bit** (error-correctable matches), it was assigned

to the corresponding RNA species (FIG. 6D).”), Ex. 10, 64:45-48 (A0411) (“[I]f the measured binary word matched the code word of a specific RNA perfectly *or differed from the code word by one single bit*, it was assigned to that RNA.”); *see also* Metzker Decl. ¶¶ 41-42 (A1335-1336). 10x’s expert cites only certain examples, ignoring others, to limit the claims to “a perfect bit by bit assessment.” Satija Decl. ¶¶ 62, 65 (A0025-27).³⁰ No such language appears in the patent. *See SuperGuide*, 358 F.3d at 875 (“[A] particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment.”).

The prosecution history did not restrict the claims to bit-by-bit matching: the applicant’s reference to “identified error-free” does not say “matching” must be perfect, only that errors are addressed during the overall identification process. **Ex. X7** at VIZ00002555 (A0436). Finally, extrinsic evidence shows that “matching” allows for imperfect matches. For example, Merriam-Webster defines “match” as “3a(1): to put in a set possessing equal or harmonizing attributes; 3a(2): to cause to correspond; 3(b(1): to be the counterpart of; 3b(2): to harmonize with; 3c: to provide with a counterpart.” **Ex. V2** (A1314-1317); *see also* **Ex. V3** (A1318-1321) (“1. to search through a database for a similar piece of information”). The Court should adopt plain and ordinary meaning.

c. Defendant 10x’s Reply Position

Vizgen ignores the clear statement made by applicant during prosecution that “matching” the binary codewords with a valid codeword means “comparing the values *at each position* of the codeword to the values at each position of the valid codeword.” Applicant made clear the meaning of “matching” to gain allowance; amending claim 1 to add such language would have been redundant. Applicant’s decision not to duplicate this concept in the claim does not broaden the

³⁰ In discussing MERFISH, 10x’s expert observed that codewords are “assigned to a specific RNA if the detected ‘word’ matches that RNA’s code *or is only one error away*.” **Ex. V1** (A1311-1313).

claim, nor does it change the fact that a POSITA, reading the specification and the prosecution history, would understand that “matching” has the meaning 10x proposes. The disclosures of “error-correctable matches,” “error-tolerant matches” or “matches having one or more one-bit errors” in the specification do not change this conclusion. There is no disclosure in the patent of “error-correctable” or “error-tolerant” matching with a codeword in the codebook *without* first performing an error correction step to eliminate the error. The term “error-correctable matches” (Ex. X6, 303 Patent, 47:25 and 49:61 (A0403-404)) is used in Example 5, which describes an MHD4 (Modified Hamming Distance 4) coding scheme, in which “every single-bit error produces a word that is uniquely close to a single code word, allowing such errors to be *detected and corrected*.” 303 Patent 44:40-45 (A0401). Thus, “error-correctable matches” are bit by bit comparisons that become “matched” only after the error has been corrected (*see also* 64:45-48 (A0411), relied on by Vizgen is similarly in the context of “16-bit MHD4 code”). Further, 34:50-52 (A0396) generally discusses error tolerance in codeword design for errors that can be detected and/or corrected while 21:63-22:17 (A0390) generally discusses the calculation of confidence ratio for a nucleic acid target.

Vizgen argues that 10x’s construction would render claims 11 and 12 meaningless. When a construction is “supported by either the specification or the prosecution history,” as it is supported by both here (*see* Br. 57-59), a dependent claim should not change that otherwise correct construction. *Tubular Roller, LLC v. Maximus Oilfield Prods., LLC*, 2023 U.S. App. LEXIS 16295, at *15-16 (Fed. Cir. June 28, 2023). Moreover, claim 11 is not rendered meaningless because “not matched ... when [the codeword] has two errors” applies only to the two-error condition, not a one-error state.

Rather than address the prosecution history cited by 10x, Vizgen argues “identified error-

free” does not mean “‘matching’ must be perfect” without explaining how an error-free identification is not bit-by-bit. Finally, Vizgen resorts to a generic English dictionary and a database-related definition, ignoring that here “matching” is performed on binary codes. Technical dictionaries support 10x’s construction. *See Ex. X30* (A1231) (defining “matching” as “[t]he process of testing whether two data items are identical or of finding a data item that is identical to a key”).

2. “if one of the codewords is not matched with one of the valid codewords in the codebook, applying an error detection or correction system, matching the one of the codewords with another of the valid codewords in the codebook, or discarding the one of the codewords”

Claim Term³¹	Vizgen’s Proposed Construction	10x’s Proposed Construction
“if one of the codewords is not matched with one of the valid codewords in the codebook, applying an error detection or correction system, matching the one of the codewords with another of the valid codewords in the codebook, or discarding the one of the codewords” 303 Patent, claim 1	Plain and ordinary meaning	The embodying system must be capable of performing the following conditional steps: “if each bit in a produced codeword does not correspond with the bit in the same location of a valid codeword, applying an error detection or correction system [as construed] and either assigning the corrected codeword to another valid codeword or discarding the codeword.”

a. Defendant 10x’s Opening Position

To start, this term requires construction because it is ambiguous on its face. There are (at least) three possible interpretations:

If one of the codewords is not matched, applying an error detection or correction system that yields two possible outcomes: matching with another valid codeword, or discarding the codeword.

If one of the codewords is not matched, there are three options: (1) applying an error detection or correction system; (2) matching with another valid codeword in the codebook;

³¹ D.I. 164-2 at 6-7 (261 Case); D.I. 55-2 (1375 Case); D.I. 203-2 (595 Case)

or (3) discarding the codeword.

If one of the codewords is not matched, there are two options: (1) applying an error detection or correction system to match the codeword with another valid codewords, or (2) discarding the codeword.

10x's construction, corresponding to the first interpretation, resolves the ambiguity and is supported by the intrinsic evidence. Vizgen's "plain and ordinary meaning" construction does not provide any clarity to an ambiguous term and is not helpful to the court or the jury.

The specification makes it clear that the error detection or correction system is able to detect errors in the codeword and decide whether the errors are correctable; correctable codewords are corrected and uncorrectable codewords are discarded. *See Ex. X6*, 303 Patent 11:16-23, 12:51-55, 20:6-13, 21:19-25, 36:54-57, 47:59-48:3, 65:36-68:63 (A0385, 389-390, 397, 403, 412-413). As explained regarding "error detection or correction system" term, the "error detect or correction system" described in the patent can detect errors and correct correctable errors and discard uncorrectable errors. *See, e.g.*, 42:37-46 (A0400) (a SECDED code can be decoded "as either perfect matches to target mRNA codewords, correctable errors which can be unambiguously mapped back to target mRNA, or uncorrectable errors"), 44:43-48, 46:15-36 and Figure 12 (A0401-402, 359) (describing error detection and correction using a Hamming system); 21:5-11 (A0390) (characterizing Golay code as having error detection and correction capabilities).

10x's construction also gives meaning to all words of the claim language. When the claim recites two alternative scenarios (here, matching with another codeword when correctable and discarding when not correctable), the recited system "must be capable of addressing each alternative, regardless of which alternative occurs at any particular point." *Interdigital Tech. Corp. v. Lenovo Holding Co.*, No. 19-1590-LPS, 2021 U.S. Dist. LEXIS 88682, at *15-16 (D. Del. May 10, 2021). During prosecution, the 303 Patent was only allowed by the PTO after the examiner amended the claim to add this limitation. *Ex. X10* at VIZ00002860 (A0477) (May 18, 2021

Examiner Amendment and Reason for Allowance). The examiner's amendment replaced the previous language "if no match is found, applying error correction to the codeword to match one of the valid codewords or discarding the codeword." **Ex. X7** at VIZ00002558 (A0439). The changes made by the examiner in order to allow the claim confirm that "matching" and "discarding" are what the error detection or correction system is configured to achieve in different scenarios.

b. Plaintiff Vizgen's Answering Position

10x's construction raises two issues: (1) whether "each bit" must "correspond" for matching, and (2) the sequence of steps in claim 1(j). Regarding the first issue, 10x's definition would import its construction of "matching the codewords . . ." as requiring exact matching of "each bit," which is incorrect for the reasons above.

For the second issue, 10x's construction is unnecessary and changes the words of the claim. Vizgen does not dispute that claim 1 recites "applying an error detection or correction system," and then "matching the one of the codewords with another of the valid codewords in the codebook, or discarding the one of the codewords." However, this arises from the plain language of the claims and the specification. *See* '303 Patent at 11:8-28, 21:25-34, 47:23-26 (A0385, 390, 403). 10x's attempt to rewrite the claim and add terms like "each bit," "assigning," and "corrected" are unsupported and would only confuse the jury. Notably, 10x's expert does not opine on this phrase. There is no need for the Court to construe this phrase as 10x proposes.

c. Defendant 10x's Reply Position

Vizgen ignores the primary dispute—whether the accused method must be capable of addressing each alternative, "regardless of which alternative occurs" (*see Interdigital*, 2021 U.S. Dist. LEXIS 88682, at *15-16), or whether it is an optional step such that a system not capable of correcting "errors" or non-matches can infringe (or invalidate) this claim. That dispute should be resolved to address infringement and validity. Vizgen does not dispute that this term is ambiguous

and susceptible to multiple interpretations. Instead, Vizgen’s one-sentence argument³² focuses on the terms “assigning” and “corrected” in 10x’s construction. 10x’s construction clarifies that the corrected codeword, not the original codeword with error(s), is determined to be the same bit by bit with another codeword in the codebook, consistent with intrinsic evidence.

3. “an error detection or correction system”

Claim Term ³³	Vizgen’s Construction	Plaintiffs’ Construction
“an error detection or correction system” '303 patent claim 1	This claim limitation is not governed by 35 U.S.C. § 112(f). No construction necessary.	This limitation is governed by 35 U.S.C. § 112(f). • Function: detecting or correcting unmatched bits in a produced codeword. • Structure: “A Hamming system, a Golay code, or an extended Hamming system (or a SECDED system, i.e., single error correction, double error detection)” as disclosed in Col. 11:12-28, Col. 20:51-21:34, Col. 38:4-17, Col. 65:36-68:63.

a. Defendant 10x’s Opening Position

The term “an error detection or correction system” should be construed as a means-plus-function limitation under 35 U.S.C. § 112(f) because it recites functions without reciting sufficient structures to perform the function and is not understood by a POSA to have a “sufficiently definite meaning as the name for structure.” *Williamson v. Citrix Online*, 792 F.3d 1339, 1348 (Fed. Cir. 2015). Because the patentee used functional claim drafting under § 112(f), the claim scope should be limited to the error detection and correction algorithms actually described in the specification.

When a claim term lacks the word “means,” the rebuttable presumption that § 112(f) does not apply is overcome if the term recites “‘function without reciting sufficient structure for performing that function.’” *Id.* at 1349. “An error detection or correction system” merely recites function (detecting or correcting errors), not structure.

³² In the same sentence Vizgen also takes issue with “each bit,” which is addressed in the above “matching” term.

³³ D.I. 164-2 at 7-8 (261 Case); D.I. 55-2 (1375 Case); D.I. 203-2 (595 Case)

“System” is a well-established nonce word that substitutes for “means.” *See* MPEP § 2181 (listing “system for” as a “non-structural generic placeholder[] that may invoke 35 U.S.C. 112(f)”; *Team Worldwide Corp. v. Intex Rec. Corp.*, No. 2020-1975, 2021 U.S. App. LEXIS 27284, at *17 (Fed. Cir. Sep. 9, 2021) (“[a]ny device or system’... together with the functional language, suggests the ‘black-box nature’ of the term”); *Verint Sys. v. Red Box Recorders, Ltd.*, 166 F. Supp. 3d 364, 381 (S.D.N.Y. 2016) (“‘system’ standing alone is a nonce word that does not describe a structure that could perform the listed functions and the modifier ‘communication monitoring’ provides a functional description of the system”); *Joao Control & Monitoring Sys. LLC v. Protect Am., Inc.*, No. 1-14-CV-134-LY, 2015 U.S. Dist. LEXIS 109187, at *16-17 (W.D. Tex. Aug. 18, 2015) (“system” in the term “a system for detecting a failure...” functions merely as a nonce word); *Velocity Patent LLC v. FCA US LLC*, No. 13 C 8419, 2018 U.S. Dist. LEXIS 149907, at *16 (N.D. Ill. Sep. 4, 2018) (“processor subsystem” is a nonce word); *Intellectual Ventures I, LLC v. Canon Inc.*, No. 13-473-SLR, 2015 U.S. Dist. LEXIS 38910, at *46 (D. Del. Mar. 27, 2015) (“processing device” was not “inherently capable of performing” the claimed function). The modifier “error detection or correction” merely provides functional description—correcting or detecting error—and does not impart structure. The claim language only provides that the function of the system is to match the codeword to another valid codeword or discard the codeword, without any further language in the claim that might inform structure. **Ex. X6**, 303 Patent, claim 1 (A0422-423); **Ex. X1** ¶¶ 66-67 (A0027-28).

The specification consistently describes the error detection or correction system in functional terms. Only two paragraphs in the specification mention error correction or detection systems (**Ex. X6**, 303 Patent, 11:8-28, 12:45-55 (A0385)) and both describe the error correction or detection system in functional language. *See* 303 Patent 11:16-20 (A0385) (“such systems can

be used to identify where errors have occurred, and in some cases, such systems can also be used to correct the errors and determine what the correct codeword should have been”); *see also* 12:51-55 (A0385) (same).

The term “error detection or correction system” does not connote a well-understood structure or class of structures to a POSA. Courts have held that a term is subject to § 112(f) where various methods or algorithms may perform the recited function. *See Visual Networks Operations, Inc. v. Paradyne Corp.*, No. DKC 2004-0604, 2005 U.S. Dist. LEXIS 49287, at *78 (D. Md. June 15, 2005) (“‘Logic for determining at least one dedicated time slot(s)’ describes only a function, not a structure. Any number of different algorithms, in the form of either computer code or hard-wired circuit logic, could perform the recited function.”); *XR Commc’ns, LLC v. Ruckus Wireless, Inc.*, No. 18-cv-01992-WHO, 2021 U.S. Dist. LEXIS 166218, at *14 (N.D. Cal. Sep. 1, 2021) (“A so-called ‘known class of circuit structures’ cannot be sufficient under the *Williamson* standard.”). A POSA would understand that the term encompasses endless ways to detect and correct errors: it would just need to determine whether an unmatched codeword should match with another codeword in the codebook or be discarded. A POSA reading this term would have recognized that error detection or correction for a binary codeword can be achieved in many different ways, *e.g.*, through a simple brute force algorithm (*e.g.*, changing “0” to “1” and “1” to “0” position by position until it matches a code), establishing a rule for the codebook and determining whether a produced codeword follows the rule, a Hamming system, a parity bit, convolutional coding, or many others. **Ex. X1 ¶¶** 68-73 (A0028-30). The infinite possibilities of algorithms that can perform the claimed function do not place any “specific constraints on how such a limitation is to be construed” and place the term in the scope of § 112(f). *Williamson*, 792 F.3d at 1347.

Because § 112(f) applies, the construction must identify the claimed function and the

structure disclosed in the specification that corresponds to the claimed function. *Id.*, 792 F.3d at 1351 (“Construing a means-plus-function claim term is a two-step process. The court must first identify the claimed function ... Then ... determine what structure, if any, disclosed in the specification corresponds to the claimed function.”). It is evident from the claim language that the claimed function is detecting or correcting unmatched bits in a produced codeword. As explained above, the 303 Patent repeatedly and consistently describes a decoding system that matches codewords bit by bit with codewords in the codebook, and, if no match is found, the error correction or detection system is applied that will attempt to locate the erroneous bit and correct it. *See, e.g.*, 303 Patent 36:40-54, 42:41-46, 20:8-13, 21:21-25, 36:54-57 (A0397, 400, 389, 390, 397); **Ex. X1 ¶¶** 74-75 (A0030).

10x’s proposed corresponding structure, “a Hamming system, a Golay code, or an extended Hamming system (or a SECDED system, i.e., single error correction, double error detection),” is taken directly from the portion of the specification that discloses the structures for performing error correction and detection. 303 Patent 11:12-16 (A0385); *see also* 12:46-51 (A0385) (same). The specification consistently describes the use of Hamming, Golay, and extended Hamming (or SECDED) codes (and only these structures) to design codewords and codebooks that support the application of an error detection and correction system. 303 Patent 20:19-22 (A0389) (describing Golay and Hamming codes), 20:51-21:34 (A0389-390) (describing designing codewords using Hamming, SECDED, and Golay codes), 34:63-35:18 (A0396-397) (describing error-correcting encoding schemes using Hamming codes), 44:37-59 (A0401) (same), 46:15-36 (A0402) (same), 38:4-17 (A0398) (describing codebook design using SECDED codes), 65:36-68:63 (A0412-413) (describing the error-correcting and detecting capability of Hamming distance 4 (HD4) codes); *see also* **Ex. X1 ¶¶** 76-79 (A0030-32). Therefore, the corresponding structure of this term should be

limited to what the patent actually describes, which are the specific algorithms disclosed in the cited portions of the specification that perform error correction and detection using Hamming system, Golay code, or an extended Hamming (or SECDED) system. *Aristocrat Techs Austl. Pty. Ltd. v. Int’l Game Tech.*, 521 F.3d 1328, 1331–32 (Fed. Cir. 2008) (in a means-plus-function claim “in which the disclosed structure is a computer or a microprocessor programmed to carry out an algorithm, a corresponding structure must be a specific algorithm disclosed in the specification.”).

b. Plaintiff Vizgen’s Answering Position

10x erroneously argues means-plus-function rules govern this phrase—even though the claim does not recite “means for”—and then compounds its error by improperly reading the specification into the claim. Section 112(f) does not apply because “an error detection or correction system” does not include means-plus-function language, while the claims recite sufficient structure to perform the relevant functions. As 10x acknowledges, the claims do not say “means for,” so the presumption is § 112(f) does *not* apply. *See Williamson*, 792 F.3d at 1348-49.

In this case, 10x cannot overcome this presumption and show “by a preponderance of the evidence, that persons of ordinary skill in the art would not have understood the [term] to connote structure in light of the claim as a whole.” *Dyfan LLC v. Target Corp.*, 28 F.4th 1360, 1367 (Fed. Cir. 2022). 10x’s contention that “system” is a “well-established nonce word” is misplaced. Br. 65. The MPEP notes that “system *for*” can be a generic placeholder under a given case’s “unique set of facts,” MPEP § 2181, but also identifies an entire class of system claims, which do not automatically invoke § 112(f), *id.* § 2111. The cases that 10x cites involve different circumstances and do not show that “system” is means-plus-function. For example, *Team Worldwide Corp. v. Intex Recreation Corp.* addressed a *dictionary quotation* referring to “[a]ny device or system.” 2021 U.S. App. LEXIS 27284, at *17. 10x’s remaining cases involve disparate terms like “processing device” and “processor subsystem,” or entirely different technologies. *E.g., Verint*

Sys., 166 F. Supp. 3d at 381-82 (interpreting “communication monitoring system” in patent for secure electronic communications). Moreover, 10x ignores numerous cases holding that “system” is not a nonce word. *See, e.g., Dyfan*, 28 F.4th at 1370 (“system” not a nonce word, and not means-plus-function); *CDN Innovations v. Grande Commc’ns Networks*, No. 4:20-cv-653-SDJ, 2021 U.S. Dist. LEXIS 153232, at *111 (E.D. Tex. Aug. 13, 2021) (“mapping system” not means-plus-function); *Hillman Grp., Inc. v. Keyme, LLC*, No. 2:19-CV-209-JRG, 2020 U.S. Dist. LEXIS 115981, at *45-46 (E.D. Tex. July 2, 2020) (“key analysis system” not means-plus-function); *Automatic Equip. Mfg. Co. v. Danko Mfg.*, No. 8:19-CV-162, 2020 U.S. Dist. LEXIS 147240, at *17-19 (D. Neb. Aug. 14, 2020) (“an arm drive system” not means-plus-function); *Perdiem Co. LLC v. IndusTrack LLC*, No. 2:15-cv-727, 2016 WL 3633627, at *37-39 (E.D. Tex. July 7, 2016) (“administrator system” not means-plus-function); *Blue Spike LLC v. Grande Commc’ns Inc.*, No. 4:20-cv-671, 2021 WL 5094911, at *28-30 (E.D. Tex. Nov. 2, 2021) (“a vending system” and “a purchasing system” not means-plus-function).

In this specific case, the ’303 patent provides structural context for the term through the claims and specification. “[E]rror detection or correction” modifies “system” and indicates structure because a POSA would understand that various known code systems could perform these functions. Metzker Decl. ¶¶ 44-45 (A1337-1338); *Williamson*, 792 F.3d at 1351 (“the presence of modifiers” to a claim term can connote structure). The ’303 patent describes recognized code systems applied innovatively in a new context to detect and correct errors when imaging single-cell gene expression. For example, claim 1(i) discusses a codeword system where “each of the codeword represents one of the plurality of different nucleic acid targets.” Claim 8 notes an embodiment where “the valid codewords form an error-checking or an error-correcting code space.” Thus, the claims indicate the design of the error detection or correction system. Metzker Decl.

¶ 44 (A1337). The specification further teaches: “A variety of different error-correcting codes can be used, many of which have previously been developed for use within the computer industry” ’303 Patent at 11:23-27 (A0385). The patent provides non-limiting “examples of such error-correcting codes.” *Id.* at 11:27-28 (A0385). “Such error-detecting and/or the error-correction code may take a variety of forms. A variety of such codes have previously been developed in other contexts such as the telecommunications industry, such as Golay codes or Hamming codes.” *Id.* at 20:18-24 (A0389). At minimum, the ’303 patent explains that an error detection or correction system can be a class of recognized code structures. *See Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1300 (Fed. Cir. 2014) (a limitation “may describe a class of structures”). In this context, a POSA would have understood that the claim “connotes sufficiently definite structure.” *Id.* at 1296; Metzker Decl. ¶ 45 (A1337-1338).

10x’s argument that “error detection or correction” supplies only function and not structure is misplaced. *See Zeroclick, LLC v. Apple Inc.*, 891 F.3d 1003, 1008 (Fed. Cir. 2018) (“the mere fact that the disputed limitations incorporate functional language does not automatically convert the words into means for performing such functions”). “[T]he claim language and specification” can disclose structure “within the context of the invention.” *Apple*, 757 F.3d at 1301. For example, *CDN* held § 112(f) did not apply to “mapping system” because “[t]he specification further refers to the mapping system in the context of computer systems, as evident from discussion of databases, application servers, and the end-user devices.” 2021 U.S. Dist. LEXIS 153232 at *111.

If the Court determines that § 112(f) applies, Vizgen disagrees with 10x’s proposed function and structure. Both are overly restrictive and contradict the specification. 10x’s function of “detecting or correcting unmatched bits in a produced codeword” attempts to include bit-by-bit comparison, which is incorrect for the reasons above. The proper function is simply “detecting or

correcting errors,” as the claims state. Metzker Decl. ¶ 47 (A1338). 10x’s structure proposal improperly seeks to limit the claim to three named approaches. However, the ’303 patent states those approaches are only examples: “The codewords may be assigned within a code space *in some embodiments* using an error-detection or an error-correcting system, *such as* a Hamming system, a Golay code, or an extended Hamming system or a SECDED system.” ’303 Patent at 12:46-51 (A0385); *see also id.* at 20:18-24 (A0389) (“*such as* Golay codes or Hamming codes”); 21:5-8 (A0390) (“For example, *a code with the same error correcting properties* of the SECDED code may be formed . . .”). 10x’s expert fails to acknowledge the existence of other systems, or explain why a POSA would not have known or used other structures. *See* Satija Decl. ¶¶ 76-79 (A0030-32); Metzker Decl. ¶¶ 48-49 (A1338-1340).

If the Court determines that § 112(f) does not apply, plain and ordinary meaning should govern because 10x offers no alternative construction. *E.g., Blue Spike*, 2021 WL 5094911 at *29 (“plain meaning” where “Defendants present no alternative proposed construction”).

c. Defendant 10x’s Reply Position

The claim term “an error detection or correction system” in Claim 1 is written in purely functional terms with no known physical structure. None of Vizgen’s cited cases involve similar claim language. In *Dyfan*, the Federal Circuit found that “the term ‘system’ may well be a nonce term” (28 F.4th at 1370) but found that a claim which recites “[a] system, comprising...”, followed by various components is not written in functional terms. Vizgen’s other cases involve situations where the “system” was a class of physical mechanisms or devices with known locations and components (“key analysis system” in *Hillman Grp.*, 2020 U.S. Dist. LEXIS 115981, at *47-51; “arm drive system” in *Automatic Equip. Mfg.*, 2020 U.S. Dist. LEXIS 147240, at *17-19); a system with definite structure used in “common parlance” (“vending system” and “purchasing system” in *Blue Spike*, 2021 U.S. Dist. LEXIS 211010, at *76-80) or that the patent provides a detailed

description of the “system” that included various servers, files, and databases (*CDN Innovations*, 2021 U.S. Dist. LEXIS 153232, at *111-112). In contrast, “an error detection or correction system” does not correspond to a physical device, is not a term for structures of common parlance, and neither the claim language nor the specification describes the location or components of the system. Vizgen also attempts to distinguish the nonce word “system” with the phrase a “system for” in the MPEP, but the phrase “an error detection or correction system” in the context of the 303 Patent claims is indistinguishable from a “system for detection or correction of errors.”

Vizgen’s attempts to identify a structural context in the specification and other claims are so vague and circular (“known code systems could perform these functions,” “recognized code structures,” (Br. 69) or “codeword systems used for error detection or correction” (Ex. V4, Metzker Decl., ¶ 44 (A1337))) that they confirm the claim phrase provides no structure. The claims cited by Vizgen merely describe the purpose of codewords (representing nucleic acid targets, claim 1(i)) or rehash the “error-checking” and “error-correcting” functions (claim 8). Vizgen does not dispute that the term encompasses endless ways to detect and correct errors and its expert opined that other unspecified “code structures” can perform the function. Ex. V4, Metzker Decl., ¶ 49 (A1339-1340).

The law is clear that any corresponding structure is limited to what is actually described in the specification, contrary to Vizgen’s argument. The scope of a means-plus-function limitation is “sharply limited to the structure disclosed in the specification and its equivalents.” *Genuine Enabling Tech., LLC v. Sony Corp.*, 2020 U.S. Dist. LEXIS 40277, at *41 n.7 (D. Del. March 9, 2020). “Where a patent says alternative structures may be used but does not identify them, the structure is limited to the example disclosed.” *Dragon Intellectual Prop., LLC v. AT&T Servs.*, C.A. No. 13-2058-RGA, 2015 U.S. Dist. LEXIS 119506, at *15 (D. Del. Sept. 9, 2015).

III. NANOSTRING ASSERTED PATENTS (1375 CASE)

A. INTRODUCTION

1. Defendant 10x's Introduction

NanoString's 689 (**Ex. X2** (A0046-164)) and 142 Patents (**Ex. X3** (A0165-282)) (the "NanoString Patents") arose out of NanoString's development of its GeoMx Digital Spatial Profiler (DSP) product for examining RNA or protein analytes in specific user-defined regions of interest within a sample. **Ex. X2** ("689 Patent")³⁴ at Abstract (A0047). The shared specification of the NanoString Patents is directed to the GeoMx product and workflow. For example, Figure 20 of the patents (described as "a schematic overview of **the methods of the present disclosure**" (**Ex. X2**, 15:32-33 (A0097))) is the same GeoMx workflow diagram used in NanoString's GeoMx marketing and presentations. *Compare* 689 Patent Fig. 20 (A0069) *with* **Ex. X4** at 588 (A0286) *and* **Ex. X5** at 568 (A0312), Fig. b. Many of the experimental examples also describe the use of the "DSP" instrument. **Ex. X2**, Figs. 21B, 22B, 23-25, 75:51-78:40 (Examples 7-10) (A0071, 75, 78-80, 127-128).

2. Plaintiff NanoString's Introduction

NanoString's '689 and '142 Patents broadly describe methods and compositions for detecting large numbers of analytes at the same time, including, for instance, the use of nucleic acid probes to simultaneously detect analytes in multiple locations of a tissue sample. 10x, however, ignores the broad disclosure in the patent specifications and instead attempts to pigeonhole the claimed inventions to particular embodiments reflected in NanoString's commercially available GeoMx product. As documented herein, nothing in the intrinsic record justifies this.

³⁴ For brevity, 10x cites only to the 689 Patent specification throughout its 1375 Case briefs.

B. AGREED UPON CONSTRUCTION

Claim Term³⁵	Agreed Construction
“spatially detecting” 689 Patent, claim 16; 142 Patent, claim 1	“identifying the presence of a specific target analyte within a specific region of interest in a sample”

C. DISPUTED TERMS (Terms Proposed by Defendant 10x)**1. “under conditions that release”**

Claim Term³⁶	10x’s Proposed Construction	NanoString’s Proposed Construction
“under conditions that release” 689 Patent, claim 16; 142 Patent, claim 1	“providing a force to a location of the tissue sample sufficient to release”	Plain and ordinary meaning

a. Defendant 10x’s Opening Position

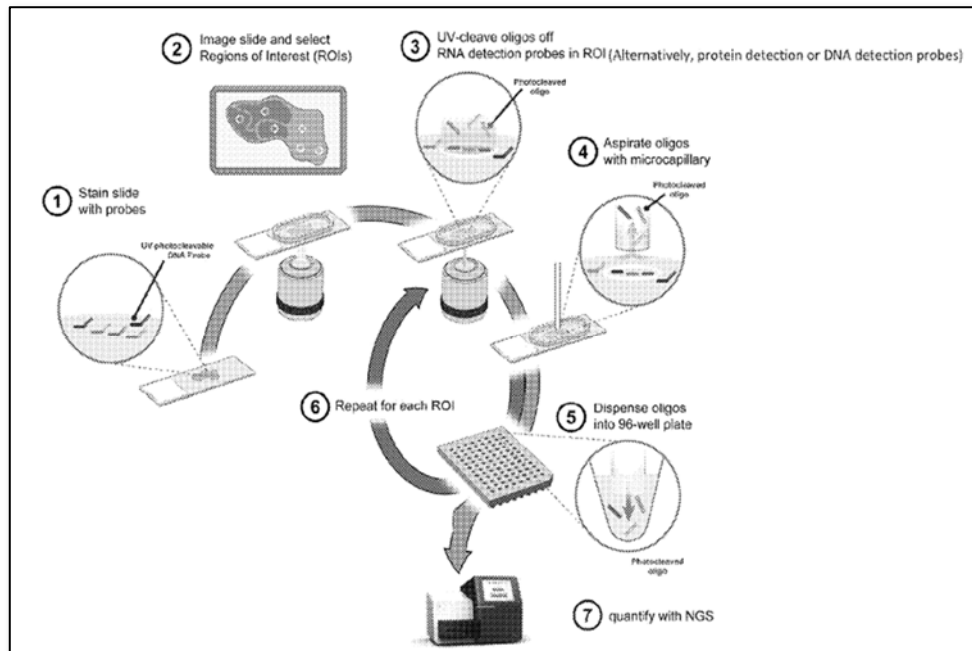
“Under conditions that release” means “providing a force to a location of the tissue sample sufficient to release” in the context of the NanoString specification.³⁷ D.I. 55-3 at 1 (1375 Case). The “release” of probe material fills a critical role in NanoString’s overall spatial detection method. As the patents describe and illustrate, an entire sample slide is stained with identical probes that contain target-binding regions (*i.e.*, each binds to a single RNA sequence on the sample) and a cleavable oligonucleotide barcode (the unique sequence is a code that identifies the target). Once a user selects a particular region of interest (“ROI”), the system shines a UV light on that region exactly, and solely that region. The identifier oligonucleotide portions of the probes are cleavable by UV light and are thus unbound and released from the region of interest in the sample. The free-floating oligonucleotides can then be collected for later analysis by sequencing (to identify the

³⁵ D.I. 164-3 at 5 (261 Case); D.I. 55-3 (1375 Case); D.I. 203-3 (595 Case)

³⁶ D.I. 164-3 at 1-2 (261 Case); D.I. 55-3 at 1-2 (1375 Case); D.I. 203-3 (595 Case)

³⁷ Representative claim 16 [(c)/(d)] includes: “collecting the ligated probes . . . under conditions that release the ligated probes . . . from the [first/second] location of the tissue sample.”

targets at the region of interest). This process is depicted in Figure 20 of the 689 Patent, (**Ex. X2**, 15:32-33 (A0097)), “a schematic overview of the methods of the present disclosure”:



The “release” mechanism must be precise—“identifier oligonucleotides are only released from probes within that location and not from probes located outside that location. Thus, identifier oligonucleotides are collected only for 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.” **Ex. X2** (689 Patent) 17:13-21 (A0098).

The reference to “conditions that release” appears vague on its face (and is not a term of art in the field). **Ex. X1** ¶¶ 42-43 (A0015-16). The phrase does not appear in the patent verbatim outside of the claims. But the patent does provide definitional language for the “conditions” at issue by equating the “conditions” sufficient to release to “providing a force to a location” for that purpose:

[A]s used herein the phrase “providing a force to a location of the sample sufficient to release an identifier oligonucleotide” is used in its broadest sense to describe changing the conditions within a certain region of interest in a sample such that, for any probe bound to a target analyte within that region of interest, the linker between the target binding domain

of the probe and the identifier oligonucleotide of the probe is cleaved, thereby separating the identifier oligonucleotide from the target binding domain so that the identifier oligonucleotide can be subsequently collected from solution. **Ex. X2**, 49:11-21 (A0114).

There is no discussion of “conditions” that release outside of this “as used herein” definition. Instead, the patent repeats the more descriptive and definite “force” version throughout. For example, the Summary of the Invention refers to this step repeatedly as “providing a force to a location of the tissue sample sufficient to release” the oligonucleotide. **Ex. X2** (689 Patent), 1:44-54, 2:1-11, 2:26-36, 3:26-35, 3:48-59, 4:34-45, 5:3-14, 5:44-54, 6:9-19, 6:44-53, 7:10-20, 8:18-27, 8:54-63, 9:24-34, 9:59-10:2, 11:1-13, 11:53-63, 12:5-16, 12:29-39, 12:58-13:4 (A0090-96).

“[W]hen the patentee act[s] as his own lexicographer and clearly set[s] forth a definition of the disputed claim term in either the specification or prosecution history,” the Court adopts that definition, regardless of ordinary meaning. *Edwards Lifescis. LLC v. Cook Inc.*, 582 F.3d 1322, 1329 (Fed. Cir. 2009). The use of the phrase “as used herein” is typically found to be definitional. *See, e.g., Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1097 (Fed. Cir. 2013) (“[T]he ’137 patent expressly and uniquely defines ‘anti-CD20 antibody’ for use therein, that is, within the ’137 patent. (*‘As used herein*, the term ‘anti-CD20 antibody’ is’)); *Halliburton Energy Servs. v. M-I LLC*, 514 F.3d 1244, 1246 (Fed. Cir. 2008) (“The specification defines ‘fragile gels’ as follows: A ‘fragile gel’ *as used herein* is a ‘gel’ that is easily disrupted. . .”). When patents use two terms interchangeably (as here with force and conditions), “[t]he interchangeable use of the two terms is akin to a definition equating the two.” *Edwards*, 582 F.3d at 1329.

The 689 Patent provides only three examples of a force/condition sufficient to release an oligonucleotide from a region of interest. The cleavable linker can be “chemically cleavable,” where the force/condition is chemical reaction conditions that catalyze cleavage (49:21-28 (A0114)); the linker can be cleavable by UV light (49:28-35 (A0114)); the linker can be broken by enzymatic action (49:35-42 (A0114)). All three examples of using changed conditions to effect

release of an oligonucleotide from a region of interest are forces applied to the region, confirming the definitional language. There are no examples or disclosures that suggest there are conditions beyond this “broadest sense” of using a force at a location to release the oligonucleotide. **Ex. X1** ¶¶ 44-50 (A0016-19).

Where the only examples in the specification are consistent with the description of the meaning of the term, that consistency supports construing the term to match the description. *See Arista Networks, Inc. v. Cisco Sys.*, 908 F.3d 792, 798 (Fed. Cir. 2018) (We “instead construe the term based on the specification’s consistent focus on broadcasting via a multicast address. *See* ’597 patent col. 11 ll. 45-51, col. 14 ll. 15-17, col. 15 l. 66-col. 16 l. 1.”); *Edwards*, 582 F.3d at 1329.

While the patent makes clear that in context, “conditions” that release means “providing a force” that releases, the “force” version of the language will be easier for a lay jury to understand. It is more descriptive of the actual mechanism of action in NanoString’s patented method. The patent equated the terms but chose to use “force” throughout the specification to describe this step. *See, e.g., Ex. X2*, 39:11-13 (A0109) (“A probe of the present disclosure can include a region which permits the release of an identifier oligonucleotide following the application of a suitable force.”). The term “under conditions that release” should be construed as “providing a force” to match the patent’s sole description of the term and to assist the jury with understanding the term in context.

b. Plaintiff NanoString’s Answering Position

The dispute between the parties is whether the term “conditions” should be construed to mean “providing a force” (10x’s position) or be given its plain and ordinary meaning (NanoString’s position). 10x’s proposed construction is unnecessary and has the potential for misuse and hence should be rejected.

Claim language. “In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction

in such cases involves little more than the application of the widely accepted meaning of commonly understood words.” *Phillips*, 415 F.3d at 1314.

The term “conditions” here reflects just such a case. The asserted claims specifically lay out steps a-g, including “collecting the ligated probes, or portions thereof ... ***under conditions that release*** the ligated probes, or portions thereof.” *See, e.g., Ex. X2*, cl. 16 (A0163). There is nothing whatsoever in the claim term itself or the surrounding claim language calling for the term to be altered from its plain meaning. A skilled artisan would thus understand that the term “conditions” is not limited to a “force,” but instead refers to its plain meaning, such that it would encompass any manner of physical and/or chemical parameters sufficient to release the ligated probes or portions thereof.

Specification. “Claim terms are generally given their plain and ordinary meaning. [Courts] depart from the plain and ordinary meaning in only two instances: lexicography and disavowal.” *Guardant Health, Inc. v. Vidal*, 2023 WL 3262962, at *2 (Fed. Cir. May 5, 2023) (cleaned up). There is no disavowal in the specification, and 10x does not even contend that there is.³⁸ Instead, 10x’s argument is based solely on alleged lexicography in the specification. Br. 76-77. But the “bar for lexicography is exacting. Lexicography applies only where the patentee clearly sets forth a definition of the ***disputed*** claim term and clearly expresses an intent to redefine the term.” *Guardant Health*, 2023 WL 3262962 at *2 (emphasis added) (cleaned up).

10x fails to meet the exacting bar for lexicography. Contrary to 10x’s argument, the patent specification does not define the disputed term “under the conditions.” Br. at 76-77. Instead, it

³⁸ 10x contends that the “689 Patent provides only three examples of a force/condition sufficient to release an oligonucleotide from a region of interest.” Br. 77-78. 10x, however, does not argue that the purported examples constitute a disavowal of the claim scope. Nor could it, because the law is clear that “courts ordinarily should not limit the claimed invention to preferred embodiments or specific examples in the specification.” *Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1381 (Fed. Cir. 2022) (internal quotation and citation omitted).

defines a different phrase—“providing a force to a location of the sample sufficient to release an identifier oligonucleotide.” **Ex. X2** at 49:11-21 (A0114). The specification provides a complex and detailed definition for this specific term:

Thus, as used herein the phrase “providing a force to a location of the sample sufficient to release an identifier oligonucleotide” is used in its broadest sense to describe changing the conditions within a certain region of interest in a sample such that, for any probe bound to a target analyte within that region of interest, the linker between the target binding domain of the probe and the identifier oligonucleotide of the probe is cleaved, thereby separating the identifier oligonucleotide from the target binding domain so that the identifier oligonucleotide can be subsequently collected from solution.

Id. (A0114). For its construction, 10x extracts a tiny portion of this definition (*i.e.*, its use of the term “conditions”) and then equates it to a tiny portion (*i.e.*, the words “providing a force”) of the otherwise lengthy term that the specification actually defines. Br. 76-77. 10x, however, cites no cases suggesting that this manner of claim construction based on using a portion of a definition in reverse is appropriate.

In fact, there is no basis to equate “conditions” to “providing a force” as 10x alleges. The passage that 10x relies upon is part of a discussion of specific embodiments involving probes with “a target binding domain [] linked to an identifier oligonucleotide by a cleavable linker.” **Ex. X2** at 49:1-11 (A0114). The specification provides three non-limiting examples of how to break the cleavable linker—including a chemical approach (49:21-28 (A0114)), a light-based approach (49:28-35 (A0114)), and an enzymatic approach (49:35-42 (A0114)). *Id.* at 49:11-42 (A0114). Thus, while a skilled artisan would understand that “conditions”—by its plain meaning—encompasses all of the foregoing examples, they would not consider the written description here as defining the term “conditions” to mean only a “force.”

Contrary to 10x’s argument, the patent specification does not use “force” and “conditions” interchangeably. Br. 77. The patent specification also discusses “conditions” suitable for other

processes related to the claimed inventions, including protein-target binding conditions, DNA denaturing conditions, and DNA hybridization conditions. *See, e.g., Ex. X2* at 40:39-45, 44:41-47, 48:12-33 (A0109, 111, 113). Nowhere in connection with these processes does the specification refer to a “force.”

10x’s proposed construction, while unsupported by the intrinsic record, further presents potential for misuse. “The terms, as construed by the court, must ensure that the jury fully understands the court’s claim construction rulings and what the patentee covered by the claims.” *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1348 (Fed. Cir. 2010) (internal quotations omitted). The word “force,” if adopted as the Court’s construction, could be misunderstood by a lay jury as being limited to some sort of physical push or pull brought about by physical contact between two objects. Construing “conditions” as “force” creates such an unnecessary risk based on no good evidence in the intrinsic record.³⁹

For these reasons, the term “under conditions that release” should simply be given its plain and ordinary meaning.

c. Defendant 10x’s Reply Position

NanoString fails to identify any evidence—intrinsic or extrinsic—that a POSA would understand “under conditions that release” to mean anything other than “providing a force.” NanoString concedes that the only conditions to release in the specification are the “forces” cited by 10x in its opening brief (76-77). Br. 79 (“how to break the cleavable linker—including a chemical approach (49:21-28 (A0114)), a light-based approach (49:28-35 (A0114)), and an enzymatic approach (49:11-42 (A0114))”). These are the conditions for releasing a probe from a

³⁹ To the extent that the Court construes the term “condition” to mean “providing a force,” it should make clear that such “forces” encompasses broadly “changing the conditions” by at least a chemical approach, a light-based approach, and/or an enzymatic approach. *Ex. X2* at 49:11-42 (A0114).

tissue sample described in the patent.

Instead NanoString hunts for uses of the word “condition” in the patent in unrelated contexts like hybridization and denaturing that a POSA would not consider relevant to “release.” Hybridization is a method of bringing genetic materials together, not releasing, and the “denaturing conditions” occur “following the cleavage step,” where the identifier oligonucleotide has already been cleaved from the tissue sample. **Ex. X2**, 44:41-45 (A0111). The only disclosures that describe conditions for releasing genetic material from a tissue sample are the descriptions of providing a force through chemical, enzymatic or light means.⁴⁰ “Providing a force” is consistent with the definition and every embodiment, showing patentee intended to provide its own definition of “under conditions that release.” *Homeland Housewares, LLC v. Whirlpool Corp.*, 865 F.3d 1372, 1377 (Fed. Cir. 2017).

NanoString asserts (without support) that lexicography requires a specific sentence structure, but Courts have found it applies when the definition precedes the disputed term. *See Kyocera Senco Indus. Tools, Inc. v. ITC*, 22 F.4th 1369, 1378 (Fed. Cir. 2022) (“Acting as their own lexicographers, the patentees defined ‘driven position’: Referring now to FIG. 3, the piston is depicted at its bottom-most travel position, and in this configuration . . . *This bottom position is also sometimes referred to herein as the ‘driven position.’*”); *Bot M8 LLC v. Sony Interactive Ent. LLC*, No. 2022-1569, 2023 U.S. App. LEXIS 22911, at *7-8 (Fed. Cir. Aug. 30, 2023) (“[P]atentee defined ‘fault inspection program,’ such that lexicography applies here. The specification states that ‘a program for inspecting whether or not a fault such as damage, change or falsification occurs

⁴⁰ NanoString’s attorney argument—untethered to the specification—cannot support plain meaning, when here Dr. Satija testified (**Ex. X1** at ¶¶ 42-43 (A0015-16)) that a POSA would not understand “under conditions that release” to be a term of art with an ordinary meaning. *See Power Integrations, Inc. v. Fairchild Semiconductor Int’l, Inc.*, 711 F.3d 1348, 1361-62 (Fed. Cir. 2013) (attorney argument insufficient for plain meaning when expert testified that it is not a term of art, would not have a plain meaning, and the specification defined the term).

in the programs or data’ is ‘hereinafter, abbreviated as’ a ‘fault inspection program.’”).⁴¹

2. “[first/second] location of the tissue sample”

Claim Term ⁴²	10x’s Proposed Construction	NanoString’s Proposed Construction
<p>“[first/second] location of the tissue sample”</p> <p>689 Patent, claims 16, 24, 27; 142 Patent, claims 1, 9</p>	<p>“[first/second] region of interest of the tissue sample”</p>	<p>Plain and ordinary meaning</p>

a. 10x’s Opening Position

The surrounding claim language and the specification confirm that when the claims refer to locations of the tissue sample, they are referring to “regions of interest,” such that “first/second location of the tissue sample” means “[first/second] region of interest of the tissue sample.” D.I. 55-3 at 1 (1375 Case). Claim 16 of the 689 Patent (and 142 Patent, claim 1) are directed to spatial detection. “First/second location of the tissue sample” is repeated throughout each claim, *see, e.g.*, claim 16 (A0163):

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

e/f) 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 ligated probes, or portions thereof, collected in step [(c)/(d)], thereby forming a [first/second] plurality [of] extension products that comprise the ligated probes, or portions thereof, collected in step[s] [(c)/(d)] and the at least one nucleic acid sequence that identifies the **[first/at least second] location of the tissue sample**;

g) identifying the first plurality of extension products and the second plurality of extension products by sequencing the first plurality of extension products and the second plurality of extension products, thereby **spatially detecting** the at least one target analyte in the **first**

⁴¹ Contrary to NanoString’s assertion (Br. 80), a jury would not be confused by “force” because the specification consistently describes forces as chemical or light-based means (not push/pull).

⁴² D.I. 164-3 at 3-4 (261 Case); D.I. 55-3 (1375 Case); D.I. 203-3 (595 Case)

location of the tissue sample and the **second location of the tissue sample**.⁴³ **Ex. X2** (689 Patent), Claim 16 (c-g) (A0163).

Each method step is in service of *spatial detection* of a target analyte in a **first and a second location**. The parties have agreed to the construction of “spatially detecting,” which is to be construed as “identifying the presence of a specific target analyte within a *specific region of interest in a sample*.”⁴⁴ D.I. 55-3 at 5 (1375 Case). The surrounding claim language strongly supports construing “location” to match the construction of “spatially detecting”—there is no meaningful dispute that when the claimed methods refer to steps taken for each “location” (e.g., collecting portions of probes, incorporating sequences that identify locations, spatially detecting in a location), the location is a “specific region of interest.”

The patent specification confirms the proper construction by using definitional language to equate “location” with “region of interest” in the context of the written description:

As used herein, the terms “region of interest” and “ROI” are used in their broadest sense to refer to a *specific location within a sample* that is to be analyzed using the methods of the present disclosure. **Ex. X2** (689 Patent), 46:51-54 (A0112).

When the specification discusses steps for identifying locations, it equates “location” and “region of interest/ROI” by swapping the terms back and forth with the same meaning. *See, e.g.*, “The nucleic acid adapter can comprise a nucleic acid sequence which identifies the specific *location* of the sample. . . . For example, if the identifier oligonucleotide was released from *location* of the sample designated ‘*ROI #1*’ the nucleic acid adapter would comprise a nucleic acid sequence that

⁴³ 142 Patent Claim 1 (**Ex. X3**, A0282) contains the same language—“[first/second] location of the tissue sample”—and similar steps, including collecting, creating a DNA product by incorporating a nucleic acid sequence into each product that identifies each respective first/second location, and sequencing to identify the product to spatially detect each molecule collected at the respective first/second location. The 142 Patent does not include the “contacting” step of 689 Patent Claim 16 (**Ex. X2**, A0163).

⁴⁴ The agreed construction is taken from the definition in the specification: “As used herein, the term ‘spatially detecting’ is used in its broadest sense to refer to the identification of the presence of a specific target analyte within a specific region of interest in a sample.” 47:10-15 (A0113).

corresponds to ‘**ROI #1.**’” **Ex. X2**, 17:26-32, 18:31-40, 20:11-20, 20:65-21:7, 32:6-19 (A0098-100, 105). The first and second locations of collecting and detecting analytes are the first and second regions of interest. “[W]hen a patentee uses a claim term throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term by implication.” *Homeland Housewares*, 865 F.3d at 1377; *Edwards*, 582 F.3d at 1329 (“The interchangeable use of the two terms is akin to a definition equating the two.”).

b. Plaintiff NanoString’s Answering Position

The dispute between the parties is whether the term “location” should be construed to mean “region of interest” (10x’s position) or given its plain and ordinary meaning (NanoString’s position). 10x’s position fails to account for the definition of “region of interest” in the specification. Accordingly, 10x’s proposed construction should be rejected.

The starting point of 10x’s argument is the claim term—“spatially detecting.” Br. 83-84. The parties agreed to adopt the definition of this term from the patent specification, which is “identifying the presence of a specific target analyte within a specific region of interest in a sample.” *Id.* 10x argues because this definition uses the phrase “region of interest,” the term “location” in the remaining claim language should be construed to match the phrase. *Id.* at 83-84. The specification, however, further defines “region of interest” to mean “a specific location within a sample.” **Ex. X2** at 46:51-54 (A0112) (“As used herein, the terms ‘region of interest’ and ‘ROI’ are used in their broadest sense to refer to a specific location within a sample that is to be analyzed using the methods of the present disclosure.”). Apparently, 10x selectively applies one definition (“spatially detecting”) but not the other (“region of interest”). There is no justification to do so.

Applying both definitions, the end point of the claim construction is that “location” means “location.” The patentee here chose a term that is clear on its face when drafting the claims. There is no need for the Court to rewrite the claims. *See Phillips*, 415 F.3d at 1316 (“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.”) (internal citation omitted).

For these reasons, the term “[first/second] location of the tissue sample” should be given its plain and ordinary meaning.

c. Defendant 10x’s Reply Position

NanoString does not dispute that the patent uses “region of interest” and “location” interchangeably. Instead, NanoString faults 10x for not also relying on the definition of region of interest—“‘region of interest’ and ‘ROI’ are used in their broadest sense to refer to a *specific location within a sample* that is to be analyzed”—and asserts that the definition leads to “location” having its ordinary meaning. The “region of interest” definition supports 10x’s construction, further confirming that location means “region of interest” in these patents. *Edwards*, 582 F.3d at 1329 (“The interchangeable use of the two terms is akin to a definition equating the two.”).

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