

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

|                                     |   |                        |
|-------------------------------------|---|------------------------|
| 10X GENOMICS, INC. and THE BOARD OF | ) |                        |
| TRUSTEES OF THE LELAND STANFORD     | ) |                        |
| JUNIOR UNIVERSITY                   | ) |                        |
|                                     | ) |                        |
| Plaintiffs,                         | ) |                        |
|                                     | ) |                        |
| v.                                  | ) | C.A. No. 22-1117 (JHS) |
|                                     | ) |                        |
| PARSE BIOSCIENCES, INC.,            | ) |                        |
|                                     | ) |                        |
| Defendant.                          | ) |                        |

**JOINT CLAIM CONSTRUCTION BRIEF**

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## I. INTRODUCTION

### A. Plaintiffs' Opening Introduction

This is a patent infringement case brought by 10x Genomics, Inc. and The Board of Trustees of the Leland Stanford Junior University (collectively, “10x”) against Parse Biosciences, Inc. (“Parse”). 10x respectfully requests that the Court adopt 10x’s proposed constructions for five disputed claim terms: “combinatorial tagging,” “wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence,” “random sequences,” “digital count,” and “adapter sequence.”

Each of 10x’s constructions “stays true to the claim language and most naturally aligns with the patent’s description of the invention,” as would be understood by one of ordinary skill, and is thus “the correct construction.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). In contrast, Parse’s attempts to improperly import limitations into the patent claims. Parse’s proposed constructions are contrary to the intrinsic evidence and run counter to common sense.

#### 1. Plaintiffs' Introduction to the Asserted Patents

The parties dispute the claim construction of five patent terms, four of which appear in 10x’s U.S. Patent Nos. 10,155,981, 10,240,197, and 10,697,013 (collectively, the “Brenner Patents”): “combinatorial tagging,” “wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence,” “random sequences,” and “digital count.” The Brenner Patents each claim novel, unconventional laboratory methods to differentiate and quantify nucleic acid sequences within a sample. *See* D.I. 78 (Memorandum Opinion regarding Defendant’s Motion to Dismiss (D.I. 12)) at 6–7. Unlike prior art methods, the Brenner Patents allow users to track each polynucleotide the user is interested in analyzing to its cell of origin and to differentiate between each polynucleotide originating from that cell. *Id.* This

is accomplished by using at least two tag sequences, also referred to as MIDs, that are added to the sample polynucleotides. *Id.*; *see also, e.g.*, D.I. 80, Ex. D at 6:33–7:22, 30:19–48. The first tag sequence identifies the cell from which a polynucleotide originated and the second tag sequence is a unique sequence that differentiates each polynucleotide in that cell. *Id.* For example, users can now determine which cells are expressing which genes and in what amounts by tagging the mRNA from each cell because one can determine the number of each otherwise identical mRNA present in each cell at the time of tagging. *Id.* This novel method unlocked the ability to do high-resolution single-cell analysis. *Id.*

The remaining disputed claim term, “adapter sequence,” appears in U.S. Patent Nos. 10,150,995 and 10,619,207 (collectively, the “Giresi Patents”). The Giresi Patents claim unconventional laboratory methods and compositions requiring steps and elements relating to the innovative ATAC-seq method, which stands for Assay for Transposase-Accessible Chromatin using sequencing. *See, e.g.*, D.I. 80, Ex. E at 29:63–30:19, 43:56–44:57. The Giresi Patents relate to a field known as epigenetics, or modifications to a chromosome that impact what genes are transcribed to mRNA (which can then be expressed as proteins) *without* changing the chromosome’s DNA sequence—*e.g.*, which portions of chromatin are “open” or not in a cell at any given time based on cellular signals and gene activity. D.I. 78 at 5–6; *see also, e.g., id.* Prior art methods of analyzing epigenomes were complex, time consuming, and required a large cell sample. *Id.* For example, DNase-seq, is **44-steps**, requires **50 million cells** and **3 days** (two overnight incubations) to get results. *Id.* In contrast, ATAC-seq can be practiced on as little as a **one-cell** sample in **two steps** in **less than a day**. *Id.* Users practicing ATAC-seq first introduce a transposase into a cell’s nucleus where the transposase will fragment the chromatin in areas of open chromatin and insert tags (this process is known as “tagmentation” or “tagmenting”). *Id.*

The user then lyses and, if needed, amplifies the tagmented DNA before the DNA is sequenced and analyzed. *Id.* This elegant and simple solution transformed epigenetics.

## **B. Defendant's Answering Introduction**

Parse's constructions for the five disputed claim terms seek to ensure that the claims as a whole are construed consistent with the intrinsic evidence and the understanding of a person of ordinary skill in the art. Plaintiffs, however, seek to broaden the scope of the claims through the use of extrinsic evidence and offer little or no affirmative evidence to support their constructions. For the reasons stated herein, the Court should adopt Parse's proposed constructions.

### **1. Technology Background**

#### **a. Brenner Patents**

The Brenner Patents purport to solve a problem with prior art DNA sequencing methods, namely, that such methods were only able to resolve a short stretch of DNA sequence within much larger fragments of genomic DNA. To do so, the Brenner Patents describe the "reflex method," a technique for breaking up a long sequencing project into a series of smaller individual sequencing projects. The results of these projects can be pieced together to generate a long stretch of a DNA sequence. *See generally* D.I. 80, Ex. A at 16:62-19:6.<sup>1</sup>

This technique purportedly works by introducing multiple copies of a "reflex" sequence along a nucleic acid molecule, which can then be used to introduce additional sequences needed for sequencing. *Id.* By introducing these sequences in close proximity to one another, one can allegedly sequence the longer DNA in bite-sized chunks. *Id.* at 17:26-33. Indeed, in the

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<sup>1</sup> The three Brenner Patents share a common specification. Any citations to the D.I. 80, Ex. A i.e. the '981 patent should be understood to encompass parallel citations to the specification of the other two Asserted Brenner Patents.

Summary of the Invention, the “present invention” of the Brenner Patents is characterized as “processes for moving a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide, also referred to as a ‘reflex method’ (or reflex process, reflex sequence process, reflex reaction, and the like).” D.I. 80, Ex. A at 1:51-56.

The claims of the Asserted Brenner Patents, however, are directed merely to tagging and counting target nucleic acids by introducing two tags, rather than the reflex method. A first tag permits tracking the particular cell the molecule came from and the second tag distinguishes the tagged molecule from other molecules in the sample. This concept is exemplified by representative claim 1 of the ’981 patent, which is reproduced below:

A method of analyzing nucleic acids from a plurality of single cells, the method comprising:

- (a) providing a sample comprising a plurality of single cells, wherein each single cell of the plurality of single cells comprises a plurality of sample polynucleotides;
- (b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides, wherein each tagged polynucleotide comprises:
  - (i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and
  - (ii) a multiplex identifier (MID) sequence comprising:
    - I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and
    - II. a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell;
- (c) sequencing the plurality of tagged polynucleotides to obtain a plurality of identified polynucleotide sequences;
- (d) using the first tag sequence to correlate the identified polynucleotide sequence with the single cell from which the identified polynucleotide sequence is derived; and
- (e) using the second tag sequence to correlate the identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived.

The claim thus purports to encompass routine and well-known steps of providing a DNA sample, tagging the sample with two tags to track the DNA molecules, and then sequencing the resulting DNA sample. Notably, the Brenner patents characterize the use of tags for tracking DNA molecules not as an invention, but rather as a prior art technique. *See, e.g.*, D.I. 80, Ex. A at 1:26- 29 (“We have previously described methods that enable tagging each of a population of fragmented genomes and then combining them together to create a ‘population library’ that can be processed and eventually sequenced as a mixture.”).

#### **b. Buenrostro Patents**

The Buenrostro patents pertain to a prior art process known as “tagmentation,” which can be used to prepare DNA for sequencing. Tagmentation uses an enzyme known as a transposase, capable of attaching an external DNA sequence to another strand of DNA while cleaving the target DNA at the point of attachment. In tagmentation, the transposase is outfitted with a payload of DNA sequences necessary for a DNA sequencer to operate properly. The natural activity of the transposase is exploited to introduce those sequences into the sample DNA. Thus, tagmentation can be used to simultaneously fragment and tag a DNA sample in preparation for sequencing.

#### **C. Plaintiffs’ Reply Introduction**

Parse’s Answering Brief confirms that 10x’s constructions should be adopted. Parse proposes narrow constructions of the disputed claim terms in the Brenner Patents to try to limit the claimed invention, which it argues is “nothing more than prior art technique[s]” and should be limited to the “reflex method.” *Supra* at 3-4. This is contrary not only to the intrinsic evidence but also the Court’s ruling denying Parse’s § 101 Motion in which the Court determined both that the Brenner Patents cover more than just the “reflex method,” and that the method was novel. Specifically, as the Court found, the Brenner Patents:

- “contain methods allowing scientists to ‘tag’ nucleotide sequences in a way that indicated which cell they were derived from . . . using a novel multiplex tagging approach that the inventors termed ‘MID’” (D.I. 78, at 7); and
- “disclose a novel method for copying or ‘reflecting’ the MID-tagged polynucleotides—a technique that can be useful when the polynucleotide is long” that the inventors termed “the ‘reflex method’” (*id.*).

Parse’s attempt to narrow the claims by importing limitations is contrary to the law. And Parse’s construction fails regardless of whether it is based on the plain and ordinary meaning under the principles set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), or whether it is a special definition based on the patentee either acting as its own lexicographer or disavowing the full scope of the claim term. *See Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014) (“To act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term other than its plain and ordinary meaning’ and must ‘clearly express an intent to redefine the term.’”); *Thorner v. Sony Computer Entm’t Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012).

## II. LEGAL STANDARD

### A. Plaintiffs’ Legal Standard for Claim Construction

Unless the patentee acts as her own lexicographer by setting forth a definition or disavows the full scope of a claim term, the words of a patent claim are to be given their ordinary and customary meaning, which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips*, 415 F.3d at 1313; *see Thorner v. Sony Comp. Ent. Am., LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). “The standards for finding lexicography and disavowal are exacting.” *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014). “[T]he person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the

specification.” *Phillips*, 415 F.3d at 1313. Being part of a “fully integrated written instrument” that consists principally of a specification that concludes with claims, the claims “must be read in view of the specification, of which they are a part.” *Id.* at 1315. Indeed, the specification is “the single best guide to the meaning of a disputed term” and is usually considered “dispositive.” *Id.* In addition, the prosecution history of the patent is intrinsic evidence to be considered in interpreting claim terms. *Id.* at 1317.

Although claims are generally interpreted to include preferred embodiments disclosed in the specification, *Accent Packaging, Inc. v. Leggett & Platt, Inc.*, 707 F.3d 1318, 1326 (Fed. Cir. 2013), “claims are not necessarily and not usually limited in scope simply to the preferred embodiment,” *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 805 F.3d 1368, 1375 (Fed. Cir. 2015). It is improper to “read limitations from the embodiments in the specification into the claims.” *Hill-Rom*, 755 F.3d at 1371.

Extrinsic evidence, which is evidence that is not the patent’s claims, specification, and prosecution history, “is less significant than the intrinsic record in determining the legally operative meaning of claim language” and while such evidence “may be useful to the court” it must be considered in the context of the intrinsic evidence. *Phillips*, 415 F.3d at 1317–19; *see Teva Pharma. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 331–32 (2015).

## **B. Defendant’s Legal Standard**

Claim terms are generally given “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention[.]” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). In the event that the meaning of a claim term as used by a person of ordinary skill in the art (“POSA”) is not immediately apparent, courts look to sources available to the public, including “the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific

principles, the meaning of technical terms, and the state of the art.” *Id.* at 1314 (internal citations omitted). Construction begins with the words of the claim themselves because claims “mean precisely what they say.” *E.I. Du Pont De Nemours & Co. v. Unifrax I, LLC.*, 921 F.3d 1060, 1079 (Fed. Cir. 2019) (internal citations omitted).

Intrinsic evidence is the patent itself, including the claims and the specification, and the prosecution history. *Vitrionics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Intrinsic evidence is the starting point for claim construction, as it is “the most significant source of the legally operative meaning of disputed claim language.” *Id.* Claims should be construed in light of the entire intrinsic record read as a whole. *Phillips*, 415 F.3d at 1315. It is particularly important to read the claims in light of the specification, which is “the single best guide to the meaning of a disputed term.” *Vitrionics*, 90 F.3d at 1582.

Courts may consider extrinsic evidence, or additional information outside the intrinsic evidence, when it is not used to alter or contradict meaning established by intrinsic evidence. *Vitrionics*, 90 F.3d at 1584. For example, dictionaries may help a court better understand underlying technology because they “endeavor to collect the accepted meanings of terms used in various fields of science and technology” and “those resources have been properly recognized as among the many tools that can assist the court in determining the meaning of particular terminology to those of skill in the art of the invention.” *Phillips*, 415 F.3d at 1317.

Pre-AIA 35 U.S.C. 112 ¶ 2 requires a patent’s claims to “[point] out and distinctly [claim] the subject matter which the applicant regards as his invention.” This requires that a patent’s claims, “viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty.” *Nautilus, Inc. v. Biosig Instrument, Inc.*, 572 U.S. 898, 910 (2014). In determining definiteness, it “cannot be sufficient that a court

can ascribe *some* meaning to a patent’s claims; the definiteness inquiry trains on the understanding of a skilled artisan at the time of the patent application, not that of a court viewing matters post hoc.” *Id.* at 911.

### III. AGREED-UPON CONSTRUCTIONS

The parties agree upon the following constructions:

| No. | Claim Term(s)                                                                                                                                                                                                                                                                                                                                                                       | The Parties’ Agreed-Upon Construction(s)                                                                                                                                                                                                                                                                                                                                                                           |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | “multiplex identifier (MID) sequence”<br>'981 Patent, Claim 1                                                                                                                                                                                                                                                                                                                       | “a tag or combination of tags associated with a polynucleotide whose identity (e.g., the tag DNA sequence) can be used to differentiate polynucleotides in a sample”                                                                                                                                                                                                                                               |
| 2   | “second tag sequence”<br>'981 Patent, Claim 1; '197 Patent, Claims 1, 13–14, 17, 24; '013 Patent, Claims 1, 10, 15, 18, 23                                                                                                                                                                                                                                                          | “a tag sequence distinct from the first tag sequence”                                                                                                                                                                                                                                                                                                                                                              |
| 3   | “sample”<br>'981 Patent, Claims 1, 3; '197 Patent, Claims 1, 8, 13, 14, 17, 20, 23, 24; '013 Patent, Claims 1, 2, 9, 15, 23, 24                                                                                                                                                                                                                                                     | “a quantity of material from a biological, environmental, medical, or patient source in which detection, measurement, or labeling of target nucleic acids is sought”                                                                                                                                                                                                                                               |
| 4   | “sequences of the amplified polynucleotides corresponding to the sample sequence”<br>'013 Patent, Claim 1                                                                                                                                                                                                                                                                           | “sequences of the amplified polynucleotides that are either the same as or complementary to the sample sequence”                                                                                                                                                                                                                                                                                                   |
| 5   | “wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises: (i) a sample sequence from a sample polynucleotide of the plurality of sample polynucleotides”<br>'197 Patent, Claim 1<br><br>“wherein each tagged polynucleotide comprises: (i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides”<br>'981 Patent, Claim 1 | “wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises: (i) a sample sequence, or a sequence complementary to a sample sequence, of the plurality of sample polynucleotides”<br><br>“wherein each tagged polynucleotide comprises: (i) a sequence from a sample polynucleotide, or a sequence complementary to a sample polynucleotide, of the plurality of sample polynucleotides” |

| No. | Claim Term(s)                                                                                                                                                                                                                   | The Parties' Agreed-Upon Construction(s)                                                                                                                                                                                                                   |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | “wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises: (i) a sample sequence corresponding to said sample polynucleotide of the plurality of sample polynucleotides”<br>'013 Patent, Claim 1 | “wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises: (i) a sample sequence, or a sequence complementary to a sample sequence, corresponding to said sample polynucleotide of the plurality of sample polynucleotides” |
| 6   | “insertional enzyme complex”<br>'357 Patent, Claims 1, 2, 8, 16; '995 Patent, Claims 1, 5                                                                                                                                       | “a complex comprising an insertional enzyme and two adaptor molecules (the ‘transposon tags’) that are combined with polynucleotides to fragment and add adaptors to the polynucleotides”                                                                  |
| 7   | “insert element”<br>'357 Patent, Claims 1, 2, 8; '995 Patent, Claims 13, 17                                                                                                                                                     | “nucleic acid for insertion in a polynucleotide by an insertional enzyme, such as a transposase”                                                                                                                                                           |
| 8   | “tagged fragments”<br>'207 Patent, Claims 1, 23                                                                                                                                                                                 | “polynucleotide fragments that are attached to tags”                                                                                                                                                                                                       |

#### IV. DISPUTED CONSTRUCTIONS

##### A. Brenner Patents

##### 1. “combinatorial tagging”

| 10x's Proposed Construction                                                                                                        | Parse's Proposed Construction                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Plain and ordinary meaning, which is “using a combination of tags, which may be added in different steps and by different methods” | “approach in which one MID is attached by ligation and a second MID is attached by primer extension” |

##### a. Plaintiffs' Opening Position

“Combinatorial tagging” should be construed to have its plain and ordinary meaning, which is “using a combination of tags, which may be added in different steps and by different methods.”

That is, “combinatorial tagging” is *tagging* with a *combination* of tags.

Parse proposes a narrower construction of an “approach in which one MID [*i.e.*, multiplex identifier] is attached by ligation and a second MID is attached by primer extension.”<sup>2</sup> Parse’s attempt to limit the scope of claims fails because it is contrary to the claim language itself, which is the starting point for claim construction. *Phillips*, 415 F.3d at 1313. **First**, Parse’s construction renders claim elements (A) and (B) superfluous by limiting the term to tags added by primer extension and ligation. **Second**, Parse’s construction limits combinatorial tagging to the addition of MIDs but the claims require only “oligonucleotide tags.”<sup>3</sup>

**i. 10x’s Construction is Correct**

10x’s construction is supported by the claim as a whole, the specification, and the extrinsic evidence to the extent the Court considers it. Claim 1 of the ’013 Patent simply recites “performing combinatorial tagging to generate a plurality of tagged polynucleotides” and then goes on to specify that “a first oligonucleotide tag” is added during primer extension and a “second oligonucleotide tag” is added via ligation. D.I. 80, Ex. C at Claim 1. Nothing in the claim limits “combinatorial tagging” to any particular method(s) of adding tags, let alone that the tags must be added in the precise manner set forth in Parse’s construction. Rather, the recitation in the claim of “combinatorial tagging” means just that—a combination of tags. Indeed, the additional limitations

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<sup>2</sup> Based on the parties’ meet and confer, 10x understands that Parse’s construction does not require any particular order in which the tags are added to a polynucleotide of interest and that Parse is applying the agreed-upon construction of “MID,” which is “a tag or combination of tags associated with a polynucleotide whose identity (e.g., the tag DNA sequence) can be used to differentiate polynucleotides in a sample.” D.I. 80, Attach. C at 1; D.I. 80, Ex. C at 6:41–44. To the extent that Parse attempts to argue the claim term implies a particular order, that is contradicted by the plain language of Claim 1, which has the first oligonucleotide tag added by primer extension and the second added by ligation. D.I. 80, Ex. C at Claim 1.

<sup>3</sup> A “MID” is “a tag or combination of tags associated with a polynucleotide whose identify (e.g., the tag DNA sequence) can be used to differentiate polynucleotides in a sample.” D.I. 80, Ex. C at 6:41–44. In contrast, a tag is any DNA sequence that is added to a polynucleotide.

in Claim 1 specifying how the tagged polynucleotides are generated would be entirely unnecessary if, as Parse argues, at least one tag must be added via primer extension and another via ligation. *See Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 792 (Fed. Cir. 2021) (observing that claims should not be construed in ways that render the other portions of the claim redundant).

The specification also supports 10x's construction. "Combinatorial tagging" is not expressly defined in the specification. *See* D.I. 80, Ex. C at 3:23–12:55 ("Definitions" section of the specification without a definition for "combinatorial tagging"). And the portion of the specification describing MIDs makes clear that Parse's proposed construction is only one example and not a requirement of the claims:

Further, MIDs can be generated in a variety of different ways, *e.g., by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension*. Thus, MIDs can be designed and implemented in a variety of different ways to track polynucleotide fragments during processing and analysis, and thus no limitation in this regard is intended.

*Id.* at 7:23–30 (emphasis added). It follows the common precepts of the English language that any clause following "e.g.," is not meant to indicate that the *only way* MIDs could be generated using a "combinatorial tagging approach" is through a combination of ligation and primer extension. *See In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983). And the first part of the sentence before the e.g. as well as the second sentence of that passage make clear that there are "a variety of ways" to generate MIDs and that the preceding examples were meant to be examples of how a MID may be "designed [or] implemented." Holding otherwise would be contrary to Federal Circuit law. For example, in *Nevro Corporation v. Boston Scientific Corporation*, the Federal Circuit reversed a district court claim construction of "therapy signal" as "electrical impulses" because a lone statement in the specification saying "therapy signals (e.g., electrical impulses)" did not define therapy signals to be limited to electrical impulses. 955 F.3d 35, 44 (Fed. Cir. 2020) (the lone statement "does not meet the exacting standard for redefining" a claim term). The same logic

applies here.

To the extent that the Court considers extrinsic evidence, 10x's construction is also consistent with the dictionary definition of "combinatorial" to mean "of, relating to, or involving combinations." Merriam-Webster's Collegiate Dictionary (11th Ed. 2020), Ex. D at JA036. Thus, when "combinatorial" modifies "tagging" it means "combinations of tags." Neither term indicates any preference, let alone requires, that the tags be added in any particular order or by any particular method (e.g., ligation, hybridizing, primer extension) as Parse proposes.

## ii. Parse's Arguments Fail

No exception justifies departing from the plain and ordinary meaning of "combinatorial tagging," nor has Parse identified one. *Thorner*, 669 F.3d at 1365. Nor does Parse identify anything in the prosecution history of the '013 Patent (or any related patent) that requires a narrower construction of "combinatorial tagging." D.I. 80, Attach. A at 1. That should end the inquiry. *Thorner*, 669 F.3d at 1365.

The intrinsic evidence does not support limiting "combinatorial tagging" to the context of adding "MIDs" *i.e.*, a "MID" be added as part of the combination as opposed to a "tag." As discussed above, the specification makes clear that the MID context is a simply a non-limiting example of "combinatorial tagging." And the claims are not so limited, as discussed above. Further, Claim 1 does not specify that MIDs must be added in each step, just "oligonucleotide tag[s]" need be added and the claim differentiates between "oligonucleotide tags" and the first and second tag sequences that act as MIDs. Specifically, Claim 1 refers to a "first tag sequence" which identifies the cell of origin and a "second tag sequence" which distinguishes between polynucleotides arising from the same cell. D.I. 80, Ex. C at Claim 1. These "tag sequence[s]" "differentiate polynucleotides in a sample," and are therefore MIDs. *Id.* at 6:41–52. Thus,

“combinatorial tagging” is plainly not limited to adding “MIDs” in a combinatorial manner according to Claim 1 because it covers adding any set of “tags” combinatorially, and those tags may or may not combine to form a MID. *See id.* (“(MID) as used herein refers to a tag or combination of tags . . .”).

The only argument Parse offered in the Joint Claim Construction Chart (D.I. 80, Attach. A at 1) and during the parties’ meet and confer for its limiting construction is that the term “combinatorial tagging” is discussed within the definition of “MID.” This fails. The Federal Circuit has explained that even where the specification repeatedly discusses a claim term in a particular manner, it is improper to limit claims based on that description unless the patentee acted as its own lexicographer or disavowed that claim scope. *See Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1347–48 (Fed. Cir. 2009) (declining to limit claim when “the patentee did not act as his own lexicographer or disavow claim scope.”); *Nevro*, 955 F.3d at 43–44 (vacating district court’s construction where it limited claim term to the example identified with an “e.g.” in the specification); *Hill-Rom*, 755 F.3d at 1371 (“The standards for finding lexicography and disavowal are exacting.”). Because 10x did not disavow this claim scope or evince an intent in the specification to limit “combinatorial” to a particular method of combinatorial tagging or with a predetermined order of steps, Parse’s construction is incorrect. Indeed, as discussed above, the very paragraph that Parse cites to support its construction says that the example Parse relies on is just one approach that can be used to generate MIDs. *See* D.I. 80, Ex. C at 7:23–30.

#### **b. Defendant’s Answering Position**

“Combinatorial tagging” should be construed in line with its use in the specification and the claims to encompass an approach that involves both ligation and primer extension. 10x’s proposed construction, however, seeks to broaden “combinatorial tagging” far beyond what the

intrinsic record supports so as to encompass any combination of tags added by any method. For the reasons stated below, this construction should be rejected and Parse's construction should be adopted.

Beginning with the plain language of the claim, "combinatorial tagging" must refer to an approach in which one molecular identifier is attached by ligation and a second is attached by primer extension. D.I. 80, Ex. C at Claim 1. This confirmed by the claim structure, which recites in elements (A) and (B) the use of "primer extension," and "ligation," respectively:

(b) ***performing combinatorial tagging*** to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:

(A) providing an extension product by ***primer extension*** using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and

(B) ***ligating*** a second oligonucleotide tag to said extension product, and

D.I. 80, Ex. C at Claim 1. In other words, the claim elements (A) and (B) act to describe what "combinatorial tagging" is, and Parse's construction is thus precisely in line with what a skilled artisan would understand claim 1 to mean from this evidence. *See TIP Sys., LLC. v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1369 (Fed. Cir. 2008) (holding that where the "claim itself contains a precise definition of the term," that definition should be used).

Contrary to 10x's contention, Parse's construction does not "render claim elements (A) and superfluous." Under Parse's construction, "combinatorial tagging" requires both primer extension and ligation, and these processes may be performed in any order. The claims, however, narrow the "combinatorial tagging" to a particular type of "combinatorial tagging" wherein the extension takes place first and then ligation.

Parse's proposed construction aligns not only with the plain language of the claim, but also

the definition in the specification. The *one time* the specification uses the term “combinatorial tagging,” it confirms that “combinatorial tagging” requires both ligation and primer extension:

Further, MIDs can be generated in a variety of different ways, e.g., by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension.

D.I. 80, Ex. C at 7:25-27. This language from the specification is, in fact, the exact construction Parse proposes and thus confirms that Parse’s construction is correct. *See Tip Sys., LLC.*, 529 F.3d at 1369 (holding that where the specification has an “identical definition” as the claim term, such a definition is the construction).

10x misreads this passage from the specification, stating that because “e.g.” is used, it is “not meant to indicate that the *only way* MIDs could be generated using a ‘combinatorial tagging approach’ is through a combination of ligation and primer extension.” *Supra* at 12. The use of “e.g.,” however, is plainly meant to show only that “combinatorial tagging” is an exemplary method to generate MIDs, not to suggest that the combination of ligation and primer extension is merely one type of “combinatorial tagging.”

The prosecution history further confirms Parse’s construction. When the application that resulted in the ’013 patent was first filed, the Applicant did not include the term “combinatorial tagging” in any claim. Ex. A at JA002. But subsequently, the Applicant filed a Preliminary Amendment and introduced the term “combinatorial tagging,” adding the steps of “primer extension” and “ligation” to perform said “combinatorial tagging.” *Id.* at JA004. Commenting on the Amendment, the Applicant remarked that “exemplary support for these claim amendments *can be found in the specification as originally filed*. As these amendments add no new matter and *are supported by the specification as originally filed*, entry of these amendments is respectfully requested.” *Id.* at JA009. The only location where the specification mentions “combinatorial tagging” at all is the passage describing it the same way as the claim—that is,

attaching one MID by “ligation” and one by “primer extension.” 10x cannot now expand the scope of the claim beyond what it originally intended.

10x does not cite any intrinsic evidence to support construing “combinatorial tagging” to mean “using a combination of tags, which may be added in *different steps and by different methods*.” Rather, 10x’s nebulous construction is based solely on extrinsic evidence, specifically, a dictionary definition of “combinatorial” to mean “combinations”. *Supra* at 12. This generic extrinsic evidence, however, cannot overcome the unambiguous intrinsic evidence documented above. *See David Netzer Consulting Eng’g LLC v. Shell Oil Co.*, 824 F.3d 989, 997 (Fed. Cir. 2016) (“extrinsic evidence may not be used to contradict claim meaning that is unambiguous in light of the intrinsic record”).

### **c. Plaintiffs’ Reply Position**

The parties dispute (1) whether the oligonucleotide tags are limited to MIDs (Parse’s position) or whether the claim’s “oligonucleotide tag” is not so limited (10x’s position); and (2) whether the term “combinatorial tagging” should be limited to tagging using primer extension and ligation (Parse’s position) or whether the tags may be added by any method (10x’s position). 10x’s construction is consistent with the intrinsic evidence, and Parse’s attempt to add limitations is incorrect. *Supra* at 10-14, 14-17.

**First**, Parse does not respond in its Answering Brief to 10x’s arguments that oligonucleotide tags are not limited to MIDs, *supra* at 13-14, and thus Parse has waived that argument. *Trackthings LLC v. Netgear Inc.*, No. 22-981-RGA-JLH, 2023 WL 5993186, at \*2 (D. Del. Sept. 15, 2023). To the extent Parse were nonetheless permitted to argue otherwise, the claims make clear there is no such limitation. *Supra* at 13-14. The claims call for the generation of polynucleotides tagged with oligonucleotide tags. For example, Claim 1’s elements (A) and (B)

are directed to the use of a “first oligonucleotide tag” and a “second oligonucleotide tag.” However, nothing in the claims or specification suggests that those oligonucleotide tags are limited to MIDs. Rather, the specification makes clear that while all MIDs can be considered tags, not all tags are MIDs. For example, the specification repeatedly discloses the addition of tags such as primer sites, sequencing adapters, restriction enzyme sites, and reflex sequences in addition to MIDs. *See, e.g.*, D.I. Ex. 80, Ex. C at 16:60-17:3, 17:20-25, 17:57-60, 19:16-22, Fig. 1B, Figs. 2-8. Further, the claim language, when referring specifically to tag sequences that serve as MIDs allowing the polynucleotide to be distinguished from other polynucleotides, uses the terms “first tag sequence” and “second tag sequence” not “oligonucleotide tag.” *See, e.g., id.* at Claim 1(b)(ii) and (iii).

**Second**, Parse’s construction of “combinatorial tagging” improperly imports limitations into the claim term. *See, e.g., Apple Inc. v. Wi-LAN Inc.*, 25 F.4th 960, 968 (Fed. Cir. 2022) (rejecting argument that disclosing one embodiment of a term “is a redefinition” where there were “no ‘words or expressions of manifest exclusion or restriction’”); *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed. Cir. 2004) (holding that it is improper to read limitations from a preferred embodiment in the specification into the claims absent clear indication that the patentee intended to limit the claim).

**The claims.** The claim language does not support Parse’s construction. The parties agree that claim elements (A) and (B) are required in Claim 1 for the claimed “combinatorial tagging.” Because claim elements (A) and (B) are already separately recited in Claim 1, there is no need for this Court to construe “combinatorial tagging” to require those elements; that would render claim language superfluous by stating it twice in the same claim. Specifically, under Parse’s construction, Claim 1 would be interpreted to mean:

(b) ~~performing combinatorial tagging~~ *an approach in which one MID is attached by ligation and a second MID is attached by primer extension* to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:

(A) providing an extension product by *primer extension* using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and

(B) *ligating* a second oligonucleotide tag to said extension product,

D.I. 80, Ex. C at Claim 1 (emphases added). In addition to rendering (A) and (B) superfluous, Parse’s construction injects confusion and ambiguity to an otherwise clear claim term. The law is otherwise. *See Wasica Finance GmbH v. Continental Automotive Sys., Inc.*, 853 F.3d 1272, 1288 n.10 (Fed. Cir. 2017) (“It is highly disfavored to construe terms in a way that renders them void, meaningless, or superfluous.”).

**The specification.** There is nothing in the specification that defines “combinatorial tagging” as Parse has construed it. According to Parse, the specification’s use of the term “combinatorial tagging” in discussing a different term, “Multiplex Identifier (MID),” is definitional. *Supra* at 15-16. Parse is wrong. The language Parse relies upon provides an example of how MIDs can be generated. It says “[f]urther, MIDs can be generated in a variety of different ways, e.g., by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension.” D.I. 80, Ex. C at 7:23-30. This language is not definitional. *Supra* at 15-16; 11-14 (citing, e.g., *Nevro Corp. v. Boston Scientific Corp.*, 955 F.3d 35, 44 (Fed. Cir. 2020)); *Apple*, 25 F.4th at 968. Parse also argues that “e.g.”—“exempli gratia” or “for example”—means the opposite of what it says and expresses “an intent to redefine the term.” *Supra* at 16. This too is incorrect. The term “e.g.” in the context here means it is exemplary and not a mandatory definition. And the “e.g.” phrase that Parse cites is found in a definition for an entirely different term that does not appear in the asserted claims. *Supra* at 14-16, 11-12.

Parse cites to *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364 (Fed. Cir. 2008), but that case is inapposite. There, the Federal Circuit affirmed the district court’s construction of “handset” because the claim required “a telephone handset *being* a handle with an earpiece at one end and a mouthpiece at an opposite end” and the identical definition was also found in the specification. *TIP Sys.*, 529 F.3d at 1369 (emphasis added). That is not the case here. Claim elements (A) and (B) do not define “combinatorial tagging”; nor does the specification’s description of methods for creating MIDs through “combinatorial tagging” define the term. *Supra* at 11-14.

**The prosecution history.** Parse’s construction is not supported by its citation to the preliminary amendment<sup>4</sup> in the prosecution history adding the ’013 Patent’s claims. *Supra* at 16-17. The preliminary amendment merely identifies the continuation application’s new claims. Nothing in the prosecution history further limits the claims to the narrower construction that Parse proposes, whether it is under *Phillips* or based on a clear disavowal. Identifying written description support for the claims is not expressing an intent to limit the claims to that example in the specification, and thus 10x is entitled to “the full scope of its claim language.” *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004); *Phillips*, 415 F.3d at 1322-23 *see Hill-Rom*, 755 F.3d at 1371; *Thorner*, 669 F.3d at 1366.

#### **d. Defendant’s Sur-Reply Position**

At the outset, 10x’s Reply misstates the disputes, contending for the first time that the parties dispute “whether the oligonucleotide tags are limited to MIDs.” *Supra* at 17. The dispute

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<sup>4</sup> A preliminary amendment replaces the original application’s claims with the continuation application’s new claims. *See generally* MPEP § 714; 37 C.F.R. § 1.115(b)(3)(ii). The applicant identifies the claims’ support to demonstrate that the new claims are entitled to the same priority date. *See generally* MPEP § 714.

around the construction of “combinatorial tagging” is properly limited to whether the term encompasses what is disclosed in the specification (using primer extension and tagging) or whether tags can be added with any method. The latter reflects an overbroad construction inconsistent with the intrinsic evidence.

Whether or not oligonucleotide tags are limited to MIDs is irrelevant to the construction of this claim term. “Oligonucleotide tag” is not a disputed term for construction, and the parties have already agreed to a construction of MID. *See* D.I. 80 at Attachment C. Parse has not attempted to interject any argument about the construction of oligonucleotide tags into the parties’ dispute regarding “combinatorial tagging,” and 10x’s attempt to do so now confuses the issues.

10x proceeds to restate erroneous arguments that Parse already addressed above. As discussed at length, Parse’s construction of “combinatorial tagging” is in line with the claim language and does not render any claim elements superfluous. *Supra* at 14-17. Defining “combinatorial tagging” to require the addition of one MID by primer extension and a second by ligation captures a **genus** of combinatorial tagging methods. Claim 1 explicitly claims only a **species** of that genus—that is, claim elements (A) and (B) define a specific order for the steps of ligation and primer extension. This is clear from the plain language of the claim, which recites “providing an extension product by primer extension using a first oligonucleotide tag” and then “ligating a second oligonucleotide tag **to said extension product.**” D.I. 80, Ex. C at Claim 1. Contrary to 10x’s assertion, Parse’s proposed construction does not interject “confusion and ambiguity to an otherwise clear claim term,” but rather clarifies the genus of combinatorial tagging from which a species is claimed.

To support its overbroad construction, 10x again misreads the specification. Combinatorial tagging is mentioned once and only once in the entirety of the specification. *Id.* at 7:24-27. The

“e.g.” in this passage is not meant to describe an exemplary method of combinatorial tagging. “Combinatorial tagging” is, in fact, listed after the “e.g.” to describe it as an exemplary method of generating MIDs. Nothing about that passage points to the only method described for combinatorial tagging to be an “exemplary method.”

10x also incorrectly argues that Parse’s construction improperly imports claim limitations, relying on *Apple Inc.* and *Lieber-Flarsheim Co.* These cases, however, are inapposite because they both center on whether only one embodiment or a preferred embodiment can be read into the claim. Parse’s construction does not come from one embodiment of many, nor a preferred embodiment—it is based on the *sole mention* of the claim term in the specification.

The prosecution history further supports this construction. When “combinatorial tagging” was added as a step to claim 1 in prosecution, the Applicant was clear that no new matter was added to the specification. *Supra* at 16. As already discussed in Parse’s Answering Brief, the only support for combinatorial tagging found in the specification was in the cited passage, defining it as adding one MID by primer extension and a second MID by ligation. *Id.*

Parse’s construction, consistent with the intrinsic evidence, clarifies that the “combinatorial tagging” claimed in the ’013 Patent is what was actually in possession of the inventors at the time of invention—in other words, is consistent with the “full scope of [10x’s] claim language.” *Phillips v. AWH Corp.*, 415 F.3d 1303 at 1322-23 (Fed. Cir. 2005); *see Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367 at 1371 (Fed. Cir. 2014); *Thorner v. Sony Computer Entertainment Am, LLC*, 669 F.3d 1362 at 1366 (Fed. Cir. 2012). 10x’s construction, however, expands the claim scope beyond the specification and is unsupported by the intrinsic record.

**2. “wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence”**

| <b>10x’s Proposed Construction</b>                                                                                                    | <b>Parse’s Proposed Construction</b>                                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| “wherein at least 90 percent of said plurality of sample polynucleotides of interest is associated with a unique second tag sequence” | “wherein at least 90 percent of said plurality of sample polynucleotides of said cell is associated with a unique second tag sequence” |

**a. Plaintiffs’ Opening Position**

It is not clear whether the parties have a dispute as the differences between the parties’ constructions appear to be semantic in nature. Parse’s proposed construction comes from a prior litigation involving this patent, *10x Genomics, Inc. v. Celsee, Inc.*, No. 19-cv-00862-CFC-SRF (D. Del.) in which 10x and Celsee disputed whether this term referred to all polynucleotides of the cell (Celsee’s position) or fewer than all of the polynucleotides of the cell (10x’s position). *Celsee Claim Construction Hr’g Tr.*, Ex. B at 8:13–17 (JA019). The district court (Chief Judge Connolly) rejected Celsee’s argument that this term meant “all of the polynucleotides of that cell,” stating “it clearly means fewer than all *because it’s a sample.*” Ex. B at 8:13–20 (JA019) (emphasis added). That court then adopted the construction Parse proposes here. 10x agrees with the substance of the ruling, but respectfully submits its proposed construction provides additional clarity. The “sample polynucleotides” are the polynucleotides in a cell that are being sampled (*i.e.*, the polynucleotides of interest), not all polynucleotides of that cell. And the substance of the *Celsee* court’s construction as reflected in 10x’s proposed construction is the more natural read in view of the claims, specification, and the common precepts of the English language.

However, if Parse’s construction is intended to adopt Celsee’s rejected argument and encompass each and every polynucleotide in the cell, it fails for the reasons relied on by the district court as stated during the claim construction hearing in that action. A construction that the claims

require 90% of the polynucleotides “of said cell” to be tagged is also disconnected from the purpose of the claimed methods. Ex. B at 9:24–10:2 (JA020-021). These methods allow users to analyze polynucleotides of interest to analyze different aspects of the cell, such as tagging mRNA to understand gene expression. *See* D.I. 80, Ex. B at 6:33–7:22, Claim 25. The purpose is not to blindly tag any and all polynucleotides present in a cell.

**i. 10x’s Construction is Correct**

10x’s construction is supported by the plain language of the claims. Claim 13 modifies the method of Claim 1. Claim 1 states that “the plurality of cells comprises a plurality of sample polynucleotides” and “generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides of said cell.” D.I. 80, Ex. B at Claim 1. And the parties agree that “sample” means “a quantity of material from a biological, environmental, medical, or patient source *in which detection, measurement, or labeling of target nucleic acids is sought.*” D.I. 80, Attach. C at 1. Thus, Claim 1 makes clear that the “sample polynucleotides” are only the polynucleotides the user wants to “detect[], measur[e], or label[]”—which is consistent with 10x’s construction. *Id.* To argue that “sample polynucleotides” means every polynucleotide of the cell would rewrite the claim and replace “sample” with “all.” This is contrary to the parties’ agreed-upon construction and the law. *See Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003) (“[W]e presume, unless otherwise compelled, that the same claim term in the same patent or related patents carries the same construed meaning.”).

The specification also supports 10x’s construction. The specification’s descriptions and embodiments consistently label a particular type of polynucleotides from a cell, not “all” of them. For example: “In certain embodiments, *each individual polynucleotide* (e.g., *double-stranded or single-stranded, as appropriate* to the methodological details employed) *in a sample to be*

*analyzed is tagged with a unique MID* so that the fate of each polynucleotide can be tracked . . . .”

D.I. 80, Ex. B at 15:36–44 (emphases added). A cell contains both double-stranded and single-stranded polynucleotides (e.g., DNA and RNA respectively) and the “sample to be analyzed” contains one or the other “[i]n certain embodiments . . . as appropriate.” *Id.* This is not an isolated disclosure. Another “exemplary embodiment” disclosed is:

[A] large collection of sequences is tagged with MID such that each polynucleotide molecule in the sample has a unique MID. In other words, each polynucleotide in the sample (e.g., each individual double stranded or single stranded polynucleotide) is tagged with a MID that is different from every other MID on every other polynucleotide in the sample.

*Id.* at 22:48–54. Thus, here too the “sample” is not “all polynucleotides in the cell” but just the double stranded or single stranded polynucleotides the user is interested in analyzing. *Id.* There are more. The ’197 Patent describes tagging just the “viral genomes (or a specific genome region) or one thousand copies of a gene present in somatic cells. After tagging each polynucleotide in the sample with a . . . MID . . . .” *Id.* at 23:1–9. This is yet another disclosure of a “sample” including less than all polynucleotides in the cell. Moreover, in “Example III” the tagged polynucleotides are the “polynucleotide of interest being analyzed.” *Id.* at 27:8–30. Thus, the descriptions and embodiments consistently label less than all polynucleotides in a cell.

10x’s position is further supported by U.S. Patent No. 7,537,897, which is incorporated by reference with respect to MIDs being used to tag individual polynucleotides. *Id.* at 6:45–53; *see Cook Biotech Inc. v. Acell, Inc.*, 460 F.3d 1365, 1375–76 (Fed. Cir. 2006) (when a patent incorporates another patent by reference, the patent incorporated-by-reference is considered intrinsic evidence for claim construction). The ’897 Patent consistently notes that the tagged nucleotides are the target nucleotides in the sample, not “all polynucleotides,” including, for example, “combining in a reaction mixture the plurality of nucleic acid probes *with the target polynucleotides.*” D.I. 80, Ex. G at 3:40–43 (emphasis added). The ’897 Patent states that its

invention is a “method of counting molecules . . . [where] every molecule to be counted *in a sample* . . . is associated with a problem having a different tag.” *Id.* at 5:15–20 (emphasis added).

## ii. Parse’s Arguments Fail

To the extent that Parse is attempting to adopt the *Celsee* defendant’s rejected construction, such a construction requiring “sample polynucleotides” be all polynucleotides of the cell is contrary to the claims and the specification. Under that construction, some of the claims would be redundant of others. For instance, dependent Claim 25 recites that “said plurality of sample polynucleotides comprises substantially all mRNA molecules of said cell.” D.I. 80, Ex. B at Claim 25. Under Parse’s construction that “sample polynucleotides” are “all polynucleotides of the cell,” dependent Claim 25 would have the same scope as independent Claim 1 because “all polynucleotides of the cell” would already include “substantially all mRNA molecules of said cell.” *Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022) (“By definition, an independent claim is broader than a claim that depends from it . . .”). Under 10x’s construction that “sample polynucleotides” means the polynucleotides of interest, Claim 25 is narrower than Claim 1 in that Claim 25 specifies an additional limitation of tagging “substantially all mRNA molecules of said cell.”

Parse’s citations to the Brenner patent specification do not support the *Celsee* defendant’s rejected construction. Parse cites to the definition of MID in the Joint Claim Construction Chart. D.I. 80, Attach. A at 1. But that definition does not require that all polynucleotides be tagged and notes only that a polynucleotide tagged with a MID is identifiable such that “polynucleotides in a sample” can be “differentiate[d].” D.I. 80, Ex. B at 6:35–36. If anything, the MID definition supports 10x’s construction: that “MIDs are employed to uniquely tag each individual polynucleotide *in a sample*” is further support that only the sample of polynucleotides being

analyzed need be tagged, not that **all** polynucleotides are tagged. *Id.* at 6:45–47 (emphasis added). Notably, the discussion in the MID definition consistently refers to tagging **samples** and not tagging all polynucleotides of a cell. *See id.* at 6:33–7:22.

Parse’s citation to 15:36–50 in the Joint Claim Construction Chart fares no better. Column 15 refers to certain embodiments where “each individual polynucleotide . . . **in a sample** to be analyzed is tagged with a unique MID so that the fate of each polynucleotide can be tracked.” *Id.* at 15:36–40 (emphasis added). This requires only that the sample polynucleotides be tagged with a MID; it does not define “the sample” as all polynucleotides in a cell. Similarly, that “each nucleic acid tagged with a unique MID allows analysis” does not support a construction that all polynucleotides of a cell be tagged. *Id.* at 15:44–48.

Nor is Parse’s construction correct based on the antecedent “of said cell.” The claim discusses a plurality of sample polynucleotides that come from “said cell.” 10x does not dispute that the sample polynucleotides come from a cell. But any argument that “sample polynucleotides” are **all** polynucleotides in a cell does not logically follow. The polynucleotides of interest also originate from “said cell.” There is no reason that the **origin** of the “sample polynucleotides” necessitates a construction that “all polynucleotides” from that cell are part of the “sample.”

#### **b. Defendant’s Answering Position**

There ought to be no dispute about this claim term since 10x has previously agreed to Parse’s proposed construction in a prior litigation. *Supra* at 23; *see also* Ex. B at 6:8-9 (JA017). The sole point of contention now is that 10x strangely wishes to deviate from its previously agreed-upon stance. Specifically, 10x seeks to replace “said cell” in its prior construction with the words “of interest,” claiming that this will provide “additional clarity.” *Supra* at 23. But 10x’s new construction actually just invites confusion and interjects subjectivity in determining whether there

is infringement by requiring an inquiry into what is “of interest,” whatever that means.

The plain language of the claim supports Parse’s construction. Claim 13 depends from Claim 1 of the ’197 patent, which recites

A method of counting nucleic acids in a sample, the method comprising:

- (a) providing a sample comprising a plurality of cells, wherein a cell of the plurality of cells comprises a plurality of sample polynucleotides;
- (b) generating a plurality of tagged polynucleotides from ***the plurality of sample polynucleotides of said cell*** and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises:

D.I. 80, Ex. B at Claim 1. Claim 1 limits the counting of sample polynucleotides to the “said cell,” which is one of the plurality of cells in the sample being analyzed, as is clear from Claim 1’s step (a). As a result, Claim 13’s “sample polynucleotides” are the polynucleotides from each cell within the plurality of cells in a sample. Thus, based on the claim language alone, 90% of sample polynucleotides of said cell are associated with a unique second tag sequence. This was the exact rationale previously adopted by Judge Connolly when construing this claim term. Ex. B at 11:19-24 (JA022) (*Markman* Hearing Transcript where Judge Connolly narrowed the reading of the claim terms of the ’197 patent starting from a plurality of cells to one cell to “plurality of sample polynucleotides in that cell.”)

While Parse’s construction is clear and fully supported by the claim language, 10x’s construction improperly introduces subjective intent into the claims. 10x’s proposal construe “sample polynucleotides” as referring to those that are “of interest” could conceivably encompass any amount or percentage of polynucleotides based on unclear and unspecified criteria regarding what the experimenter deems “of interest.” The law is clear that such constructions are disfavored. *See Becon Med., Ltd. v. Bartlett*, No. CV 18-4169, 2019 WL 3996619, at \*3 (E.D. Pa. Aug. 23, 2019) (rejecting construction that would “only add confusion to the claims”); *see also Really Right*

*Stuff, LLC v. Field Optics Rsch., Inc.*, No. 2:20-CV-00345-DBB, 2023 WL 6377596, at \*5 (D. Utah Sept. 29, 2023) (finding construction problematic since “invitation to consider subjective intent when construing the claim language invites more confusion than clarification.”).

There is nothing in the specification to support 10x’s vague and ambiguous construction. If anything, what little evidence 10x points to in the intrinsic record confirms Parse’s construction. *See supra* at 24-25; *see also* D.I. 80, Ex. B at 6:45-7:53; 15:36-44. Indeed, 10x acknowledges in its brief that these “descriptions and embodiments consistently label less than all polynucleotides *in a cell*.” But nothing in this passage teaches sample polynucleotides “of interest” that are uniquely tagged with a second tag sequence or anything of that sort. 10x’s reliance on Example III likewise offers no support for 10x’s proposed construction because it pertains only to the reflex method, not the generation of tagged polynucleotides in a sample of polynucleotides. *See* D.I. 80, Ex. B at 27:15-17 (“The data shown in prior Examples used ‘artificial’ reflex sites. In this Example, the reflex site is a genomic sequence present in the polynucleotide being analyzed.”).

In sum, the Court should adopt the previous construction entered by Judge Connolly and agreed to by 10x, not its new construction that injects ambiguity and uncertainty.

### **c. Plaintiffs’ Reply Position**

The parties dispute whether “sample polynucleotides” in the claim term “wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence” refers to all of the polynucleotides (Parse’s position) or whether it refers to the sample polynucleotides of interest (10x’s position). In the *Celsee* case, Chief Judge Connolly rejected the same construction Parse asserts in this case, and 10x respectfully submits that this Court should do the same here. In *Celsee*, the parties disputed whether the claim term “sample polynucleotides” refers to (1) all polynucleotides from a cell in the sample or (2) a sampling, i.e., less than all, of

polynucleotides from a cell in the sample. Chief Judge Connolly rejected the former construction and adopted the latter construction:

[Celsee Counsel]: Well, Your Honor, I think the parties' dispute here is really about whether or not the plurality of sample polynucleotides of said cell means all of the sample – all of the polynucleotides of that cell or fewer than all of the polynucleotides of the cell.

[The District Court]: Well, it clearly means fewer than all because it's a sample. It says, the plurality of sample polynucleotides.

Ex. B at 8:13-20 (JA019). As in *Celsee*, Parse now argues that “Claim 13’s ‘sample polynucleotides’ are *the polynucleotides* from each cell within the plurality of cells in a sample.” *Supra* at 27-28 (emphasis added). This fails. While “sample polynucleotides” are polynucleotides that are from a cell in the sample, “sample polynucleotides” does not mean all of the polynucleotides in the cell. Holding otherwise would ignore the word “sample” in “sample polynucleotide,” as the district court held in *Celsee*. *See, e.g.*, Ex. B at 9:18–11:1 (JA020-021).

Contrary to Parse’s assertion, 10x’s proposed addition of the term “of interest” does not inject ambiguity. 10x’s construction accurately reflects that the user of the claimed method may select the type of polynucleotides to be included in the “sample polynucleotides” to be counted. Cells contain many types of polynucleotides, including DNA such as nuclear DNA and mitochondrial DNA (mtDNA), and RNA such as transfer RNA (tRNA), messenger RNA (mRNA), and ribosomal RNA (rRNA), that can be counted using the claimed invention. *See, e.g.*, D.I. 80, Ex. B at 14:8-14. The claims of the ’197 patent expressly contemplate the user may select the type of polynucleotide to be counted. For example, Claim 3 is directed to the method of Claim 1 “wherein the plurality of sample polynucleotides is selected from DNA and RNA” and Claim 4 is directed to the method of Claim 1 “wherein the plurality of sample polynucleotides comprises mRNA.” D.I. 80, Ex. B at Claims 1, 3, & 4. 10x’s proposed construction is consistent with the claim language, the specification, and aligns with Chief Judge Connolly’s reasoning in *Celsee*.

#### d. Defendant's Sur-Reply Position

As an initial matter, 10x continues to unnecessarily prolong a false dispute. 10x contends that “Chief Judge Connolly rejected the same construction Parse asserts in this case.” *Supra* at 29. 10x is incorrect, however, as Parse proposes *exactly the same* construction that Chief Judge Connolly adopted. In fact, 10x’s proposal alters the construction adopted by Chief Judge Connolly by adding in the unnecessary and ambiguous clause “of interest.”

10x asserts that Parse’s construction is incorrect because it encompasses all polynucleotides in the said cell. Parse’s construction says no such thing. The issue is not whether “sample polynucleotides” refer to all of the polynucleotides or sample polynucleotides of interest. *Id.* Rather, the dispute is about 10x’s attempt to replace the phrase “said cell,” which it previously agreed to, with “of interest.”

10x fails to adequately address that its new construction injects ambiguity and subjective intent, thus potentially confusing the jury. What does “of interest” mean? On what criteria is “of interest” supposed to be quantified? By amount? By percentage? By type? 10x’s phrase opens an unclear domain of possibilities, with no guidance on what the bounds of “of interest” might be. As a strawman argument, 10x confusingly argues that “of interest” refers to a “type” of polynucleotides a “user of the claimed method may select.” *Supra* at 30. “Type” is not a term used in the claim to describe “sample polynucleotides of interest.” 10x’s reliance on claims 3 and 4 is also without merit. These claims do not use or explain what “of interest” means.

10x nonetheless argues that its new construction “is consistent with the claim language, the specification, and aligns with Chief Judge Connolly’s reasoning in *Celsee*.” *Id.* 10x is wrong. First, 10x’s “of interest” construction lacks support in the claim language. Claim 13 depends from Claim 1, which limits counting sample polynucleotides and not “sample polynucleotides of

interest” to the said cell. 10x does not meaningfully address this claim language, thus failing to rebut Parse’s detailed explanation showing that the plain language mandates Parse’s construction. *See supra* at 27-29. Second, the specification provides no guidance on how to apply the phrase “of interest” in the context of claim 13. 10x fails to rebut Parse’s argument that the intrinsic record confirms Parse’s construction. *Supra* at 29-30. Third, nowhere is 10x able to explain how Chief Judge Connolly’s reasoning in *Celsee* aligns with 10x’s construction. Judge Connolly in *Celsee* reasoned “sample polynucleotides” in Claim 13 to be the sample polynucleotides from each cell within the plurality of cells in a sample, as clear from Claim 1. *See* Ex. B at 11:19-24 (JA022). The reasoning is silent on polynucleotides “of interest” or any “type.” Parse is adopting Judge Connolly’s construction verbatim which does not use the phrase “of interest.” Accordingly, if it is 10x’s position to adopt Judge Connolly’s reasoning, 10x should not be disputing Parse’s construction.

Overall, Parse and 10x agree that this Court should adopt the previous construction entered by Judge Connolly. 10x has agreed to such a construction previously. Its new addition of “of interest” provides no clarity and injects ambiguity and uncertainty. This Court should thus adopt Parse’s construction.

### 3. “random sequences”

| 10x’s Proposed Construction                                          | Parse’s Proposed Construction                                                                                     |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Plain and ordinary meaning, which is “sequences having random bases” | “a sequence consisting of randomly selected bases such that the sequence is unknown in advance of the experiment” |

#### a. Plaintiffs’ Opening Position

The parties dispute whether “random sequences” should be construed as “sequences having random bases” (10x’s position) or “a sequence consisting of randomly selected bases such that the

sequence is unknown in advance of the experiment” (Parse’s position). Thus, while the parties agree that this term requires the “second tag sequence” be generated with random bases, Parse seeks to add a further limitation that the sequences are “unknown in advance of the experiment.” 10x’s construction is supported by the claims, the specification, and reason, whereas Parse’s addition is narrower than the plain and ordinary meaning and unsupported by its cited intrinsic evidence.

**i. 10x’s Construction is Correct**

10x’s construction is consistent with Claims 1 and 10.<sup>5</sup> Claim 1(b)(iii) and 1(d) recite that the “second tag sequence distinguish[e]s said sample polynucleotide from other sample polynucleotides” and that the sequencing of amplified polynucleotides to determine sequences corresponding to “the second tag sequence.” Then Claim 10 recites that the “second tag sequences of said plurality of oligonucleotide tags are random sequences.” The claims recite only that the “second tag sequences” are “random sequences,” *i.e.*, the second tag sequences are generated randomly, regardless of whether the user knows the makeup of the randomly generated sequence. D.I. 80, Ex. C at Claim 10. The claims and their context do not require that the sequences themselves be unknown before the experiment, only that they be randomly generated. *See Phillips*, 415 F.3d at 1314.

10x’s construction is also supported by the incorporated-by-reference ’897 Patent. D.I. 80, Ex. C at 6:4–61. The ’897 describes using “random sequences” of ten nucleotides in length to ensure there is a high probability of selecting individual fragments created during the process of

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<sup>5</sup> Further, the term is plural “random sequences” and 10x’s construction captures that fact by referring to sequences, unlike Parse’s construction.

using particular restriction endonucleases. D.I. 80, Ex. G at 19:39–43. Nothing in that disclosure says that those sequences must be “unknown.”

Consider a real-world example that illustrates that 10x’s “plain and ordinary” construction is correct. A Pennsylvania Lottery Pick 4 winner is determined by selecting four numbers between 0 and 9 in the correct sequence or order. The numbers of the lottery balls that can be drawn is known (0 to 9), but the sequence of numbers selected in the drawing is random. Here too, “random sequences” merely means the second tag sequences were generated with random bases to form tags that will uniquely identify the sample polynucleotides. The fact that the bases used to generate the sequences are known (adenine, thymine, cytosine, and guanine) does not make the sequence of the bases known. Rather, the universe of possible sequences that could be generated, and even the actual sequences generated are “random.” “Non-random sequences,” in contrast, would be using many different *predetermined* sequences.

## ii. Parse’s Arguments Fail

In the Joint Claim Construction Chart, Parse cites two pieces of intrinsic evidence, neither of which supports its narrow construction. **First**, Parse incorrectly suggests that the “MID” definition supports its construction. *See* D.I. 80, Ex. C at 6:41–7:30. Nothing in that passage speaks to the knowledge of the user or demands an understanding of “random” in the ’013 Patent that departs from its plain and ordinary meaning. Further, the Brenner patent specification describes that MID sequences may be reused which is inconsistent with Parse’s construction as a sequence that was known under Parse’s construction is not a “random sequence” and thus cannot be reused. *E.g., id.* at 7:9–23.

**Second**, Parse’s citation to 22:57–23:9 of the ’013 Patent does not support Parse’s construction. This passage teaches those skilled in the art to use many times more MIDs than the

number of sample polynucleotides in order to ensure that the majority of each polynucleotides will have a unique MID. *Id.* It is silent as to knowledge and does not mention using “random sequences” for the second tag.

In addition, Parse’s construction is incorrect because refers to “*the* experiment.” The claim does not require an experiment and this would inject unnecessary ambiguity into the claims if Parse’s construction were adopted.

### **b. Defendant’s Answering Position**

“Random” by its plain meaning requires that the event be unpredictable or unknown in advance. 10x, however, contends that the term “random sequences” should be broadened to read out the word “random” and include any predetermined barcode sequence—contrary to the plain language of the claims and the state of the art at the time of the ’013 patent’s priority date. Parse’s proposed construction is consistent with the plain language of the claims, specification, and extrinsic record, which all use the term “random” to refer to occurrences that are unplanned and unknown in advance.<sup>6</sup> 10x’s inaccurate broadening of this claim should be rejected.

### **i. Parse’s Construction Is Supported By The Intrinsic Record**

As to the claim language, the term “random sequences” occurs in ’013 Patent Claim 10 modifying the method of Claim 1. D.I. 80, Ex. C at Claims 1, 10. The method provided by Claim 1 includes the step of tagging polynucleotides, including by “ligating a second oligonucleotide tag,” which may be the “random sequence.” *Id.* This tagging is step “(b)” in the provided method. Step “(d)”, which occurs afterwards, requires “sequencing said tagged polynucleotides.” *Id.* This

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<sup>6</sup> 10x argues that Parse’s construction is incorrect because it is singular while the claim term is plural. *Supra* at 33. 10x is wrong because Parse’s construction can be correctly applied as is, or altered to be plural: “sequences consisting of randomly selected bases such that the sequences are unknown in advance of the experiment.”

“sequencing” step is when the sequence of the sample polynucleotides and the attached “tag” are first determined. Thus, as the claims make clear, prior to the sequencing step, the sample sequence and the random barcode sequence are unknown. *Id.*

The specification is consistent with the foregoing. The claimed “random sequences” are part of a multiplex identifier (MID) sequence, which is used to tag and track sample molecules (typically DNA or RNA). The definition of “multiplex identifier (MID) sequence” included in the patent and agreed to by the parties, provides that “[i]dentification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present.” *Id.* at 6:55-57. Thus, the unique MIDs are “identified” *after* being associated with sample polynucleotides. In the specification, this is done by sequencing. *Id.* at Claim 1; 2:40-45; 15:37-43; 19:54-63. Thus, the sequence of the random barcode is unknown in advance.

Further, the MID definition provides that “MIDs can range in length from 2 to 100 nucleotide bases or more and may include multiple subunits, where each different MID has a distinct identity and/or number of subunits” and that MIDs “can be used to differentiate polynucleotides in a sample.” *Id.* at 6:43-44, 60-64. The only guidance provided in the specification for generating a sufficient number of MIDs to differentiate sample polynucleotides is that “the number of distinct MID tags to be used should be many times greater than the actual number of molecules to be analyzed.” *Id.* at 22:64-65. As acknowledged by 10x, a sample may contain hundreds of thousands of polynucleotides. Ex. C at 38:13-25 (“what we’re talking about is grinding up a huge amount of genetic material. And you could very easily need to have millions of different – to identify, you need millions of different things.”). To generate the massive number of unique random barcodes necessary to tag each sample polynucleotide, a POSA would understand that they are generated randomly together in large batches. Ex. E at JA047-048. The

precise random barcodes generated and included in any given batch is not predetermined. *Id.* The sequences of each of these many unique random barcodes would not be sequenced (i.e. identified) in advance of the experiment. There is no need to identify them in advance so long as they can be used to distinguish amongst samples after amplification and sequencing. Nothing in the patent suggests any reason why one would pre-sequence the random barcodes before being used in the claimed process.

Therefore, the intrinsic record supports the plain reading of the term “random sequences” such that they would not be known in advance of the experiment.

## **ii. Parse’s Proposed Construction Is Supported By The Extrinsic Record**

Parse’s proposed construction is also supported by the extrinsic evidence, including not just an understanding of how random barcodes are generated and used but also accepted definitions of the word “random.”

As of the priority date of the Brenner Patents, it was well known how to generate random barcodes. *See* Ex. E. The claimed random barcode is a strand of DNA made up of the same four “base pairs” as a typical strand of DNA (adenine, thymine, cytosine, and guanine, or A, T, G, and C). Common methods for generating synthetic DNA involve chemistries that add these base pairs one by one to the growing strand. *Id.* at JA038-040. To generate a strand with a random sequence of base pairs requires using a pre-mixed solution of ***all four*** base pairs:

If a statistically random distribution of nucleotides is required or if long stretches of random sequence are to be made, it is better to manually mix the phosphoramidites together and use this mixture for the degenerate position. A true random distribution may be obtained by mixing A, C, G, and T phosphoramidites in a 3:3:2:2 molar ratio to compensate for the faster coupling times of G and T phosphoramidites

*Id.* at JA047.

The chemistry then proceeds by a process wherein one of the four bases is randomly pulled

from the mix and added to the growing strand. *Id.* at JA047-048. The process of adding a random base from a mix is repeated for each base as the strand grows, generating a random sequence. This method for generating random sequences can be done many times in parallel to generate a large batch of random barcodes, all with unique sequences. The key point, though, is that the technology from the relevant time frame for generating “random” barcodes was such that the sequence of the barcodes was not observed at the time of creation, but was only learned *after* sequencing (the process of determining the precise order of base pairs in a DNA strand).

It is unsurprising that such “barcodes” would be referred to as “random” because this aligns with the lay-persons understanding “random.” Dictionary definitions, for instance, consistently provide that “random” occurrences lack a plan and are unknown in advance:

- “lacking any definite plan or prearrange order; haphazard; a random selection” Ex. F, *Random*, Collins Dictionary (10th ed. 2009);
- “Governed by chance: used of a process in which the outcome is indeterminate but may assume any of a set of values (the domain) with probabilities specifiable in advance. Although the random process is widely used in probability theory, empiric justification for the term is more complicated. The minimum requirement is that repeated realization of the process will settle down to a stable distribution or, if not metric, a stable set of frequencies if the trait is classifiable only.” Ex. G, *Random*, Stedman’s Medical Dictionary (28th ed. 2006).

Each of these definitions provides that “random” occurrences lack a prearranged order or plan. For a “random sequence” to lack a prearranged order or plan means that the random sequence would be unknown in advance or the experiment.

Thus, Parse’s proposed construction is consistent with the common understanding and definition of the word “random.” Such definitions may help a court better understand underlying technology because they “endeavor to collect the accepted meanings of terms used in various fields of science and technology” and “those resources have been properly recognized as among the

many tools that can assist the court in determining the meaning of particular terminology to those of skill in the art of the invention.” *Phillips*, 415 F.3d at 1317.

10x argues that because “the universe of possible sequences that could be generated” would be known in advance, the specific “random sequence” would be known. *Supra* at 33. 10x’s argument is inconsistent with the plain and ordinary meaning of “random.” For example, as noted above, Stedman’s Medical Dictionary provides that “the outcome is indeterminate but may assume any of a set of values (the domain) with probabilities specifiable in advance.” Ex. G, *Random*, Stedman’s Medical Dictionary (28th ed. 2006). Consistent with this definition and others, though the world of possible sequences may be known in advance, a “random sequence” would not be known in advance of an experiment.

10x nonetheless provides the example of the Pennsylvania lottery where “the number of lottery balls that can be drawn is known (0 to 9), but the sequence of numbers selected in the drawing is random.” *Supra* at 34. 10x’s position amounts to an argument that you “know” the result of a coin toss before it occurs simply because you know what the two sides of the coin are. Similarly, simply knowing the hypothetical universe of millions of possible sequences does not actually determine the sequences of a specific “random” tag used in a given experiment. This is nonsensical and inconsistent with the plain understanding of the term random

### **c. Plaintiffs’ Reply Position**

Contrary to Parse’s assertion, 10x’s construction does not read out the term “random” or include any predetermined barcode sequence. *Supra* at 35. 10x has not proposed that “random sequences” should be construed to include predetermined sequences. As 10x stated in its Opening Brief: “‘Non-random sequences,’ in contrast, would be using many different *predetermined* sequences.” *Supra* at 33-35. “Random sequences” are simply sequences *generated* at random.

The parties appear to agree that “random sequences” should be construed as having or consisting of random bases. Thus, the dispute centers upon Parse’s insertion of an ambiguous knowledge requirement by which “the sequence is unknown in advance of the experiment.”<sup>7</sup> *Supra* at 36. But nothing in the claim language, other intrinsic evidence, or extrinsic evidence supports a requirement that the sequences remain unknown for some indefinite period.

Further, Parse’s argument misunderstands the timing of the knowledge that is determinative of whether something is “random.” The outcome of any given “random” event is unknown at the time of the event, but the “random” nature of the event does not depend on events after the outcome is determined. Otherwise, all “random” events would become “non-random” after the result is known. Even in Parse’s coin-flipping scenario, one can know the universe of possible outcomes (heads or tails), yet the outcome of any individual flip remains random because it is uncertain as to whether a given flip will be heads or tails. For example, the outcome is random for an individual coin that is flipped and lands on its head because that outcome was not determined. That flip does not become non-random if one learns the coin landed on heads: it is a “random” outcome regardless of whether the result becomes known later. In contrast, a weighted coin that always lands on its head is not capable of generating a random outcome because its outcome is predetermined by design.

**i. The intrinsic evidence does not support Parse’s construction.**

Parse’s construction is not supported by the intrinsic evidence. Parse cites no case in support of its order-of-the-steps argument because there is none. *Supra* at 35-37. Although the claim requires “sequencing” after the second tag is ligated to the fragment, the claim does not

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<sup>7</sup> The claims do not use the term “experiment” and Parse’s construction does not define “experiment.”

require this to be the first time any portion of the tagged fragment is sequenced; nor does the claim require the user be ignorant of the sequences. Rather, the claim says “comprising” meaning it is “open-ended and allows for additional steps.” *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003). Parse’s attempt to limit the claim to only the specified sequencing steps would write out the “comprising” term. *See id.* To be clear, although some users practicing the claimed methods may first learn of the sequences during the sequencing step, this does not mean that learning the sequences prior to that step renders the sequences non-random and thus outside the claim’s scope.

Parse also attempts to rely on the specification’s “MID” definition to import a knowledge requirement. *Supra* at 36. This too fails. Parse’s argument misunderstands the “MID” definition. *Id.* The agreed-upon construction— “[i]dentification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present”—does not require the use of random, as opposed to unique, sequences. Nor does it require ignorance of the sequences in advance of sequencing them. And the construction does not require that MID sequences be learned for the first time after sequencing. D.I. 80, Ex. C, at 6:55-57. The construction merely explains that one can count the number of unique MIDs (eliminating redundant copies resulting from amplification) to determine the number of polynucleotides that were present in the cell at the time of tagging. *Id.*

## **ii. The extrinsic evidence does not support Parse’s construction.**

Parse’s extrinsic evidence supports 10x’s construction. Parse asserts “it was well known how to generate random barcodes” using “all four base pairs.” *Supra* at 37-38. Parse concedes this is exactly the process referred to by this claim term. *Supra* at 35-38. The simplest approach to generate enough unique sequences to tag the polynucleotides being targeted, such as mRNA, is

to randomly generate nucleic acids for tagging in large batches. *Supra* at 37. These sequences are not predetermined. Yet Parse argues that “[n]othing in the patent suggests any reason why one would pre-sequence the random barcodes before being used in the claimed process.” *Supra* at 37. That is irrelevant. As explained above, learning the sequence of any such randomly generated nucleic acids *after* they are randomly generated does not convert the “random sequences” into non-random ones. Indeed, the extrinsic evidence cited by Parse discusses the creation of large pools of random sequences that can then be used as reagents in various types of experimental techniques. *See, e.g.*, Ex. E at JA047. As described, the use of oligonucleotide synthesizers allows the creation of large batches of oligonucleotides of a specified length and a random distribution of bases. *See id.* The synthesized random oligonucleotides can then be purified and used in an array of assays including being used as oligonucleotide tags.

Further, Parse’s extrinsic evidence is inconsistent with its own construction. The cited evidence teaches that it may be desirable to confirm the sequence of the generated oligonucleotides prior to their use; Parse does not assert that such confirmation renders the oligonucleotides non-random as would be the case under the logic of Parse’s construction. *Id.* at JA049–JA050.

#### **d. Defendant’s Sur-Reply Position**

The dispute centers on whether or not the “random sequences” synthesized for tagging and counting are known prior to the sequencing step. 10x’s arguments ignore the plain language of the claim, the teachings of the specification, and the state of the art at the time of the invention to interject ambiguity into the claim.

The claim language confirms that the sequences of the tag are not known prior to sequencing. Claim 10 depends from claim 1, modifying step (b)’s “ligating a second oligonucleotide tag” by specifying that the tag be a “random sequence.” D.I. 80, Ex. C at Claims

1, 10. Sequencing, however, occurs at step (d), where “said tagged polynucleotides” are “sequenced.” *Id.*

The specification further supports this interpretation. The recited “random sequences” are part of the MID, which is used to tag and track sample molecules. As discussed at length above, the unique MIDs are “identified” after being associated with sample polynucleotides. *Id.* at Claim 1; 2:40-45, 15:37-43, 19:54-63. Further, the MID definition from the specification provides that “MIDs can range in length from 2 to 100 nucleotide bases or more and may include multiple subunits, where each different MID has a distinct identity and/or order of subunits” and that MIDs “can be used to differentiate polynucleotides in a sample.” *Id.* at 6:43-44, 61-64. The specification only provides guidance for generating a sufficient number of MIDs in teaching that “the number of distinct MID tags to be used should be many times greater than the actual number of molecules to be analyzed.” *Id.* at 22:64-66. As explained in Parse’s Answering Brief, these disclosures are consistent with the state of the art—the sequence of the random barcode would not be *known* until the sequencing step. *See supra* at 35-37.

In response to the foregoing, 10x first misrepresents Parse’s argument as changing the meaning of the disputed term, and then nebulously seeks to add steps that are not recited in the claim and that are inconsistent with the specification. Nothing in Parse’s construction converts a “random sequence” to “a non-random sequence,” nor can 10x actually cite to Parse making such an argument. Parse’s construction acknowledges that the sequences are randomly generated, and that they are only read in the final sequencing step so that the outcome of random generation is not known until that point. 10x proceeds to argue that the sequencing step of the claim need not be “the first time any portion of the tagged fragment is sequenced; nor does the claim require the user be ignorant of the sequences.” *Supra* at 40. The only support from the patent that 10x cites,

however, is that the word “comprising” is open ended. *Id.* But there is nowhere in the specification nor in any of the claims that actually disclose such a step. As the Federal Circuit has acknowledged, “the word ‘comprising’ does not mean that the claim can be read to require additional unstated elements, only that adding other elements to the device or method is not incompatible with the claim.” *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019). 10x’s arguments amount to little more than hand waving to introduce additional steps taught nowhere in the Patent to strangely contend that “random sequences” are known prior to the sequencing step.

10x also misreads and misconstrues the extrinsic evidence. According to 10x, “it may be desirable to confirm the sequence of the generated oligonucleotides prior to their use.” *Supra* at 42. 10x fails to mention, however, that the cited portion of the extrinsic evidence is specific to “cases where a sequence will be used in a ***structural application*** such as mobility shift assays, filter binding assays, or crystallography,” and that in such cases “it is desirable to confirm the sequence.” Ex. E at JA049-050. The ’013 Patent is not directed to such structural applications, but to tagging and counting sample molecules. At best, 10x’s argument provides that a random sequence ***may*** be confirmed prior to use—but the ’013 Patent does not contain any disclosure of a sequencing step prior to use.

10x’s construction is not rooted in any intrinsic evidence, nor is it consistent with the understanding in the state of the art. For the foregoing reasons, Parse’s construction should be accepted.

#### 4. “digital count”

| 10x’s Proposed Construction                              | Parse’s Proposed Construction |
|----------------------------------------------------------|-------------------------------|
| Plain and ordinary meaning, which is “a numerical count” | Indefinite                    |

##### a. Plaintiffs’ Opening Position

The parties dispute whether “digital count” has its plain and ordinary meaning, “a numerical count” (10x’s position), or whether the claim term is indefinite (Parse’s position). This is not a close call. The specification and common sense provide those skilled in the art—and those that are not—reasonable certainty as to the scope of the claim. *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014) (“[A] patent’s claims, viewed in light of the specification and prosecution history, [is not indefinite if they] inform those skilled in the art about the scope of the invention with reasonable certainty.”); *f’real Foods, LLC v. Hamilton Beach Brands, Inc.*, 388 F. Supp. 3d 362, 365 (D. Del. 2019) (“[I]t is obvious and a matter of common sense” that “sufficient mass” with regards to a splash shield is not indefinite because “it is very easy for one of ordinary skill in the art to determine whether sufficient mass has been achieved for their particular blender by simply observing whether the cup stays in the holder during blending or not.”) (internal citation omitted). Indefiniteness must be proven by clear and convincing evidence and a claim term is not indefinite where the claim provides reasonable certainty. *See Sonix Tech. Co. v. Publ’ns Int’l, Ltd.*, 844 F.3d 1370, 1377 (Fed. Cir. 2017) (“Indefiniteness must be proven by clear and convincing evidence.”); *see also* 35 U.S.C. § 282 (“A patent shall be presumed valid.”). A patent owner can rebut a challenge of indefiniteness by providing a reasonable interpretation of the term. *See Sonix Tech.*, 844 F.3d at 1377 (overcoming indefiniteness only requires that a “skilled artisan would understand, with reasonable certainty, [the scope of the claims].”).

The term appears in Claim 23 of the '013 Patent:

The method of claim 1, wherein step (e) comprises (i) **determining the number** of different second tags sequences associated with said sample sequence, thereby **estimating the number** of sample polynucleotides having said sample sequence from said single cell and/or (ii) using second tag sequences of said plurality of amplified polynucleotides to provide a **digital count** of said sample polynucleotides.

D.I. 80, Ex. C at Claim 23 (emphases added). This claim further limits step (e) of Claim 1, which reads: “(e) using the sequences determined in step (d) to **count** sample polynucleotides for multiple different sample polynucleotides of multiple different single cells of said plurality of cells.” *Id.* at Claim 1 (emphasis added).

This term requires no expertise to understand—just common sense. It is clear from the plain language of the claims that to “provide a digital count” is simply providing a readout in numerical digits, *i.e.*, an integral count (0, 1, 2, 3, . . .). For example, in its discussion of MIDs, the patent discloses that “[i]dentification of the number of unique MIDs in a sample can provide a **readout of how many** individual polynucleotides are present in the sample (or from how many original polynucleotides a manipulated polynucleotide sample was derived . . .).” *Id.* at 6:55–59 (emphases added). It is clear that “provid[ing] a digital count” is directed towards a simple counting step, by providing the “readout,” *i.e.*, to a user. The patent elaborates on what the “readout” consists of: “‘Readout’ means a parameter, or parameters, which are measured and/or detected that can be converted to a **number or value.**” *Id.* at 10:64–66 (emphasis added). The incorporated-by-reference '897 Patent then explains what the “digital count” would be for any “readout”: “Digital measures of polynucleotides have been made, **wherein measured amounts are correlated with integral numbers** of countable events.” D.I. 80, Ex. G at 1:42–44 (emphasis added); *see id.* at 1:52–55, 4:4–9. Thus, a digital count is “a count” conveyed with “integral numbers.”

Parse's first amended invalidity contentions make two arguments. The first was that the term was not discussed in the specification. This is wrong, as discussed above. It is also a red herring. It is not necessary that the exact phrase "digital count" appear in the specification for one to understand its meaning. *See ESCO Grp. LLC v. Deere & Co.*, No. 20-cv-1679-WCB, 2023 WL 4199413, at \*14 (D. Del. June 22, 2023) (J. Bryson sitting by designation stating "lock bearing surface" is not indefinite even if specification "does not use the term" because there were sufficient disclosures that "it would be clear to a skilled artisan"); *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1366 (Fed. Cir. 2017) ("The mere observation of information [the claim term] not 'recited' does not answer the question whether a person of ordinary skill in the art would *need* to be given the level and measurement information to understand, with reasonable certainty." (emphasis added)). Parse's second argument is that no embodiment discloses how a digital count may be provided. This too is wrong. As discussed above, the specification contains disclosures regarding obtaining and providing a digital count. D.I. 80, Ex. C at 6:55–59, 10:64–66; D.I. 80, Ex. G at 1:42–44, 1:52–55, 4:4–9.

#### **b. Defendant's Answering Position**

10x contends that the term "digital count," which appears nowhere in the specification, should be construed to mean "a numerical count," which is yet another term that appears nowhere in the specification. 10x does not contend that "digital count" is a known term of art and the intrinsic record provides no guidance on the term. The term is thus indefinite.

Claim 23 of the '013 Patent recites the use of second tag sequences to provide a "digital count" of sample polynucleotides. The term "digital count," however, is indefinite because its unbounded language fails to inform a POSA, with reasonable certainty, about the scope of the invention. The term "digital count," does not appear anywhere in the Brenner Patent's

specification, nor do any embodiments provide any guidance on how a “digital count” may be provided.

On these facts, the term “digital count” can only be regarded as a coined term by the patentee that is left undefined in the specification. Consistent with *Phillips*, however, if “a patentee uses a coined technical term as an element of a claim and fails to clearly define the term elsewhere in the specification or prosecution history, the meaning of the term is left to speculation and subjective judgment.” *Acacia Media Techs. Corp. v. New Destiny Internet Group*, 405 F. Supp. 2d 1127, 1134 (N.D. Cal. Dec. 7, 2005); *see generally Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005).

In *IQASR LLC v. Wendt Corp.*, the Federal Circuit affirmed the district court’s finding that the term “magnetic fuzz” was indefinite because it was a coined term and the intrinsic evidence was unclear. 825 F. App’x 900, 904–07 (Fed. Cir. 2020). The Federal Circuit emphasized that “magnetic fuzz” lacked “a readily-understood definition in its field,” emphasizing that when “a term has no ordinary and customary meaning, it is a coined term, raising the question of whether the intrinsic evidence provides objective boundaries to the scope of the term.” *Id.* at 902-04 (internal quotations omitted). Noting that the specification “fail[ed] to offer any meaningful and functional explanation of the definitional characteristics of ‘magnetic fuzz,’” the court concluded that an artisan was unable to “infer reasonably certain, objective boundaries of the term.” *Id.*

As in *IQASR*, “digital count” lacks “a readily understood definition in [its] field.” *Id.* at 902. 10x does not contend that there is any common understanding in the field, nor that “digital count” is a term of art. *See generally supra* 44-47. With no “ordinary and customary meaning,” “digital count” is a coined term. *See IQASR*, 825 F. App’x at 904. Accordingly, “the question is whether the intrinsic evidence provides objective boundaries to the scope of the term.” *Iridescent*

*Networks, Inc. v. AT&T Mobility, LLC*, 933 F.3d 1345, 1353 (Fed. Cir. 2019) (citing *Interval Licensing v. AOL Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014)). The specification does not provide any “meaningful and functional explanation of the definitional characteristics of “digital count.” See *IQASR*, 825 Fed. App’x at 904.

10x nonetheless asserts that “the specification and common sense” provide “reasonable certainty as to the scope of the claim,” but cites no intrinsic or extrinsic evidence that actually discusses—or even mentions—a “digital count.” See *supra* at 45. Despite 10x claiming that the understanding of “digital count” is common sense, it can point to no common usage or passage that provides a clear meaning of the term. Instead, 10x cites to passages of the specification that discuss a “readout.” 10x, however, provides no basis for why one would equate “readout” with “digital count” beyond a one sentence explanation that “to ‘provide a digital count’ is simply providing a readout in numerical digits.” *Id.* 10x’s conclusory statement cites nothing from the intrinsic or extrinsic record for support. *Id.* If the inventors had intended to mean “readout,” they could have simply used that term, which is used and defined in the specification. Instead, they chose to use the term “digital count,” without any definition or description.

10x also cites “incorporated-by-reference ’897 Patent” in an attempt to connect “readout” to “digital count.” *Supra* at 46. 10x’s connection fails, however, because, just like the ’013 patent, the ’897 patent does not actually use the term “digital count.” *Id.* Instead, the ’897 patent discusses “digital measures.” Again, despite 10x claiming that an understanding of “digital count” is “common sense,” 10x points to no evidence that actually uses the term “digital count.”

Even assuming that the limited discussion in the specification does relate to “digital count,” that disclosure is far from sufficient to inform a POSA on how to obtain a digital count. The disclosure 10x points to merely provides that readout “means a parameter, or parameters, which

are measured and/or detected that can be converted to a number or value. In some contexts, readout may refer to an actual numerical representation of such collected or recorded data.” D.I. 80, Ex. C at 10:64-67. This disclosure, which does not mention “digital count,” does not provide any guidance on how to obtain a digital count or what a “digital count” would be. Therefore, a POSA is not given any guidance and the claim is indefinite because it fails “to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc.*, 572 U.S. at 901.

Moreover, the disclosure in the specification does not support 10x’s proposed construction because it does not say that a readout provides a “numerical count.” The specification provides that a “readout may refer to an actual numerical representation,” but not 10x’s proposed construction of “a numerical count.” D.I. 80, Ex. C at 10:66-67. 10x’s proposed construction lacks support in the specification, so they rely on the definition of a separate term, which also does not support their proposed construction. Thus, 10x’s construction should be rejected.

### **c. Plaintiffs’ Reply Position**

Parse incorrectly argues that “digital count” is indefinite because it does not appear verbatim in the specification. *Supra* at 47-48. There is no such requirement. *Bancorp Servs., L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372 (Fed. Cir. 2004) (meaning of a claim term can be inferred from the specification). Although it is Parse who bears the burden to prove indefiniteness by clear and convincing evidence, 10x nonetheless identified portions of the specification that provide reasonable certainty to a POSA as to the meaning of “digital count.” *Supra* at 45-46. Parse provides no meaningful response.

### **i. 10x’s construction is correct**

Contrary to Parse’s assertion that 10x identified no intrinsic or extrinsic evidence discussing “digital count,” *supra* at 45-46, although 10x had no burden to do so, it explained how

Claim 23’s “digital count” is connected to the specification’s description of using the MID to provide a “readout of how many individual polynucleotides are present in the sample.” *Id.*

The specification’s description of using MIDs to provide a readout provides guidance as to the meaning of “digital count.” Claim 23 is directed to “determining the number of different second tag sequences” and/or “using second tag sequences . . . to provide a digital count of said sample polynucleotides.” D.I. 80, Ex. C at Claim 23; *supra* at 46-47. The “second tag sequences” are the unique sequences that “distinguish[] said sample polynucleotide[s] from other sample polynucleotides.” D.I. 80, Ex. C at Claim 23. Thus, Claim 23 is focused on counting the number of unique second tag sequences to count the number of sample polynucleotides, and providing that number to the user. *Id.* The “MID” definition discusses this act: “Identification of the number of unique MIDs in a sample can provide a **readout of how many individual polynucleotides** are present in the sample.” D.I. 80, Ex. C at 6:55-59 (emphasis added); *supra* at 45-46. The “readout” discussed in the “MID” definition tracks “digital count” in Claim 23. *Id.* 10x explained that the patent’s definition of “readout” as well as the incorporated-by-reference ’897 Patent, cited immediately after this sentence, provide further guidance as to how the “readout” could be provided to the user.<sup>8</sup> *Supra* at 46-47. This is ample intrinsic evidence as to what a “digital count” is. A “digital count” is a type of “readout.” *Supra* at 46-47. Claim 23 does not cover any and all readouts, only readouts provided via a “digital count.”

Parse’s argument that “the specification does not support 10x’s proposed construction because it does not say that a readout provides a ‘numerical count’” also fails. *Supra* at 49-50. There is no requirement that a proposed construction be found explicitly in the specification and

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<sup>8</sup> Parse argues that “10x’s connection to the ’897 fails” because the ’897 does not use the term digital count. *Supra* at 49. That is not the law. *Infra*, § IV.A.4.c.ii; *Bancorp*, 359 F.3d at 1372.

Parse cites no case to support that proposition. *Id.* Such a requirement is also not determinative of indefiniteness. *Bancorp*, 359 F.3d 1367. In any event, 10x's construction of "digital count" to mean "numerical count" is supported by the definition of "readout" in the specification which says that "readout may refer to an actual **numerical representation**." D.I. 80, Ex. C at 10:66-67.

## ii. "Digital count" is not a "coined term"

Parse's argument that because the precise phrase "digital count" does not appear verbatim in the specification, it is thus a meaningless "coined term" also fails. *Supra* at 47-48. Parse cites no case where indefiniteness turned on whether a claim term appears in the specification. *Cf. supra* at 47-48 (citing *Acacia Media Techs. Corp. v. New Destiny Internet Grp.*, 405 F. Supp. 2d 1127, 1134 (N.D. Cal. Dec. 7, 2005) ("A patent claim is not indefinite if based on the specification, a meaning for an otherwise undefined term can be inferred from the specification.")). This is because the test for indefiniteness is not a word search. Instead, indefiniteness requires an analysis of whether the "claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901, 909 (2014); *see Bancorp*, 359 F.3d at 1372.

In *Bancorp*, the Federal Circuit reversed a finding of indefiniteness because, even though the disputed term appeared only in the claims, its meaning could be "fairly infer[red]" from the specification, and the Court stated that "an express definition is not necessary." 359 F.3d at 1370-73. The same is true here: the specification, common sense, and the knowledge one of ordinary skill provides ample guidance as to what "digital count" means. *Supra* at 45-47. Furthermore, "digital count" is a well-understood term used for example in consumer products: a "digital counter," which, as the name suggests, keeps count digitally. Exs. H-I at JA070-JA084. And

Parse’s conclusory assertions to the contrary—without evidence—do not compel a finding of indefiniteness.<sup>9</sup> See, e.g., *Ironburg Inventions Ltd. v. Valve Corp.*, 64 F.4th 1274, 1285 (Fed. Cir. 2023) (“Here, notwithstanding the lack of such precision in the patent, the record does not contain clear and convincing evidence that a person of ordinary skill in the art would fail to be reasonably certain whether a member is elongate or not.”); *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1338 (Fed. Cir. 2008) (“To the extent there are any factual findings upon which a trial court’s indefiniteness conclusion depends, they must be proven by the challenger by clear and convincing evidence.”).

Parse’s reliance on *Acacia* and *IQASR* is misplaced. See *supra* at 48-49 (citing *Acacia*, 405 F. Supp. 2d at 1134; *IQASR LLC v. Wendt Corp.*, 825 F. App’x 900, 904-07 (Fed. Cir. 2020)). The patentee in *Acacia* admitted the disputed term at issue, “sequence encoder,” was a coined term. 405 F. Supp. 2d at 1134. Even so, the *Acacia* court analyzed whether its meaning could be “fairly inferred from the terms in the specification which were commonly used in the field and which those of skill in the industry regarded as synonymous” and only after a thorough analysis of the specification did the court determine the term was indefinite. *Id.* at 1134-41. In *IQASR* “magnetic fuzz” had no ordinary meaning and the only definition provided was subjective: “the subset of disassociated magnetically active microparticles that are ‘*difficult to substantially*

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<sup>9</sup> Contrary to Parse’s assertions, whether the patents provide “[g]uidance on how to obtain a digital count” is irrelevant to indefiniteness, which analyzes whether the claim scope has reasonable certainty. *Nautilus*, 572 U.S. at 901. Parse appears to be making an enablement argument, which analyzes whether a person of skill can practice the claim’s full scope without undue experimentation. *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1224 (Fed. Cir. 2006). Parse is incorrect. The patent need not explain aspects understood by those skilled in the art. E.g., *Tech. Licensing*, 545 F.3d at 1338 (concluding claim not indefinite where the “circuit element is shown as a ‘black box’” stating “[a]s our cases demonstrate, however, the absence of internal circuitry in the written description does not automatically render the claim indefinite.”). At the time of the invention, persons of skill understood how to sequence nucleic acids, and how to count. Nothing more is needed.

*identify.*” 825 F. App’x at 906 (emphasis added). That is not the case here.

#### **d. Defendant’s Sur-Reply Position**

“Digital count” is a coined term as used in the ’013 Patent. It appears nowhere in the specification, and, as discussed at length above, the embodiments provide no guidance as to how a “digital count” is achieved. *Supra* at 47-49.

10x asserts that the meaning of “digital count” can be ascertained from “the specification’s description of using the MID to provide a ‘readout of how many individual polynucleotides are present in the sample.’” *Supra* at 51. According to 10x, this is because Claim 23 is “focused on counting the number of unique second tag sequences to count the number of sample polynucleotides, and providing that number to the user.” *Id.* 10x, however, can point to no intrinsic nor extrinsic evidence actually connecting “digital count” to “readout.” The only support it provides for its assertion that “a ‘digital count’ is a type of ‘readout’” is its own Opening Brief, which in turn points to descriptions of “readout” with no connection to “digital count.” *Id.* at 51. Circularly, 10x then argues that “Claim 23 does not cover any and all readouts, only readouts provided via a ‘digital count.’” *Id.* Thus, after spending paragraphs on argument attempting to equate “readout” to “digital count” in a misguided attempt to bring some definiteness to the term, 10x ultimately provides no clarity as to what a “digital count” actually is or how a skilled artisan is to arrive at one.

*ISQASR* is the case on point for the indefiniteness of this term. As in that case, “digital count” lacks “a readily understood definition in [its] field.” *IQASR*, 825 Fed. App’x 900 at 902. Nothing in 10x’s reply brief demonstrates a common understanding in the field or that “digital count” is a term of art, as 10x dedicates pages to trying to create a tenuous connection to a different term in the Patents. And as was the case in *IQASR*, the specification does not prove any

“meaningful and functional explanation of the definitional characteristics” of “digital count.” *See id.* at 904.

Rather than pointing to a common understanding in the field, 10x curiously appends printouts of consumer products to provide clarity on what a digital count is. Exs. H and I. These “digital counters” have nothing to do with tagging or counting biological molecules. They do not come from a scientific publication, nor is there any expert testimony connecting them to the way “digital count” is used in the Patents. Even the description of these products has no mention of how they would be applicable to the field of art of the Brenner Patents nor how a skilled artisan would make use of them to practice Claim 23. 10x has appended irrelevant extrinsic evidence in an effort to clarify a claim term that otherwise lacks any support in the intrinsic record.

## **B. Giresi / Buenrostro Patents**

### **1. “adapter sequence” (’207 Patent, Claim 13; ’995 Patent, Claim 18)**

| <b>10x’s Proposed Construction</b>                            | <b>Parse’s Proposed Construction</b>                 |
|---------------------------------------------------------------|------------------------------------------------------|
| Plain and ordinary meaning, which is “sequence of an adapter” | “sequence of an adapter, interchangeable with ‘tag’” |

#### **a. Plaintiffs’ Opening Position**

The parties do not dispute the meaning of “adapter sequence”; the parties agree it is simply the “sequence of an adapter.” D.I. 80, Attach. B at 1. The parties also appear to agree that an “adapter sequence” is a tag. *Id.* The parties’ dispute is whether “adapter sequence” is interchangeable with “tag” (Parse’s position) or whether the two different terms are not interchangeable (10x’s position). The claims, specification (and common sense) confirm 10x’s construction that they are related, but not interchangeable.

The language of the claims confirms that 10x’s construction is correct. Claim 23 of the ’207 Patent recites:

A method for generating a sequencing library from a plurality of cells, comprising:

a) lysing a plurality of cells to isolate a plurality of cell nuclei, wherein the plurality of cell nuclei comprise chromatin;

b) ***contacting a cell nucleus*** of the plurality of cell nuclei ***with a Tn5 transposase complex such that polynucleotides of the cell nucleus are tagged at regions of open chromatin to produce a plurality of tagged fragments***,

wherein the Tn5 transposase complex comprises a first sequencing adapter sequence and a second sequencing adapter sequence,

wherein the Tn5 transposase complex does not comprise an antibody specific to a protein that is part of chromatin,

***wherein a tagged fragment of the plurality of tagged fragment comprises***

i. a nucleotide sequence corresponding to a region of open chromatin,

ii. ***the first sequencing adapter sequence***, and

iii. ***the second sequencing adapter sequence***; and

c) performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

D.I. 80, Ex. E at Claim 23 (emphases added). Moreover, the parties agree that “tagged fragments” means “polynucleotide fragments that are attached to tags.” D.I. 80, Attach. C at 2. Thus, if “tagged fragment” in Claim 23 were replaced with its agreed-upon construction, both “tag” and “adapter sequence” would be used in Claim 23. Under basic principles of claim construction, different terms ***in the same claim*** are not treated as interchangeable given that the patentee chose to draft those terms as different ones. *See In re Varma*, 816 F.3d 1352, 1363–64 (Fed. Cir. 2016) (“[T]he principle that the same phrase in different claims of the same patent should have the same meaning is a strong one . . .”). And the purpose of claim construction is not to rewrite the claims. *Thorner*, 669 F.3d at 1369 (district court improperly imposed limitation when it is required by “[n]either the claims nor the specification”).

The specification similarly supports that an “adapter sequence” is a “tag,” but not all “tags”

are “adapter sequences,” and thus are not interchangeable. For example, the patent describes the disclosed method as treating chromatin “inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide.” D.I. 80, Ex. D at 2:47–50; *see id.* at 1:54–58, 2:58–62.

“Molecular tags” are the tags the insertional enzyme (a transposase) inserts during tagmentation.

*Id.* The patent then goes on to describe various “molecular tags” that can be used:

The molecular tags can comprise sequencing adapters, locked nucleic acids (LNAs), zip nucleic acids (ZNAs), RNAs, affinity reactive molecules (e.g., biotin, dig), self-complementary molecules . . . Any of the tags can further comprise fluorescence tags . . . .

*Id.* at 16:26–36. The specification contains similar language in the Summary. *See id.* at 3:46–50 (“[T]he molecular tags can comprise sequencing adaptors . . . [, i]n other cases, the molecular tags can comprise fluorescence tags.”).

The specification also discusses loading a “Hyperactive Tn5 transposase” with “adapters for high-throughput DNA sequencing,” which allow one to “simultaneously fragment and tag a genome with sequencing adapters.” *Id.* at 28:57–29:21. Thus, while the advantages of tagmenting chromatin to generate a sequencing library is to fragment the polynucleotide and add the adapter sequences simultaneously so that one can take advantage of the “simple two-step process involving Tn5 insertion and PCR,” for example, the tags need not be “adapter sequences.” *Id.* Thus, the specification confirms that “tag” and “adapter sequence” are not interchangeable terms.

Here, too, Parse cannot point to any exception justifying its proposed construction. While Parse cites to the claims of the ’995 and ’207 Patents, the claims recite only that the “[first/second] adapter sequence” comprises “[a first/second sequencing adapter sequence/a barcode sequence/a first/second primer sequence].” The claims do not support that “adapter sequence” is interchangeable with “tag.” The claims simply state that the “adapter sequence” includes other sequences that perform a specified function, such as a barcode or a primer, both of which are

defined. *See id.* at 9:46–10:10, 12:26–44. And while the definitions of barcode and primer make clear that they are tags that may be added to a polynucleotide of interest, the definitions do not support (let alone require) that all tags themselves are adapter sequences.

The only other evidence Parse cites in the Joint Claim Construction Chart similarly fails to support its construction. Lines 2:45–50 and 2:57–62 of the '995 Patent discuss inserting “molecular tags” with an “insertional enzyme” and “adapter sequence” is not even mentioned. Nor is there any support in the specification that “molecular tags” are equivalent to “adapter sequences.” Specifically, the portions of the specification cited by Parse that discuss “molecular tags” and “adapter sequences” make clear they are not interchangeable. *Id.* at 3:46–48, 16:26–36. And the definition of “insertional enzyme complex” makes clear that “adaptor molecules” are “transposon tags,” not that “transposon tags” are “adaptor molecules.” *Id.* at 13:19–26. If anything, this definition supports 10x’s construction because, as discussed above, 10x agrees that all “adapter sequences” are tags but not all “tags” are “adapter sequences.” *Cf. Baran v. Med. Device Techs., Inc.*, 616 F.3d 1309, 1316 (Fed. Cir. 2010) (holding that although the use of different terms usually implies that they have different meanings, “that implication is [only] overcome where . . . the evidence indicates that the patentee used the two terms interchangeably”).

#### **b. Defendant’s Answering Position**

The parties agree that an “adapter sequence” is the “sequence of an adapter.” Where the parties disagree is whether an “adapter” is a “tag.” As documented herein, the specification of the Buenrostro Patents uses the terms “tag” and “adapter” interchangeably and the Court should construe “adapter” accordingly.

The terms “adapter” and “tag” are used interchangeably throughout the specification. For instance, the shared specification among the three Buenrostro Patents defines an insertional

enzyme complex as a “complex comprising an insertional enzyme and two *adaptor molecules (the ‘transposon tags’)* that are combined with polynucleotides to fragment and add adaptors to the polynucleotides.” D.I. 80, Ex. D at 13:19-22.<sup>10</sup> The specification thus makes clear that an “adapter” is a “tag.” The specification repeatedly provides guidance to this effect:

- “After the chromatin has been fragmented and tagged to produce *tagged fragments of genomic DNA*, at least some of the *adaptor tagged fragments* are sequenced to produce a plurality of sequence reads.” D.I. 80, Ex. D at 14:59-62
- The method may “comprise isolating nuclei from a population of cells; and combining the isolated nuclei with *the transposase and adaptors*, wherein the combining results in both lysis of the nuclei to release said chromatin and production of the *adaptor-tagged fragments of genomic DNA*.” D.I. 80, Ex. D at 14:52-56.
- “The chromatin is tagmented (i.e., cleaved and *tagged* in the same reaction) using an insertional enzyme such as Tn5 or MuA that cleaves the genomic DNA in open regions in the chromatin and *adds adaptors to both ends of the fragments*.” D.I. 80, Ex. D at 14:27-31.

When “a patentee uses a claim term through the entire specification, in a manner consistent with only a single meaning, he has defined that term ‘by implication.’” *Bell Atlantic Network Serv. v. Covad Com*, 262 F.3d 1258, 1271 (Fed. Cir. 2001) (quoting *Vitrionics*, 90 F.3d at 1582). Here, the Patentee uses the term “tag” as interchangeable with “adapter.”

10x argues that “an ‘adapter sequence’ is a ‘tag,’ but not all ‘tags’ are ‘adapter sequences,’ and thus are not interchangeable.” *Supra* at 56. 10x relies upon the following passage to support this position:

The molecular tags can comprise sequencing adapters, locked nucleic acids (LNAs), zip nucleic acids (ZNAs), RNAs, affinity reactive molecules (e.g., biotin, dig), self-complementary molecules . . . . Any of the tags can further comprise fluorescence tags . . . .

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<sup>10</sup> Because the ’995 and ’207 Patents share a specification, any citations to relevant portions of the specification of the ’995 Patent should be understood to encompass the parallel citation in the ’207 Patent.

D.I. 80, Ex. D at 16:26–36. This, however, does not disprove the interchangeability of the terms “tag” and “adapter.” While this passage states that a “molecular tag” can have various components such as a “sequencing adapter,” it says nothing about whether the broader terms “tag” and “adapter” are interchangeable.

### c. Plaintiffs’ Reply Position

Contrary to Parse’s assertions, the “tag” and “adapter” terms are not interchangeable. *Supra* at 55-58. Parse relies on four portions of the specification in an attempt to limit the meaning of “adapter sequence,” *supra* at 58-60, but Parse fails to meet the “exacting” standard required to show that its construction is compelled by lexicography. *Hill-Rom*, 755 F.3d 1371.

None of the four portions of the specification use the “tag” and “adapter” interchangeably.<sup>11</sup> The first portion Parse points to is the definition of “insertional enzyme complex,” which does not refer to “tags”; it refers to “transposon tags.” *Supra* at 58-59. Additionally, that definition means only that the “adaptor molecules” included in the “insertional enzyme complex” are “transposon tags,” not that every “tag” is an “adapter sequence.” D.I. 80, Ex. D at 13:19-22. This is because any nucleic acids loaded into the transposase are, necessarily, the “transposon tags.” Thus, when those nucleic acids are “adaptor molecules,” the “adaptor molecules” are the “transposon tags.” But this does not mean that all “tags” are “adapters.”

Parse’s next two portions are directed to “adaptor tagged fragments.” Here again, those portions explain only that “adaptor tagged fragments” are “sequenced” and not that all tags are adaptors. This is because tagged fragments without “adaptor sequences” cannot be sequenced because “adaptor sequences” are necessary for next generation sequencers to sequence nucleic

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<sup>11</sup> A “tag” is a nucleic acid that is added to a polynucleotide. *Supra* at 11 n.3. An “adapter sequence” is a specific type of tag that, e.g., is used in sequencing the tagged polynucleotide. D.I. 80, Ex. D, at 14:55-62; 23:39-44.

acids. But fragments can be tagged with tags *other than* adaptor sequences, including any of the other tags listed in the specification. D.I., Ex. D at 16:26-36. That is also why the claimed method is focused on generating fragments tagged with adapter molecules: the goal is to create a sequencing library through tagmentation.

Parse's fourth and final citation fares no better. That portion reads: "The chromatin is tagmented (i.e., cleaved and tagged in the same reaction)." D.I. 80, Ex. D at 14:27-31. This defines "tagmented" as meaning "cleaved and tagged." The specification then explains that tagmentation with the "insertional enzyme" "adds adaptors to both ends of the fragments." *Id.* This does not equate "adaptors" and "tags." *Id.* As discussed above, the claimed method's goal is to create a sequencing library. That tags may generally be adapters does not mean they are interchangeable.

Parse's arguments fail for the same reasons set forth in *Apple*, 25 F.4th at 967-68 (Fed. Cir. 2022), where the Federal Circuit affirmed a construction rejecting the interchangeability of two claim terms where the written description showed only that the terms were related. Parse, like *Wilan*, simply identifies portions of the specification showing that "tag" and "adaptors" are related. The specification does not use the terms interchangeably; there is no statement equating the two terms; and Parse fails to identify any instance in which the terms are used to describe the same facet of an embodiment or the same element of a figure. *Id.* at 967-68. The portions of the specification cited by Parse are far cry from "a patentee us[ing] a claim through the entire specification, in a manner consistent with only a single meaning" so that 10x "defined the term 'by implication.'" *Supra* at 59 (citing *Bell Atlantic Network Serv. v. Covad Comm'ns Grp., Inc.*, 262 F.3d 1258, 1271 (Fed. Cir. 2001)).

Lastly, Parse ignores all but one portion of the specification 10x identified, which confirms Parse cannot overcome the "heavy presumption" of showing 10x redefined "tag" to mean

“adaptor” through implication. *Bell Atlantic*, 262 F.3d at 1268; *Hill-Rom*, 755 F.3d 1371. Parse’s only response to what 10x cited is to assert that the passage at D.I. 80, Ex. D at 16:26-36 “says nothing about whether the broader terms ‘tag’ and ‘adapter’ are interchangeable.” *Supra* at 59. This misses the point. The specification makes clear there are multiple types of tags, the tag can include various components, and the “sequencing adapter” need not be included in every tag. D.I. 80, Ex. D at 16:26-36. Thus, there are “molecular tags”—which Parse argues is a subset of the “broader term[]” “tag,”—that **are not** sequencing adapters. *Supra* at 59-60. This supports 10x’s construction, not Parse’s.

#### d. Defendant’s Sur-Reply Position

As detailed above, throughout the entirety of the specification the terms “tag” and “adapter sequence” are used interchangeably. *Supra* at 58-60. 10x provides no persuasive response to the numerous examples Parse identified of this interchangeable use.

Parse, for instance, noted that the specification teaches that the “term ‘insertional enzyme complex,’ as used herein, refers to a complex comprising an insertional enzyme and two **adapter molecules (the ‘transposon tags’)**”. D.I. 80, Ex. D at 13:19-23. As is clear from this passage, the specification treats tags and adapters as one and the same. But 10x reads this narrowly, contending that the passage stands for the proposition that only a particular type of tag (*i.e.* a “transposon tag”) would ever be considered an “adapter.” Yet, this ignores all the additional evidence establishing that the terms are used interchangeably. *Supra* at 58-60. It is unsurprising that the specification would refer to a specific type of “tag” (*i.e.*, a “transposon tag”) as an “adapter” because, as the specification makes clear, “tags” and “adapters” are **generally** interchangeable.

Parse also noted that the specification of the ’995 Patent describes chromatin being tagmented, or “cleaved and **tagged** in the same reaction,” using an enzyme that cleaves in open

regions of chromatin and “adds *adaptors* to both ends of the fragments.” D.I. 80, Ex. D at 14:27-31. 10x’s only response to this is “that tags may generally be adapters does not mean they are interchangeable.” *Supra* at 61. That conclusion, however, ignores the very text of the passage it claims to address. The specification makes it clear that a tagmentation reaction, in adding tags, adds adaptors. This is one of many examples across the specification where the terms are treated as one and the same, which evidences an intent to use the terms “adapter sequence” and “tag” interchangeably.

Finally, 10x states that “[t]he specification makes [it] clear there are multiple types of tags, the tag can include various components, and the ‘*sequencing adapter*’ need not be included in every tag.” *Supra* at 62. But Parse has never argued that *only* a “sequencing adapter” is interchangeable with “tag.” Rather, consistent with the specification, Parse proposes that the Court construed “adapter” so as to capture what the specification already makes clear—that “tag” and “adapter sequence,” whatever the function may be, are used interchangeably.

## V. CONCLUSION

### A. Plaintiffs’ Opening Position

10x respectfully requests that the Court adopt 10x’s proposed constructions.

### B. Defendant’s Answering Position

Parse respectfully requests that the Court adopt Parse’s proposed constructions.

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