

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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PARSE BIOSCIENCES, INC.,  
Petitioner

v.

10X GENOMICS, INC.,  
Patent Owner

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Case IPR2023-00876  
Patent 10,155,981

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**PATENT OWNER'S RESPONSE**

## LIST OF EXHIBITS

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                          |
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| EX2001  | U.S. Patent Pub. No. 2007/0020640 A1                                                                                                                                                                                                                                                                                                                                                 |
| EX2002  | File History of U.S. App. No. 13/859,450                                                                                                                                                                                                                                                                                                                                             |
| EX2003  | Dictionary of Microbiology and Molecular Biology (2d ed. 1987)                                                                                                                                                                                                                                                                                                                       |
| EX2004  | File History of U.S. App. No. 14/792,094                                                                                                                                                                                                                                                                                                                                             |
| EX2005  | File History of U.S. App. No. 13/387,343                                                                                                                                                                                                                                                                                                                                             |
| EX2006  | U.S. Patent Pub. No. 2007/0238113                                                                                                                                                                                                                                                                                                                                                    |
| EX2007  | Laird <i>et al.</i> , <i>Hairpin-bisulfite PCR: assessing epigenetic methylation patterns on complementary strands of individual DNA molecules</i> , 101 PNAS 204-09 (Dec. 12, 2003)                                                                                                                                                                                                 |
| EX2008  | Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00958, Pap.1 (May 25, 2023)                                                                                                                                                                                                                                                                                                   |
| EX2009  | File History of U.S. App. No. 14/172,694                                                                                                                                                                                                                                                                                                                                             |
| EX2010  | Declaration of Sayem Osman                                                                                                                                                                                                                                                                                                                                                           |
| EX2011  | Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00958, EX1002 (May 25, 2023) (Declaration of Gregory Cooper, Ph.D.)                                                                                                                                                                                                                                                           |
| EX2012  | Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00958, EX1054 (May 25, 2023) (Georgi K. Marinov <i>et al.</i> , <i>From single-cell to cell-pool transcriptomes: Stochastically in gene expression and RNA splicing</i> , 24.3 Genome Research 496-510 (2014) (“Marinov”))                                                                                                    |
| EX2013  | Declaration of Dr. John Quackenbush                                                                                                                                                                                                                                                                                                                                                  |
| EX2014  | Bruce Alberts, <i>et al.</i> , <i>Molecular Biology of the Cell</i> , Garland Science (4th ed. 2002)                                                                                                                                                                                                                                                                                 |
| EX2015  | Declaration of Sayem Osman                                                                                                                                                                                                                                                                                                                                                           |
| EX2016  | Piovesan <i>et al.</i> , <i>On the length, weight, and GT content of the human genome</i> , BMC Res. Notes 12:106 (2019) ( <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6391780/#:~:text=Considering%20a%20mean%20weight%20in,units%2Fcarat.htm">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6391780/#:~:text=Considering%20a%20mean%20weight%20in,units%2Fcarat.htm</a> ) |
| EX2017  | T. Chauhan, <i>T4 DNA Ligase: Introduction, Functions, Applications, and Protocol</i> , (available at <a href="https://geneticeeducation.co.in/t4-dna-ligase/">https://geneticeeducation.co.in/t4-dna-ligase/</a> )                                                                                                                                                                  |
| EX2018  | Deposition Transcript of Gregory Cooper, Ph.D.                                                                                                                                                                                                                                                                                                                                       |
| EX2019  | Li <i>et al.</i> , <i>Amplification and analysis of DNA sequences in single human sperm and diploid cells</i> , Nature 335(6189):414-417 (1998)                                                                                                                                                                                                                                      |

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## I. Introduction

U.S. Pat. No. 10,155,981's (the "'981 Patent"/"'981") Claims 1-6 (the "Challenged Claims") are directed to innovative methods of analyzing polynucleotides from a plurality of single cells that *differentiate among the different polynucleotides* in an overall sample and *track from which particular cell* each polynucleotide originated. EX1001, 6:33-7:22, 15:7-50, Cl.1 (30:18-48). Nobel Laureate Sydney Brenner and team—'981's inventors—unlocked the ability to do high-resolution single cell analysis. Petitioner's perfunctory analysis fails to establish any Challenged Claim is obvious. As laid out below, Petitioner's Linnarsson-McCloskey combination fails to disclose the limitations of claim 1 and is forced together through hindsight—skilled artisans would not have been motivated to stitch these references together.

Petitioner's **Ground 1** has multiple failings. First, Petitioner glosses over the details of Linnarsson's disclosures and fails to show that Linnarsson's sequencing of only the "5' fragments" is sequencing "the plurality of tagged polynucleotides," as required by claim 1. Petitioner further fails to address whether this limitation is met when Linnarsson never discloses sequencing the "3' fragments" of the double-stranded cDNA that "remain stuck on the beads" *or* the internal fragments that are "washed away" in the process of generating its cDNA library.

Second, Petitioner inconsistently maps the “first tag sequence”—mapping it at times to Linnarsson’s cell tag, and at others to McCloskey’s batch-stamp within its Ground 1 argument. Petitioner begins by mapping the “first tag sequence” to Linnarsson’s existing cell tag. But in arguing obviousness of the “second tag sequence,” Petitioner modifies (“conceptually divides”) Linnarsson’s cell-tag to create two portions, one of which incorporates the “function” of McCloskey’s batch-stamp as the claimed “first tag sequence.” Moreover, McCloskey’s batch-stamp does not function as a “first tag sequence.” Indeed, McCloskey uses *one batch-stamp per sample*, regardless of the number of cells contained therein, to identify contaminants from prior *samples* (not the source *cell*), and thus does not function to tag polynucleotides in different cells of the same sample differently.

Third, Petitioner’s purported motivation to combine and reasonable expectation of success (“REOS”) fails. Petitioner’s arguments rest, *inter alia*, on the premise that McCloskey stamps “*each* sample polynucleotide.” Pet.54-55. But Petitioner fails to prove this premise is true (McCloskey shows it is not). McCloskey’s barcode, which is used unmodified in Petitioner’s combination, is only seven nucleotides long and can thus distinguish between, *at most*, 16,384 sample polynucleotides. That is facially insufficient to tag the mRNA molecules present in the cells Linnarsson’s gene expression method is analyzing, which

include *at least 50,000 mRNA* molecules (and up to 300,000). Petitioner thus fails to establish REOS for the same reason.

Petitioner's **Ground 2**, targeting claim 5 by building on Petitioner's Ground 1 combination and adding "tag sequence(s)" to the cDNA synthesis primer ("CDS") and template switching oligonucleotide ("TSO") via ligation, has additional failings. First, there is no motivation to modify in the manner argued in Ground 2. For example, adding "tag sequences" via ligation would have required *additional* steps to gain some never-specified "flexibility" but, per Petitioner, merely yield an approach "*entirely equivalent*" to Ground 1's. This is nonsensical, and confirms Petitioner's hindsight-driven approach.

Second, Petitioner's Ground 2 is conclusory and again fails to confront the details of Linnarsson's method. These details confirm that ligating "tag sequences" to the CDS or TSO does not render claim 5 obvious for multiple reasons. For the CDS, (1) a biotin molecule blocks the CSD's 5' end, which prevents any nucleic acid from being ligated to it, and (2) any sequence that is somehow ligated to the CDS would be on the "3' fragment", which "remain[s] stuck on the bead" and is not sequenced. For the TSO, (1) any sequence that is ligated to Linnarsson's TSO "after extension" would not be reverse-transcribed into cDNA, and (2) even if reverse-transcribed, any sequence would be on the 5'

end of the TSO's Bts sequence and thus would be *cleaved off* of the nucleic acid prior to the sequencing step.

Third, Petitioner fails to explain how the ligation and subsequent steps are implemented and when—and Petitioner's improper reliance on Hug only creates additional incompatibilities with Petitioner's ligation theory.

Finally, Petitioner entirely fails to assert or analyze whether its references are analogous art to '981 (instead discussing only whether they are analogous to one another). This failure requires rejection of both Grounds 1 and 2, as the Federal Circuit recently confirmed.

## **II. The Challenged Claims Are Directed To A Novel, Non-Obvious Invention**

'981's Challenged Claims are directed to innovative methods of analyzing polynucleotides from a plurality of single cells that allow the user *not only to differentiate among the different polynucleotides in an overall sample, but also to track from which particular cell each polynucleotide originated.* EX1001, 6:33-7:22, 15:7-50, Cl.1 (30:18-48).

Cells contain many types of polynucleotides, including DNA and RNA (such as messenger RNA ("mRNA")). EX1001, 14:8-14; EX2013, ¶28. These polynucleotides can be analyzed using the claimed invention. The patent describes using a multiplex identifier ("MID") with *two tag sequences*: "a *first* tag sequence associated with the single cell from which the sample polynucleotide is derived"

and “a *second* tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same cell.” EX1001, Cl.1 (30:18-48). In other words, the claimed method simultaneously employs (1) *cell-specific tags* and (2) *polynucleotide-specific tags*. *Id.*

Until '981's inventions,<sup>1</sup> “bulk analysis” was primarily used to analyze polynucleotides in a sample of multiple cells. EX1003, 2; EX1006, 2. This gave users insight into the polynucleotides found in the overall population of cells in the sample, but failed to capture critical differences among *individual* cells. Pet.7; EX2013, ¶29. For example, overexpression of the HER2 gene was associated with an aggressive form of cancer, but in the early stages of cancer only a few cancerous cells might be captured amongst numerous cells in a tissue sample to be analyzed. EX2013, ¶29. Averaged across the entire sample population, it would not be possible to determine whether a small subset of the cells were overexpressing HER2 because the overexpression of HER2 in cancerous cells

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<sup>1</sup> The Challenged Claims are directed to the innovative MID and its use, but '981, like many patents, discloses multiple inventions. EX1001, 1:50-61. Another invention disclosed in '981 is the “reflex method,” which, using the MID, fragments polynucleotides to ensure they are short enough to be sequenced while enabling the user to track the origin of each fragment. *Id.*, 1:25-61.

would be masked by “normal” cells in the “bulk” analysis, which captures the amount of HER2 expression *across the entire population of cells* in a sample.

EX2013, ¶29. Using “bulk” analysis, these cancerous cells would likely have been missed, especially in the early stages of cancer growth. *See* Pet.7; EX2013, ¶29.

The specification explains that tagging the polynucleotides from a sample of cells with a first and second tag sequence (identifying the *cell* and *polynucleotide*, respectively), provides a “correlation between a polynucleotide and its source.”

EX1001, 6:44-45. This allows researchers to determine, for example, how many individual polynucleotides are in each single cell within a sample. EX1001, 6:38-51; EX2013, ¶30. The ’981’s innovative methods allowed users to do what had not previously been possible: to determine the quantity of *each polynucleotide present* in a cell *on a cell-by-cell basis*, which Linnarsson and McCloskey cannot.

EX1001, 6:33-7:22, Cl.1 (30:18-48); EX1002, ¶¶73-75. Using ’981’s invention, the medical professional of the example above could, for the first time, identify individual cells with over-expressed HER2 genes and diagnose the patient with cancer at an earlier stage. EX2013, ¶30.

### III. Petitioner's References

#### A. Linnarsson (EX1003)

Linnarsson was the basis of multiple rejections by the Office in the application that matured into '981, as well as '981's parent. EX1001, 2; EX1005, 154-156; EX2004, 1085-1087.

Petitioner relies on Linnarsson's disclosures relating to "*single-cell tagged reverse transcription (STRT)...*" Pet.24-29, 41-42, 46-47 (each citing Fig.11); EX1002, ¶¶110, 113, 117, 139, 143, 153-154, 164, 166 (same); *see also* EX1003, 5:10-11, 23:1-4, 37:31-32, Fig.11. This STRT method involves preparing a cDNA library for sequencing by reverse-transcribing mRNA initially produced by transcription of genes expressed in the cells in the sample. EX1003, 1 (Abstract), 3:25-4:2, 12:4-8; *see also* Pet.24; EX2013, ¶33-44. As part of this process, "single cells are placed in separate wells of a 96-well plate and lysed...." EX1003, 4:8-13; Pet.38. Each cell "contain[s] a plurality of mRNA molecules." EX1003, 3:26-30; Pet.39-40; EX2013, ¶33; EX2012, Abstract; EX2011, ¶256. Linnarsson then adds CDSs and TSOs, which are then incorporated into cDNA during reverse transcription from mRNA. EX1003, 18:32-33; *see also* Pet.25; EX2013, ¶33.

The CDSs are designed to anneal<sup>2</sup> to mRNA molecules. According to Petitioner, “Linnarsson discloses a cDNA synthesis primer... that includes a sequence of thymines....” Pet.25-26. The primer’s “sequence of thymines... hybridize[s] with a sequence of adenines [that] mak[e] up a poly-A tail... of [the] mRNA molecule.” Pet.41, 25-26; EX1002, ¶140; EX1003, 24:13-20, Fig.2, Fig.11. Thus, these CDSs are able to anneal to every mRNA molecule in a well. EX1003, 18:27-30; Pet.25; EX2013, ¶34.

The TSOs are designed to anneal to newly-synthesized single-stranded reverse-transcribed cDNA. EX1003, 16:18-17:2; 18:19-26; Pet.26-27; EX2013, ¶35. In the process of reverse-transcribing mRNA into cDNA, reverse transcriptase typically causes two to five cytosines to be added to one end of the single-stranded cDNA. EX1003, 16:18-31; Pet.26-27. Linnarsson’s TSOs include a poly-guanosine sequence that “‘anneals transiently’ to the series of cytosine nucleotides at the end of [a] newly-synthesized strand.” Pet.26-27; EX1003, 18:19-23. The TSO annealing to cDNA causes “the reverse transcriptase to switch

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<sup>2</sup> “Annealing” is the joining of two complementary strands of nucleic acids through hydrogen bonding. EX1002, ¶¶61, 87; EX1003, 13:3-10; EX1009, 1 (“Denaturation separates the complementary strands of DNA held together in the duplex by hydrogen bonds.”).

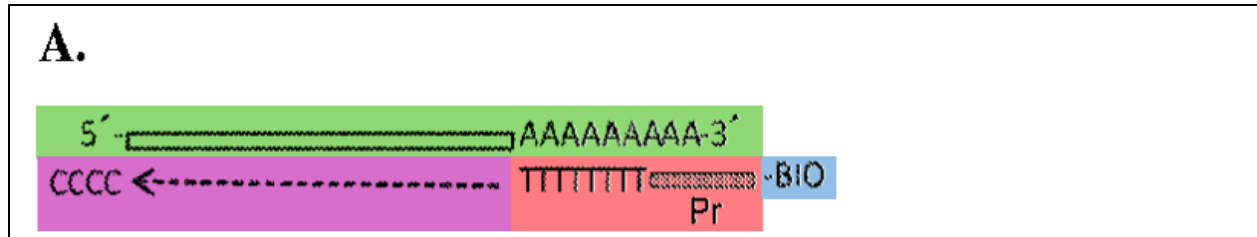
template and continue to synthesi[ze] a strand complementary to the TSO.”

EX1003, 18:23-24.

After reverse transcription is completed, the cDNA (now including a CDS and TSO) from each well is pooled, a cDNA library is created, and the “5’ fragment” is sequenced. EX1003, 18:27-19:11; Pet.28; EX2013, ¶35.

Aspects of Linnarsson’s STRT process are illustrated in Panels A-F of Fig.11, summarized here. EX1003, 37:31-32, 5:28-6:12; Pet.24-25; EX2013, ¶33.

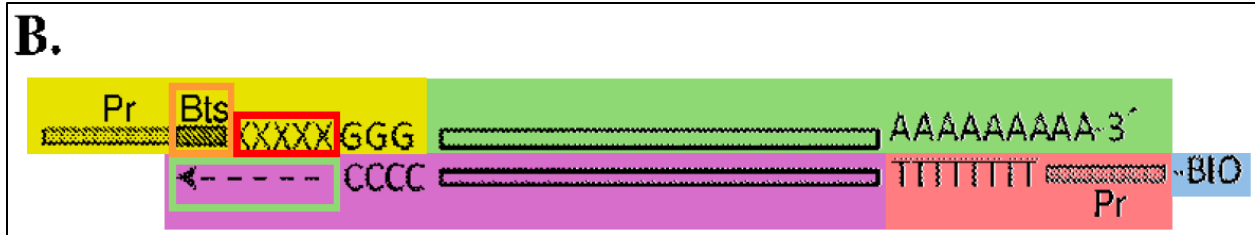
**Panel A:** The CDS (red) includes a poly-T tail, which hybridizes to the mRNA molecule’s (green) poly-A tail. EX1003, 5:28-31; EX2018, 23:21-25:21. The CDS’s primer sequence (Pr) is located on the CDS’s 5’ end, outside the poly-T tail, which is then capped by a biotin molecule (blue). EX1003, Fig.11 (Panel A), 23:13-19; Pet.27-29; EX2018, 23:21-25:21; EX2013, ¶37. A cell-tag (according to Petitioner) is optionally incorporated between the primer and the poly-T tail. Pet.26 (citing EX1003, Fig.4); EX1003, 4:17-18, 18:31-19:11. Once the CDS anneals to the mRNA molecule, a reverse transcriptase enzyme recognizes the CDS’s primer sequence, and extends the strand by reverse transcribing the mRNA to create a first strand of cDNA (purple). *See* EX1003, 5:28-31, Fig.11 (Panel A). The resulting cDNA includes a poly-C tail (“CCCC”) due to terminal transferase activity. EX1003, 5:30-32, Fig.11 (Panel A); EX2018, 25:22-26:6; EX2013, ¶37.



**Panel B:** To continue cDNA synthesis, Linnarsson uses a TSO (yellow).<sup>3</sup> EX1003, 5:31-6:1. The TSO's poly-G tail hybridizes to the poly-C tail of the cDNA created in Panel A. EX1003, 5:31-33, Fig.11 (Panel B); EX2018, 25:22-26:12. The TSO includes a cell tag (red box), a Bts sequence (orange box), and a primer sequence (Pr) on the 5' side of the poly-G tail. EX1003, 5:31-6:1, 23:13-19, Fig.11 (Panel B); EX2018, 27:14-28:15. cDNA synthesis proceeds using the yellow highlighted TSO as a template, which adds the cell-tag and Bts to the 3' end of the cDNA (purple portion boxed in green). EX1003, 5:31-33, Fig.11 (Panel B); EX2013, ¶38.<sup>4</sup>

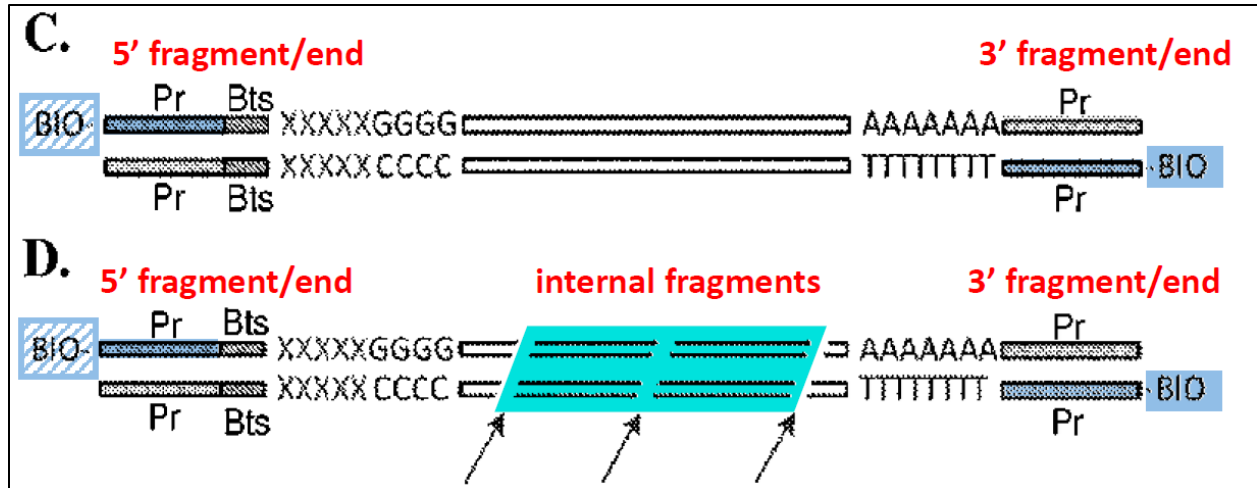
<sup>3</sup> Dr. Cooper's declaration describes Panel B's top strand as the second strand of cDNA and not as mRNA. EX1002, ¶117. But in his deposition, Dr. Cooper said the figure is "unclear" and admitted the top strand could either be mRNA, consistent with 10x's description above, or cDNA. EX2018, 26:13-27:12.

<sup>4</sup> The mRNA molecule is optionally digested by RNase. EX1003, 16:10-17. Alternatively, the top strand may be separated from the generated cDNA during the PCR process, which is known as denaturation. EX1002, ¶¶86-87.

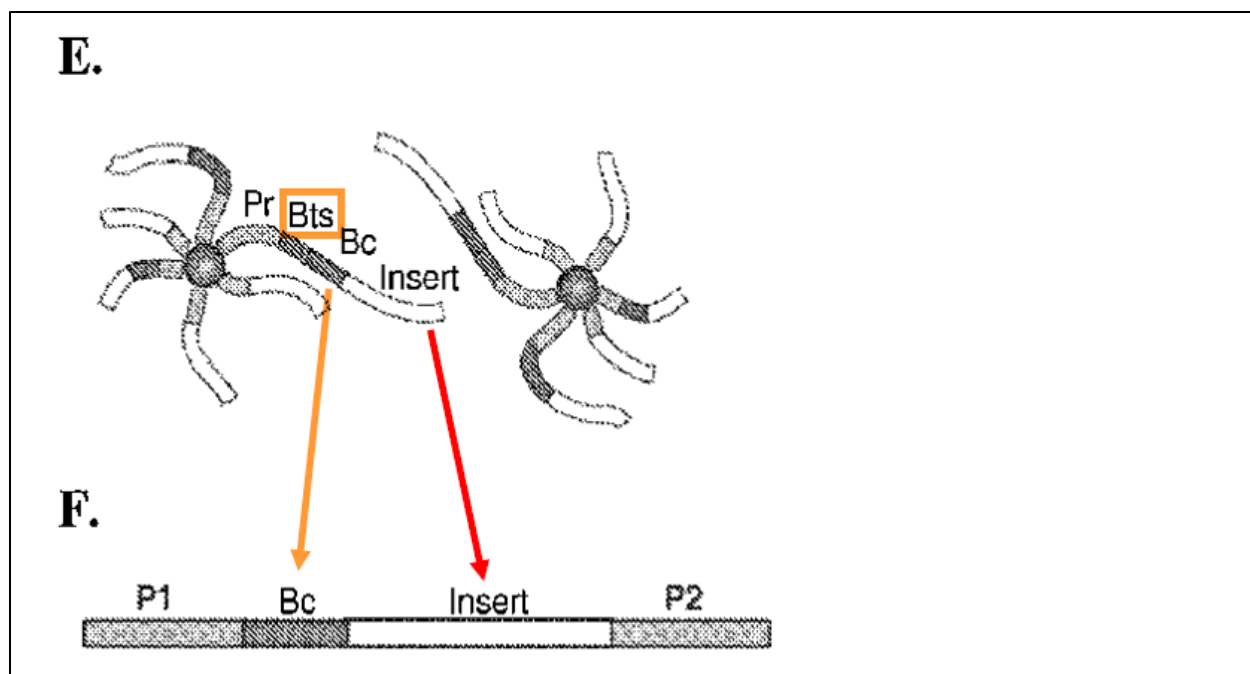


**Panels C and D:** The cDNA sequences generated in Panels A and B are then amplified via PCR, at which point a biotin (shaded blue) is added to all double-stranded cDNA on their “5’ ends,” resulting in the eventual “5’ fragments” having a biotin on their ends.<sup>5</sup> EX1003, 25:17-20, Fig.11 (Panel C); EX2018, 28:19-29:7. Following PCR, the sequences are subjected to a “fragmentation step” using a DNase enzyme. EX1003, 6:3-4, Fig.11 (Panel D), 12:4-8; EX2018, 29:8-13. The “internal fragments” (teal) from Panel D are “washed away” (and are therefore never sequenced). EX1003, 6:3-4; EX2013, ¶39.

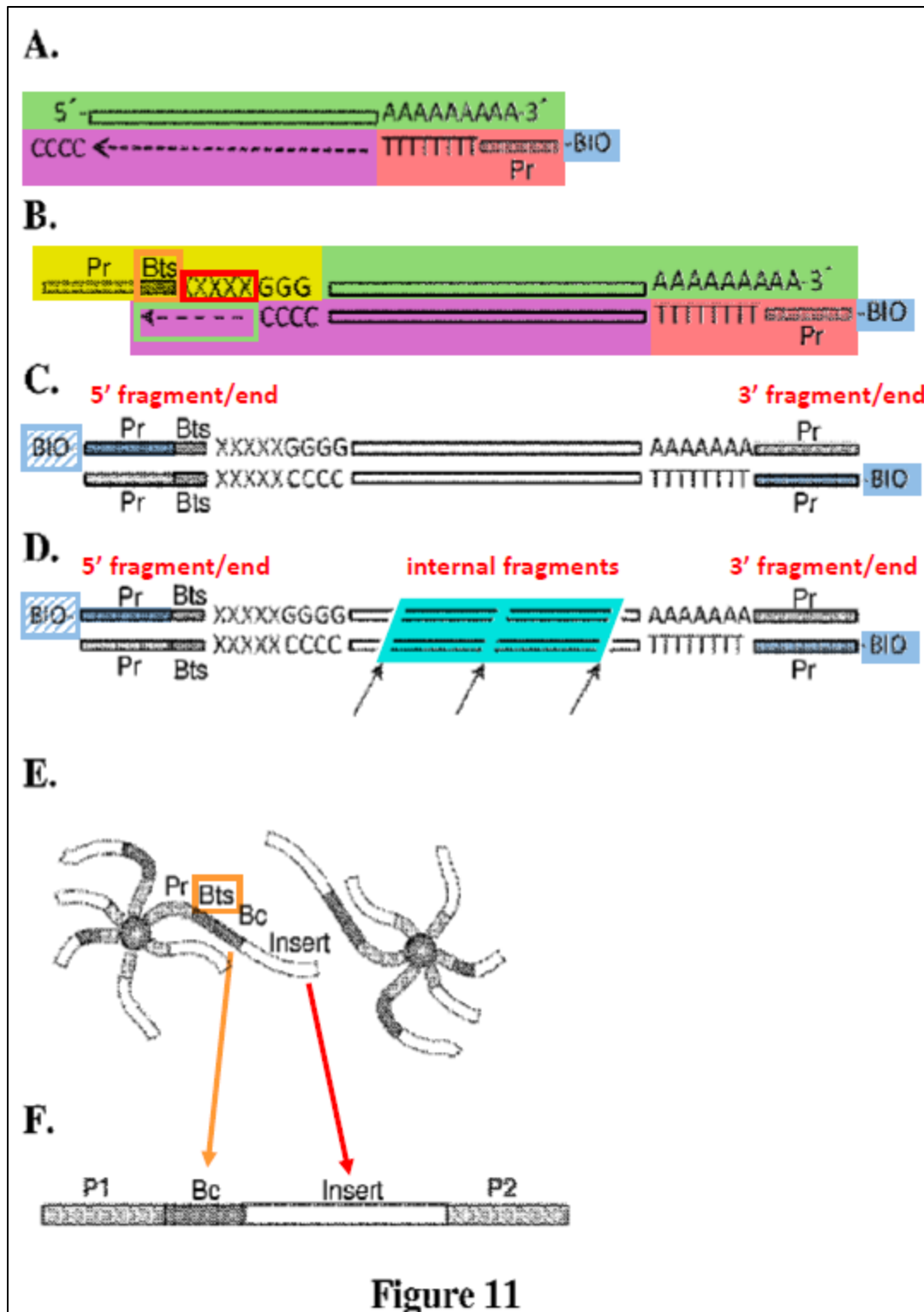
<sup>5</sup> Each single stranded nucleic acid (whether *single*-stranded RNA, or an *individual* strand of double-stranded DNA), has a 5’ and 3’ end. EX1002, ¶62. However, Linnarsson refers to the *double*-stranded ends of the double-stranded DNA generated through its process as 5’ and 3’ “fragments” or “ends.” EX1003, 6:5-8, 26:22. The “5’ fragment” is the end of the double-stranded DNA corresponding to the region with the TSO sequences, and the “3’ fragment” is the end corresponding to the region with the CDS sequences. EX1003, 6:5-8.



**Panels E and F:** The remaining biotinylated and fragmented DNA segments—the “5’ fragments” with “barcode (Br) and BtsCI site (Bts)” and the “3’ fragments” (which do not have a Bts site) from Panel D—are then bound to beads. EX1003, 6:5-6, 26:21-26, Fig.11 (Panels D-E); EX2018, 31:12-22; *see also* EX1003, 21:13-25, 27:6-28:2, 35:23-36:9; EX1002, ¶198; EX2018, 43:21-44:22; EX2013, ¶¶41-42. Another enzyme, BtsCI, is added, and cleaves the bound fragments *at the Bts sequence* (orange box). EX1003, 6:6-8, Fig.11 (Panel E). Only the portion of the “5’ fragments” to the 3’ end of the Bts sequence (the end further from the bead) are released from the beads; the “3’ fragments remain stuck on the beads” due to their lack of a Bts sequence. *See id.*; EX2013, ¶41; EX2018, 43:21-44:22. Two adapter sequences, P1 and P2, are then ligated to the ends of the released portions of the “5’ fragments” so that those fragments may be sequenced by a next-generation sequencer (Panel F). EX1003, 6:9-12; EX2018, 32:7-14.



These described steps are depicted together below.



Linnarsson's method results in mRNA molecules from the *same cell* being tagged with the *same barcode* through the process of reverse-transcribing it into

cDNA. EX1003, 3:25-4:2, Fig.11; EX2013, ¶44. However, Linnarsson does not tag endogenous mRNA molecules within a cell uniquely, and thus does not determine how many instances of each particular mRNA molecule existed in a particular cell before amplification. *See* EX1003, 22:22-28; EX2013, ¶44.

**B. McCloskey (EX1004)**

**1. McCloskey's Disclosures**

McCloskey, titled “Encoding PCR Products with Batch-stamps and Barcodes,” describes adding, during the DNA amplification process, an “encoding oligonucleotide” to copies of alleles for a particular targeted gene. EX1004, 2-4; Pet.30; EX2013, ¶¶45-49. McCloskey’s encoding oligonucleotide includes, *inter alia*, (1) a batch-stamp; and (2) a random barcode with (3) a genomic target-binding site that targets the specific gene on the chromosomal DNA to be barcoded prior to amplification. EX1004, 2; Pet.30-31. The batch-stamp anneals to a specific gene and identifies the *batch sample* from which the polynucleotides originated *to identify contamination (i.e., to identify sequences originating from a different patient or sample left over from a prior analysis)* and the barcode distinguishes between *copies of an allele for a particular gene in the sample (without identifying the particular cell of origin)*. EX1004, 2-4; Pet.30; EX2013,

¶46.<sup>6</sup> McCloskey's random barcode is composed of nucleotides, where each nucleotide is one of the four deoxyribonucleotides.<sup>7</sup> EX1004, 4; *see also* ID.21-22; EX1002, ¶192. McCloskey uses a seven-nucleotide long barcode in its disclosed example, which allows creating up to 16,384 unique barcodes—enough to uniquely tag different alleles for the same gene in McCloskey's collection of cells because there are, at most, two alleles per cell. EX1004, 4 (“We currently use seven nucleotides for the barcode, giving 16,384 possible barcodes...”); EX2013, ¶46; EX1002, ¶65.

McCloskey's method involves lysing the cells and combining their contents (including the DNA) before tagging the copies of a particular gene within this combined material to determine the presence of alleles. *See* EX1004, 2, 5; EX2013, ¶47. Copies of a particular gene (including any alleles or mutations) are tagged by annealing the genomic target-binding site of the oligonucleotide to the complementary DNA sequence found on one end of the target gene. EX1004, 5.

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<sup>6</sup> Alleles are different versions of the same gene. EX2003, 3; EX1002, ¶65.

<sup>7</sup> “Deoxyribonucleotides” are nucleotides that have a deoxyribose as their sugar component. Pet.6; EX1002, ¶¶60-61; EX2014, 31; EX1001, 7:23-48. The four natural deoxyribonucleotides are adenine (A), guanine (G), cytosine (C), and thymine (T). Pet.6; EX1002, ¶¶60-61; EX2014, 31.

According to McCloskey, the incorporation of its oligonucleotides into the amplified DNA for the particular gene of interest allows researchers to identify and remove contaminant sequences (from different batch samples) and redundant sequences (amplified copies containing the same random barcode) after the gene of interest is amplified. EX1004, 3 (Fig. 1), 7. However, McCloskey's method does *not* allow a user to determine, *e.g.*, whether or which copy of a particular allele (or mutation) is present in a given cell because *no copies of the target allele are tagged with a sequence that tracks an allele to its cell of origin*. EX1004, 3. Indeed, McCloskey pools the nucleic acids from all of the cells in the sample *prior to tagging*, such that the cell of origin for the nucleic acid cannot be tracked. EX1004, 2, 5 ("Human genomic DNA (2.71 µg)... Digested genomic DNA (0.27 µg)"); EX2013, ¶47 (explaining that 2.71 µg corresponds to the genetic material of 420,000 cells); EX2018, 34:19-35:3. Thus, unlike the Challenged Claims, McCloskey's approach to removing redundant copies simply permits a user to determine whether the target gene was present, including whether there were any alleles or mutations present, *in the sample when it was tagged (but not any particular cell in the multi-cell sample)*. EX2013, ¶¶48, 63-66. And unlike Linnarsson, McCloskey's disclosures are not focused on mRNA. EX1003, 1; EX1004, 4; EX2013, ¶49.

## **2. Petitioner Failed To Establish McCloskey Is Prior Art**

Petitioner failed to establish McCloskey is, in fact, prior art to '981.

*Standard Innovation Corp. v. Lelo, Inc.*, IPR2014-00148, Pap.41, 18-28 (Apr. 23, 2015) (concluding claims not unpatentable where reference was not qualified as a printed publication because it was not authenticated and the dates within the exhibit were inadmissible hearsay); *Dropbox, Inc. v. Synchronoss Techs., Inc.*, IPR2016-00850, Pap.41, 18-23 (Oct. 5, 2016) (similar, and rejecting petitioner's attempt to cure the evidentiary failing after the POR). For this reason alone, and because Petitioner relies on McCloskey in both of its Grounds, Petitioner has failed to show the claims are unpatentable. *Id.*

## **IV. Level Of Ordinary Skill In The Art Of '981**

POSITA would have had a Ph.D. in molecular biology, molecular genetics, biochemistry, physics, mechanical engineering, or a related discipline, with two years of academic, research, or industry experience in the field of genomic or transcriptome sequencing. EX2013, ¶¶25-26. However, the analysis below would not change if Petitioner's POSITA definition were applied. Pet.21-22.

## **V. Claim Construction**

Terms need only be construed "to the extent necessary to resolve the controversy." *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed.

Cir. 1999). Though PO does not believe any term needs construction, PO here applies the Petition's definitions for "MID" and "sample." Pet.36.

**VI. Ground 1: Petitioner's Obviousness Analysis Fails To Establish A Motivation To Combine With REOS**

Linnarsson in view of McCloskey does not render obvious claim 1 (or any dependent claim in Ground 1). Petitioner's theory, according to the Board at institution,<sup>8</sup> is that POSITA would have "conceptually divided" Linnarsson's cell tag, located within the CDS or TSO, and used six to eight of the nucleotides from Linnarsson's cell-tag as a tag that performs the function of McCloskey's batch-

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<sup>8</sup> The Petition's precise Ground 1 combination is unclear. Pet.50-56; EX2013, ¶53. PO therefore relies on the Board's articulation of this combination at institution, though Petitioner only referenced this combination in arguing REOS. ID.21-22. To the extent Petitioner attempts in Reply to argue some different articulation of its combination, any such articulation is insufficiently clear in the Petition and should be rejected. *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017) (rejecting reply brief attempting to cure petition deficiencies noting "obligation for petitioners to make their case in their petition") (citation omitted); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016) (similar); *Apple Inc. v. Smart Mobile Techs., LLC.*, IPR2022-00981, Pap.34, 35-36 (Nov. 7, 2023) (similar).

stamp, and seven of those nucleotides as a second tag that performs the function of McCloskey's barcode. ID.21-22 (citing EX1002, ¶192). Petitioner's theory fails.

**First**, Petitioner fails to explain how Linnarsson meets the requirement of sequencing "the tagged polynucleotide." *See infra* §VI.A. Linnarsson discloses that portions of the tagged polynucleotides are fragmented and the "internal fragments" are washed away. Relatedly, the "3' fragments" remain bound to the beads and *are not sequenced*. *See* EX1003 6:8 ("3' fragments remain stuck on the beads"). Thus, the *only* portion of Linnarsson's "tagged polynucleotide" that is sequenced is the "5' fragment." Petitioner fails to address whether sequencing just a *portion* of the "tagged polynucleotide" meets claim 1's requirement of "sequencing the... tagged polynucleotides."

**Second**, Petitioner fails to show its combination—as adopted by the Board and explained by Petitioner's expert—results in the claimed "first tag sequence." *See infra* §VI.B. Petitioner inconsistently maps the "first tag sequence"—mapping it at times to Linnarsson's existing cell tag, and at other times to McCloskey's batch-stamp functionality. Further, McCloskey's batch-stamp does not identify the *cell* from which a nucleic acid originated in a sample comprising a plurality of cells. Rather, McCloskey's batch-stamp identifies the *sample* from which a nucleic acid originated to eliminate contaminants from other samples. Indeed,

McCloskey nowhere discloses applying multiple batch-stamps to different cells within a single sample to track the cell from which a nucleic acid originated.

**Third**, Petitioner’s various arguments that POSITA would have been motivated to combine Linnarsson and McCloskey fail. *See infra* §VI.C. For example, POSITA would not have been motivated to modify Linnarsson’s method using McCloskey’s barcode to tag “each polynucleotide” because McCloskey’s barcode teachings used in Petitioner’s combination do not provide enough unique sequences to uniquely tag each mRNA molecule within a given cell, as required by Petitioner’s argued-for motivation. *See infra* §VI.C.1. Additionally, POSITA would not have been motivated to change Linnarsson’s existing cell-tag—specifically designed to avoid misattributing data from a first cell to a second cell if there is a transcription error—into one functioning as McCloskey’s batch-stamp, which has no such feature. *See infra* §VI.C.2. Finally, McCloskey and Linnarsson are not both about “single cell analysis,” as Petitioner asserts. McCloskey’s isolated reference to analyzing the content of a “single cell” sample is not “single-cell analysis”—which, instead, involves analyzing the nucleic acid content of ***a plurality of cells on a cell-by-cell basis***. *See infra* §VI.C.3.

**Fourth**, even if, *arguendo*, POSITA had been motivated to make the argued combination, POSITA would have had no REOS in tagging “each polynucleotide” with the modified tag, as Petitioner argues. Petitioner’s proposed combination

would result in the vast majority of a cell's mRNA molecules remaining *untagged* because there would not be enough unique tags to tag each mRNA molecule in the sample. *See infra* §VI.D. There can be no REOS on these facts.

**A. Petitioner Fails To Show Linnarsson Teaches “Sequencing The Plurality of Tagged Nucleotides” [1G]**

Petitioner argues Linnarsson discloses limitation [1G] because (1) “Patent Owner previously challenged claims directed to detecting and sequencing DNA samples as nothing but ‘generic, routine, well-known laboratory techniques’” and (2) Linnarsson refers to sequencing. Pet.56-57. Petitioner's theory fails.

To begin, with respect to (1), Petitioner's assertion concerning PO's arguments regarding Section 101 and unrelated patents is irrelevant to the particular Section 103 combination at issue here, involving different claims and different legal tests, and questions regarding motivation to combine and REOS of the particular combination. Focusing on Linnarsson—the art asserted in the Ground—confirms Petitioner's argument fails.

With respect to (2), Petitioner fails to meet its burden to show Linnarsson sequences the claimed “plurality of tagged polynucleotides.” Pet.56-57; EX2013, ¶¶54-60. Petitioner identifies the “tagged polynucleotides” in Linnarsson as the complete cDNA molecules generated during reverse transcription. Pet.40-44 (“Linnarsson teaches generating a plurality of tagged polynucleotides (*i.e.*, tagged double-stranded cDNA and/or amplified copies) from the plurality of sample

polynucleotides (*i.e.*, mRNA)...”); EX2013, ¶54. Petitioner then ignores the intermediary steps of Linnarsson, and concludes that Linnarsson sequences *the plurality of tagged polynucleotides* based simply on vague references to sequencing. Pet.57. As discussed below, Petitioner ignores that Linnarsson sequences only the “5’ fragment” and fails to address whether or how sequencing only the “5’ fragment” is sufficient to meet the claim element. EX1001, C1.1; EX2013, ¶54.

Linnarsson repeatedly discloses that the tagged sequences are fragmented, and that only the 5’ fragment is sequenced. Linnarsson *defines* “cDNA library” as “a collection of cloned complementary DNA (cDNA) *fragments*.” EX1003, 12:4-8; EX2018, 41:10-44:22; EX2013, ¶¶55-57. Linnarsson also teaches the “amplified library is *fragmented* to 200–300 bp using controlled DNase digestion,” which creates 5’, 3’, and internal “fragments.” EX1003, 6:3-6, 21:13-25; *supra*, §III.A. While the so-called 5’ and 3’ “fragments” “are bound to beads,” the “*internal fragments are washed away*.” EX1003, 6:3-6; *id.* at Figs.11 (Panels C-E); EX2013, ¶¶55-56; *supra*, §III.A. Thus, those internal fragments are not sequenced. EX2018, 41:10-44:22. Moreover, the “3’ fragments” do not contain a Bts sequence and, as a result, *are not released from the “beads”* to which they are bound. EX1003, 6:3-8; *id.* at Figs.11 (Panels C-E), 35:28-31 (“5’ fragments containing barcodes and cDNA inserts were released from the beads by BtsCI

digestion...”); EX2018, 41:10-44:22; EX2013, ¶¶55-56. Thus, the “3’ fragments” of the “tagged polynucleotide” (which includes the CDS sequence and any tag within it) are also not sequenced in Linnarsson’s method. *Supra*, §III.A; EX2013, ¶¶55-56; EX1002, ¶198; EX2018, 43:21-44:22. And despite Dr. Cooper’s explicit reliance on Linnarsson’s disclosure of sequencing only the 5’ cDNA fragment *after* fragmentation, Petitioner and its expert entirely ignore this aspect of Linnarsson’s method in their analysis and fail to explain how it satisfies limitation [1G]. Pet.56-57; EX1002, ¶198 (citing EX1003, 21:13-25); EX2018, 41:10-43:20.

Moreover, Petitioner’s own citations fail to show Linnarsson discloses sequencing the entirety of the “tagged polynucleotide.” Pet.57 (citing EX1003, 4:8-13, 19:28-32, 21:13-25). Petitioner’s first citation is to a description of Linnarsson’s Figure 1, which is an “overview of a method” that simply says “sequencing is performed,” but does not provide details or specify what is sequenced. EX1003, 4:8-13; EX2013, ¶58. Petitioner’s second citation explains that the “5’ APS can be designed to facilitate downstream processing of the cDNA library” and that it “can be designed to be identical to the primers used in [certain] sequencing methods,” but also does not indicate what is actually sequenced; it indicates only that *something* is sequenced. EX1003, 19:28-32; EX2013, ¶58. Petitioner’s third and final citation confirms Linnarsson does *not* sequence the entire “tagged polynucleotide.” EX1003, 21:13-25; EX2013, ¶58; EX1002, ¶198.

As Linnarsson explains, “the cDNA library can be processed by *fragmenting the cDNA library* (e.g., with DNase) *to obtain a short-fragment 5'-end library*.”

EX1003, 21:13-25; EX2013, ¶58; EX2018, 41:10-43:20. This is the process described in Figure 11, as well as both disclosed Examples. EX1003, Fig.11, 26:9-20 (Example I’s “DNase treatment”), 35:17-27 (Example II “was fragmented by DNase 1”); EX2018, 41:10-43:20; EX1002, ¶¶110, 113, 117, 139-140, 143, 153-154, 164, 166 (each citing Figure 11); Pet.26-27, 29, 41-42, 46-47 (same); EX2018, 21:21-22:12.

In view of Linnarsson’s disclosures about fragmenting, washing away fragments, and sequencing only the “5’ fragment,” Petitioner’s bare assertion that sequencing is disclosed in Linnarsson cannot meet its burden. Pet.56-57; EX2013, ¶¶54-58. Indeed, Petitioner has not addressed whether or how sequencing just the “5’ fragment” is sufficient to have sequenced “the tagged polynucleotide,” nor has Petitioner presented any argument or claim construction addressing how much of a “5’ fragment” would be needed to sequence “the tagged polynucleotide.” Pet.36, 56-57. For this reason alone, Petitioner’s Ground 1 fails (and, with it, Ground 2, which relies on Ground 1). EX2013, ¶¶54-58.

Additionally, with respect to Petitioner’s CDS theory specifically, it fails for the additional reason that the CDS is part of the 3’ fragment, which Linnarsson does not sequence. Petitioner’s theory, which apparently relies on incorporating

McCloskey's encoding oligonucleotide teachings, including its barcode teachings, into Linnarsson's "conceptually divide[d]" CDS, fails for this reason, too. The "3' fragment" (the end of the double stranded cDNA with the CDS) is *not sequenced*. EX2013, ¶59; *see* EX1003, Fig.11 (Panel E); EX1003, 6:8; EX2018, 43:21-44:22. As discussed above, only the TSO has a Bts sequence—the CDS does not. EX1003, 5:32-6:8. The "3' fragments remain stuck on the beads" and are *never released* for sequencing. EX1003, 6:8; EX2018, 43:21-44:22; EX2013, ¶59; EX1003, 6:8. Indeed, as Petitioner's expert admits, nowhere does Linnarsson describe releasing the "3' fragment" from the bead or sequencing it. EX2013, ¶59; EX2018, 43:21-44:22. Thus, Petitioner's CDS theory fails for Ground 1.

**B. Petitioner Fails To Show A "First Tag Sequence" Is Obvious**

Petitioner's attempt to show the claimed "first tag sequence" is obvious also fails. First, Petitioner maps it inconsistently. *Netflix, Inc. v. Avago Techs. Int'l Sales Pte. Ltd.*, IPR2021-00542, Pap.34, 30 (Sept. 6, 2022) (finding petitioner failed to show limitation disclosed where petitioner took inconsistent positions on *which* disclosure mapped to the limitation). Petitioner maps the "first tag sequence" *in elements IE and IH* to Linnarsson's "cell-tag." Pet.47-49, 57. For example, Petitioner states "Linnarsson discloses that each tagged polynucleotide comprises a multiplex identifier (MID) sequence...comprising a first tag sequence... wherein the first tag sequence is a different sequence for different

single cells in the plurality of single cells...” Pet.49. But then, in attempting to establish obviousness of *element 1F* (which requires “a *second* tag sequence distinguishing the sample polynucleotide from other sample polynucleotides...”), Petitioner and its expert improperly *abandon* Linnarsson’s relied-on existing cell-tag (the Petition’s “first tag” for elements 1E and 1H) and rely on a modified version that *functions like McCloskey’s batch-stamp* as the “first tag sequence.”<sup>9</sup> Pet.51-52, 55-56 (citing EX1002, ¶192); ID.17 (“For limitations [1A]-[1E]... Petitioner relies on Linnarsson alone.”). Dr. Cooper explains: “POSA could

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<sup>9</sup> The Petition never cites Paragraphs 175 or 176 of Dr. Cooper’s declaration, whose substance should thus not be considered. In any case, those paragraphs are inconsistent with other aspects of Dr. Cooper’s opinions (*e.g.*, EX1002, ¶¶168-169 (relying on Linnarsson for the claimed “first tag sequence”)). This is not Dr. Cooper’s only inconsistency. Elsewhere, he suggests the entirety of the encoding oligonucleotide be combined with Linnarsson’s cell-tag, not just the batch-stamp and barcode. *See* EX1002, ¶¶186, 188. His opinion should be given little to no weight for this reason, as well. *See Applied Materials, Inc. v. Demaray LLC*, IPR2021-00104, Pap.54, 29-33 (June 29, 2022) (finding petitioner’s reliance on expert’s testimony failed to show reference disclosed a claim limitation because it was “belied by [the expert’s] own testimony”).

conceptually divide each of Linnarsson's cell-tag sequence into two portions, *wherein the first portion performs the function of McCloskey's 'batch-stamp,'* [sic] *used to track individual cells*, and the second portion performs the function of McCloskey's 'barcode', used to differentiate polynucleotides within a cell."

EX1002, ¶192; *see also* ID.21-22. Petitioner cannot rely on disclosure in one reference to cover a limitation, and then *reverse course* and rely on disclosure from *another* reference to modify that same limitation when it appears later to meet its burden. *See Netflix*, IPR2021-00542, Pap.34, 30.

Second, even if, *arguendo*, Petitioner could change its mapping of "first tag" for element 1F to McCloskey's batch-stamp functionality mid-claim (it can't), Petitioner *never explains how McCloskey's batch-stamp disclosure actually functions as a cell tag*. *See* Pet.52-56; EX2013, ¶¶61-66. Petitioner also *fails to cite any portions of McCloskey* for limitation [1E]. Pet.55-56. **McCloskey includes no sequence that distinguishes among the cells in the same sample**, as required by claim 1. EX1001, Cl.1 ("providing a sample comprising a **plurality** of single cells"); EX2013, ¶¶62-66. McCloskey's encoding oligonucleotide's batch-stamp distinguishes between nucleic acids arising from *all the cells in the sample (batch)*, on one hand, and the contaminant nucleic acids arising from cells *from different, prior samples (other batches with different batch-stamps) or other contaminant nucleic acids (with no batch-stamp)*, on the other hand. EX1004, 3-4;

EX1002, ¶¶99 (“the ‘batch-stamp’...is intended to associate a polynucleotide to ‘a specific sample run on a specific date.’”), 103 (“batch stamps specific to each sample”). Confirming this, McCloskey further teaches that each *sample* uses the *same batch-stamp*, regardless of the sample size, so polynucleotides either have the batch-stamp (if they are from *any* cells in the sample) or don’t (if they are contaminants and not from any of the sample’s cells). EX1004, 4 (“The assigned batch-stamp is registered for a specific sample run on a specific date and is used only once.”); EX2018, 35:4-19. McCloskey’s batch-stamp is *not* “associated with the single cell from which the sample polynucleotide is derived,” as required by the claims—instead, it is merely associated with a particular gene from *any and every* cell in the *sample* from which the polynucleotide is derived. EX1004, 3-4; EX2018, 35:4-19; EX2013, ¶¶62-66. This is how McCloskey’s batch-stamps confirm a sequence is not from a *contaminant*. EX1004, 4. As expected, McCloskey nowhere discloses using more than one batch-stamp for a sample—it would be contrary to McCloskey’s goals of identifying contaminant sequences and inconsistent with McCloskey’s teachings of tagging the pooled polynucleotides from its multi-cell sample with one batch-stamp. EX2013, ¶¶62-66; EX2018, 35:4-19. In contrast to the function of McCloskey’s batch-stamp that Petitioner relies on for obviousness of 1F, Linnarsson’s original cell-tag (on which the Petition

relies for 1E and 1H) is *different for each of the 96 cells in Linnarsson's sample*.

EX1003, 32:18-34.

It is unsurprising that McCloskey does not provide a mechanism for identifying the cell from which each polynucleotide originated in the sample because, contrary to Petitioner's suggestion (Pet.52-53), McCloskey is not focused on single cell *analysis*, which is the study of polynucleotides and proteins in a sample of multiple cells at a cell-by-cell resolution. *Infra*, §VI.C.2; EX1002, ¶73; EX2013, ¶66. McCloskey discloses the possibility of tagging (for detecting contamination) *when the sample consists of a "single cell."* EX1004, Abstract, 7; EX2013, ¶62-66; EX2018, 38:6-39:17. In '981, such analysis relies on cell tags to distinguish amongst polynucleotides from different cells after combining them together for, *e.g.*, sequencing. Tagging a "***single-cell*** sample" would not require uniquely tagging polynucleotides from *different cells* to identify the cell from which they originated—***there is only one cell to be tagged.*** EX2013, ¶¶63-65. Moreover, tagging different cells in the same sample with different batch-stamps would be inconsistent with McCloskey's teachings, which use the same batch-stamp for the entire sample. EX2013, ¶62-66.

McCloskey's reference to a "single-cell sample" (EX1004, 2) is not "single cell analysis," nor is it within the scope of the claims, which require the sample consist of "a plurality of single cells." EX1001, Cl.1; EX2013, ¶64. Indeed,

POSITA would have understood McCloskey to be referring to a one-cell sample.

EX2013, ¶64; EX1002, ¶99. Further, a “first tag sequence” (cell tag) would not distinguish among cells when the sample is only one cell. EX2013, ¶64.

McCloskey’s batch-stamp is, however, useful for “single-cell *samples*” because contamination concerns are heightened when the initial sample is small and requires significant amplification. EX1004, 2; EX2013, ¶64. Amplification bias for a single-cell sample can be significant because many more rounds of PCR are required as compared to larger samples. EX2013, ¶64. Further, McCloskey provides additional context confirming what it means with respect to “single-cell samples” in discussing the authors’ prior work in Miner on a “single-cell sample”: “[The Miner] approach is highly successful in identifying valid, double-stranded sequences and their methylation patterns, but requires bisulfite conversion and more template material than is usually available from irreplaceable or single-cell samples.” EX1004, 2. And the three references cited in support of the sentence about “single-cell samples” do not disclose “single cell analysis.” EX2013, ¶64; EX2018, 38:6-41:9.

McCloskey’s references to “single cell... analyses” also would not have been understood by POSITA to refer to “single cell analyses,” nor demonstrate that McCloskey teaches tagging material from different cells differently. EX2013, ¶65. One of McCloskey’s excerpts reads: “We recommend that batch-stamps and

barcodes be used when amplifying *irreplaceable* DNAs and cDNAs available for forensic, clinical, single cell, and ancient DNA analysis.” EX1004, Abstract, 7. A “single cell” is an irreplaceable sample, but “single-cell analysis” is not. *Id.* “Single cell...analysis” in McCloskey would be understood by POSITA to relate to the disclosure of “single-cell samples” discussed above, and to the analysis of a sample of a single cell. EX2013, ¶65.

This understanding is further confirmed by the fact that McCloskey does not disclose a working method that could be used to perform single cell analysis (analyzing a sample of cells while maintaining information on a cell-by-cell basis) on a sample consisting of *multiple* cells (as claim 1 requires). EX2013, ¶66. In addition to lacking any sequence to track an allele to its cell of origin, McCloskey pools all the DNA from a sample *prior to tagging*, which makes it impossible to determine which cell a particular allele arose from and is incompatible with true single cell analysis. EX1004, 2, 5; EX2013, ¶66; EX2018, 33:3-35:3. Dr. Cooper identifies “isolation of single cells from a cell population” as *the first step* of “Single Cell Genomics,” but McCloskey *does not have such an isolation step*. EX1002, ¶76.

Petitioner’s combination fails, because implementing McCloskey’s batch-stamp functionality in Linnarsson means there is no longer a “first tag sequence” within the meaning of claim 1.

**C. Petitioner's Claim 1 Motivation To Combine Fails**

**1. McCloskey's Tags Are Insufficient To Tag "Each Polynucleotide" In Linnarsson's Gene Expression Analysis**

Petitioner asserts POSITA would have "conceptually divide[d]" Linnarsson's cell-tag into two portions, the first functions as McCloskey's batch-stamp and the second functions as McCloskey's *barcode*. Pet.56 (citing EX1002, ¶192). Petitioner asserts there is a motivation to combine Linnarsson with McCloskey because McCloskey "provides the exact solution" to Linnarsson's alleged problem of amplification bias. Pet.54. According to Petitioner, this amplification bias is resolved in its combination "[b]y incorporating a second tag in an oligonucleotide that uniquely identifies *each sample polynucleotide* prior to amplification." Pet.53-54; *see also* EX1002, ¶190, ¶92 ("To solve this problem [of amplification bias].... Every sample and the polynucleotides within every given sample are first uniquely tagged before being amplified..."). However, McCloskey *does not disclose a tag for "each sample polynucleotide."* EX2013, ¶¶72-76.

Petitioner's citations to McCloskey show that *McCloskey does not have enough barcodes to tag each mRNA molecule of Linnarsson*. This is no surprise as there is much less DNA than mRNA in a cell, and McCloskey only tags DNA for alleles of a specific gene to analyze. EX1004, 3-5. Indeed, McCloskey tags two pieces of DNA for each cell in its sample (since there are typically two copies

of a given gene in any cell). EX1004, 3-5; EX1002, ¶65. In contrast, according to Petitioner, Linnarsson tags each mRNA molecule in each cell of its multi-cell sample. *See* Pet.25-26; EX1003, 46:3-9 (“synthesizing a first strand of cDNA from the mRNA *in each individual mRNA sample...*”). According to Petitioner and its expert, there are between 50,000 and 360,000 mRNA molecules in any given mammalian cell. EX2008, 61-62; EX2011, ¶257; EX2012, 1; EX2013, ¶74. EX2008, 61-62. And, while McCloskey is directed to analyzing a very small number of DNA molecules, Linnarsson is directed to tagging a very substantial number of mRNA molecules. EX1003, 23:20. Indeed, at most, McCloskey discloses 16,348 barcodes, which are used in McCloskey’s encoding oligonucleotide. EX1004, 4; EX2013, ¶73. Petitioner maps these barcodes to the “second tag” (to uniquely identify each polynucleotide). Pet.55-56 (citing EX1002, ¶192); EX1004, 4 (“16,384 possible barcodes”); EX2013, ¶74.

16,384 barcodes would not be enough to tag each mRNA molecule in Linnarsson. It would be impossible, using McCloskey’s 7-nucleotide barcode (amounting to only 16,348 unique barcodes), to distinguish the 50,000 – 300,000 mRNA molecules Petitioner admits POSITA would have expected to be present in the cell. EX1004, 4; EX2012, Abstract. Indeed, as Petitioner argued and POSITA would have known, tagging all target nucleic acids, such as mRNA, would have required many more tags than the number of nucleic acids being targeted for

tagging.<sup>10</sup> EX2008, 61 (“It would have been a simple design choice to design the second tag sequences with appropriate number of nucleotides to ensure sufficient number of distinct second tag sequences in the reaction mixture (e.g., ***at least 100 times [more] than the number of sample polynucleotides***) such that each sample polynucleotide is uniquely tagged.”) (citing EX2011, ¶256); EX1001, 22:54-60 (“the number of distinct MID tags to be used should be many times greater than the actual number of molecules to be analyzed.”). POSITA would thus not have been motivated to modify Linnarsson’s method to tag “each sample polynucleotide” (Pet.54) by employing McCloskey’s 7-nucleotide barcode that would be deficient for that purpose and could not “identif[y] each sample polynucleotide” as Petitioner claims motivates its proposed combination..<sup>11</sup> EX2013, ¶¶73-74;

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<sup>10</sup> According to Petitioner’s arguments, tagging each mRNA molecule in a cell would require a minimum of 5,000,000-30,000,000 unique sequences. *See* EX2008, 61-62; EX2011, ¶256.

<sup>11</sup> To the extent Petitioner argues that tagging a subset of the sample mRNA molecules with a second tag resolves amplification bias, this is wrong. EX2013, ¶75. Tagging only some of the mRNA molecules would not allow POSITA to determine the number of molecules in the sample because many of the sample molecules would remain *untagged*. EX2013, ¶75.

*Intelligent Bio-Sys.*, 821 F.3d at 1367-69 (affirming claims not obvious where petitioner’s combination would not have been expected to provide the solution that petitioner argued motivated the combination). For this additional reason, Petitioner’s entire Ground 1 (and Ground 2, which relies on Ground 1) fails.<sup>12</sup> *Id.*; *Arctic Cat Inc. v. Polaris Indus., Inc.*, 795 F. App’x 827, 833 (Fed. Cir. 2019) (non-precedential) (affirming FWD finding claims not obvious where petitioner’s “case was doomed when it failed to prove the premise it offered for combining [the references]”).

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<sup>12</sup> Neither Petitioner nor its expert proposed any modification to McCloskey’s 7-base-pair barcode. Pet.50-56; EX1002, ¶¶186-192. In contrast to Petitioner’s argument here, in another IPR on a related patent, Petitioner included additional art and an argument directed towards modifying the length of McCloskey’s barcode. *E.g.*, EX2008, 61 (arguing for a modification to increase McCloskey’s barcode because “McCloskey II teaches using molecular-tags each comprising 30 random base pairs” which would be necessary to ensure “each sample polynucleotide is tagged” including in a “typical mammalian cell [which] comprises approximately between 50,000 to [300,000] mRNA molecules.”). Petitioner chose not to do so here.

## 2. McCloskey's Batch-Stamp Lacks Benefits Of Linnarsson's Cell-Tag

Petitioner and Dr. Cooper assert “the first portion [of the conceptually divided cell-tag] performs the function of *McCloskey's ‘batch-stamp’*” and is implemented using “the first 6-8 nucleotides of Linnarsson's [original] cell-tag sequence....” EX1002, ¶192; Pet.56; *supra*, §VI.C.1. But neither Petitioner nor Dr. Cooper sufficiently explain *why* POSITA would modify the nucleotides of Linnarsson's cell-tag using McCloskey's teachings of a 6-to-8 nucleotide batch-stamp. EX2013, ¶¶67-71. Among other issues, Dr. Cooper ignores that Linnarsson's cell-tag is specially designed for use in single cell analysis *within a sample of multiple cells*—but McCloskey's batch-stamp *is not* so designed. EX2013, ¶¶67-71. Petitioner failed to prove POSITA would have been motivated to implement Linnarsson's cell-tag (designed to identify the source cell within a sample) using McCloskey's very different teachings of a batch-stamp that is *indifferent* to cell source and is focused, instead, on tagging entire batches (samples) of material to identify non-sample contamination. *See Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1066-67 (Fed. Cir. 2020) (affirming no motivation to combine because “POSA would be deterred from pursuing the claimed combination by concerns of stimulating inflammation and aggregation,” which ran counter to argued motivation to treat autoimmune disorders); *Surgalign Spine Techs., Inc. v. LifeNet Health*, IPR2019-00569, Pap.73, 29-34 (Aug. 26, 2020)

(*aff'd* 2022 WL 1073606 (Fed. Cir. Apr. 11, 2022)) (finding petitioner's motivation arguments were undermined where POSITA would not have expected substituting a bone pin for a metal screw to achieve intended purpose of holding the graft together).

Linnarsson's STRT method includes a specifically designed cell-tag adapted for single cell analysis. EX2013, ¶68. In Linnarsson's method, "[o]nly exact barcodes were allowed, and the barcodes were designed so that ***no single error would convert one valid barcode into another.***" EX1003, 36:28-29. This is an important feature of Linnarsson. Linnarsson's barcodes identify the cell of origin. EX1003, 32:23-34 (Table 9). An error during amplification or reverse transcription that changed the barcode sequence would impact the analysis in one of two ways. Either there would be a sequence that belonged to none of the 96 cells tagged with a barcode ***or*** the error would cause a sequence to be misattributed to a different cell of origin. EX2013, ¶68. This second error distorts whether and to what extent any cell is expressing a particular gene, and Linnarsson's cell-tag barcodes are intentionally designed to prevent this error from impacting the results. EX1003, 36:28-29.

But McCloskey's batch-stamp teachings, aimed at an entirely different purpose, include no such feature. EX1004, 4. McCloskey aims to identify and eliminate contaminants from *outside the sample* altogether, and as a result does not

distinguish among the cells from which material within the sample originated and is not concerned with the impact these types of transcription errors may have. *See supra* §VI.B; EX2013, ¶¶69-70.

Dr. Cooper ignores this beneficial aspect of Linnarsson’s existing design, and offers no modification to McCloskey’s batch-stamp teachings that would maintain this feature, which POSITA would have recognized as particularly useful in Linnarsson’s method. EX1002, ¶¶178-194; EX2013, ¶71. Petitioner thus failed, for at least this reason, to show POSITA would have been motivated to modify Linnarsson’s source-identifying tag using a tag employing McCloskey’s batch-stamp approach, thus eliminating the benefits of Linnarsson’s cell-tag. EX2013, ¶¶67-71. *See Immunex*, 964 F.3d at 1066-67; *Surgalign*, IPR2019-00569, Pap.73, 29-34.

### **3. McCloskey Does Not Describe Single Cell Analysis**

Petitioner asserts that POSITA would have combined Linnarsson and McCloskey because both describe single cell analysis. Pet.52. This is insufficient to establish motivation to combine (*e.g.*, *Markforged Inc. v. Continuous Composites, Inc.*, IPR2022-00679, Pap.24, 27 (Sept. 26, 2023)), and wrong. *Supra*, §VI.B.

Even if, *arguendo*, McCloskey’s reference to “single cell” or “single-cell samples” *did* refer to “single cell analysis” (it doesn’t; *see supra* § VI.B),

Petitioner’s assertion about the references being analogous to each other does not mean McCloskey’s barcode approach would have worked or that POSITA would have been motivated to use McCloskey’s barcode teachings in any and all “single cell analyses.” EX2013, ¶¶77-78; EX2018, 38:6-39:17; *Recor Med., Inc. v. Medtronic Ireland Mfg. Unlimited Co.*, IPR2022-00431, Pap.32, 22-23 (July 14, 2023) (rejecting petitioner’s argument that a reference’s “broader statements” that its catheter could work in blood vessels taught that the catheter “could have been used effectively on *any* anatomical structures near *any* human blood vessel” when the disclosures focused on the pulmonary vein); *infra*, §VIII. As discussed above, McCloskey’s approach was designed for tagging particular *alleles* in a sample. EX1004, 4. McCloskey’s general references to using its batch-stamp and barcode analysis for analyzing a “single cell” does not mean McCloskey was suitable for “single cell” *gene expression* analysis (involving a sample of multiple cells), or any other single cell analyses—and, indeed, for the reasons detailed above (*supra* §VI.B-C.2), it clearly is not. EX1004, 4; EX1003, 1; EX2013, ¶¶77-78.

#### **D. Petitioner’s Ground 1 REOS Fails**

Petitioner’s REOS argument also fails, because it, too, expressly depends on Petitioner’s mistaken and unsupported assumption that McCloskey has a tag that “uniquely identif[ies] *each* sample polynucleotide.” Pet.55. POSITA would not have had REOS of tagging *each* sample polynucleotide—*i.e.*, *all* the mRNA

molecules in a sample—by incorporating McCloskey’s barcode into Linnarsson because McCloskey *would not have provided enough unique barcodes to do so*. *Supra*, §VI.C.1; EX2013, ¶79; *Surgalign*, IPR2019-00569, Pap.73, 29-34 (finding no REOS for substituting a bone pin for a metal screw where POSITA would not have expected the bone pin to achieve intended purpose of holding the graft together). Thus, because Petitioner cannot show McCloskey’s barcodes would be even *capable* of tagging “each sample polynucleotide,” Petitioner cannot satisfy *its own specified argument* for showing REOS. Pet.55. Nor would POSITA have had REOS of sequencing “the plurality of tagged nucleotides” in its combination for the reasons described above in connection with the “sequencing” limitation analysis. *See supra*, §VI.A. Thus, Ground 1 fails.

## **VII. Ground 2: Petitioner’s Conclusory Combination Fails**

Petitioner’s Ground 2 addresses only dependent claim 5, which adds the step of “generat[ing] through at least one ligation reaction” “the tagged polynucleotides.” EX1001, Cl.5. According to Petitioner, Ground 2 builds from Ground 1’s obviousness combination (*see* Section IX.A.1, addressing independent claim 1), but beyond that Petitioner’s precise theory is unclear. *See* Pet.66 (“As explained above in Section IX.A.1, the combination of Linnarsson and McCloskey teaches and renders obvious claim 1.”) As adopted by the Board,<sup>13</sup> Petitioner’s

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<sup>13</sup> *See supra* n.8.

Ground 1 claim 1 obviousness theory involves POSITA “conceptually divid[ing]” the alleged tag in Linnarsson’s CDS or TSO (based on McCloskey’s teachings) to create a “first tag” that is different for different single cells in a plurality of cells, and a polynucleotide tag. ID.21-22. But in building on Ground 1 and attempting to cover claim 5’s added ligation requirement, Petitioner fails to make clear *what* is allegedly ligated to the CDS or TSO—a second tag only, or both first and second tags?

Petitioner begins by stating the “oligonucleotide tag comprising the tag sequences” (plural) is ligated, thus apparently referring to *both* the first and second tag sequences being ligated to the CDS or TSO. Pet.67. But according to Petitioner, Linnarsson’s CDS and TSO already have a first tag (Pet.47-49), and the CDS and TSO of Ground 1 already (according to Petitioner) have first *and* second tags (Pet.55-56, 67, 68 (“to ligate the oligonucleotide comprising the tag sequences to Linnarsson’s CDS or TSO...”). Petitioner then states a “POSA would have had a reasonable expectation of success in ligating a second sequence [singular] to Linnarsson’s CDS or TSO,” implying either that a second sequence with two tags, or a second sequence with a “second tag sequence” is ligated. Pet.67. On the very next page, Petitioner says that “*instead of* having the tag sequence [singular] be part of the CDS or TSO prior to extension, the tag sequences [plural] are added to the CDS or TSO after extension.” Pet.68. This merely adds to the confusion about

whether Petitioner’s theory involves ligating one or two tags. And this assertion highlights an additional ambiguity: whether Petitioner’s theory *removes* tag(s) already allegedly in the CDS or TSO, or simply adds *more* tags to the tags that Petitioner alleges exist already in its Ground 1 Linnarsson-McCloskey combination, while now identifying the newly-ligated tags as the claimed “first” and “second” tags.<sup>14</sup> See Pet.68 (“*instead of having the tag sequence be part of the CDS or TSO prior to extension, the tag sequences are added to the CDS or TSO after extension.*”).<sup>15</sup>

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<sup>14</sup> In his deposition, Dr. Cooper testified his report had *implied* that the second tag sequence added in Ground 1 was removed for Ground 2. EX2018, 58:22-59:10; see also EX2018, 46:12-47:18. But nowhere is this actually indicated or explained in the Petition or his declaration. Further, to the extent this new position in his deposition testimony is credited, Dr. Cooper’s Ground 2 theory would not build on the Ground 1 “conceptual divis[ion]” of Linnarsson’s cell tag—it would create an entirely new Ground 2 approach that his declaration and the Petition never substantiate or support.

<sup>15</sup> In addition to the substantive issues addressed below, Petitioner’s Ground 2 should be rejected because it fails to clearly and consistently identify its actual combination, and lacks the particularity necessary for PO to target its response to

Petitioner’s Ground 2 fails for the same reasons as Ground 1 (§VI), and also (to the extent PO can divine Petitioner’s potential theories) for these additional substantive reasons:

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whatever precise combination might be argued—depriving PO of, *inter alia*, basic due process. *See, e.g., Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)); *Pioneer Pet Prods., LLC v. Oil-Dri Corp. of Am.*, IPR2022-00691, Pap.31, 20-21, 23-29 (Sept. 12, 2023) (rejecting new arguments and evidence in reply to fix conclusory petition argument). Indeed, Petitioner wholly fails to provide clear and consistent identification of whatever change(s) POSITA would have made to the Ground 1 combination, and “how and why” POSITA would have made the proposed combination. Pet.66-69; *Samsung Elecs. Co. v. Lynk Labs, Inc.*, IPR2022-00101, Pap.30, 28-31 (May 25, 2023) (concluding claims not unpatentable where petitioner’s combination was “not at all clear”); *ExtractionTek Sales LLC v. Gene Pool Techs., Inc.*, IPR2022-00832, Pap.32, 27-29 (Oct. 23, 2023) (finding petitioner failed to explain “how and why [POSITA] would have modified [two references] with a teaching from [a third]” finding its arguments were “cursory and unsupported”).

**First**, Petitioner cannot show POSITA would have been motivated to ligate *any* tag(s) to Linnarsson's CDS and/or TSO. Attempting somehow to add tag(s) via *ligation*, as Petitioner argues, is at best confusing given Petitioner's Ground 1 combination, which involves (per the Petition's theory) annealing a CDS or TSO ***already containing "conceptually divide[d]" tags***. ***Ligating*** a (first and/or) second tag *to a CDS or TSO* is incompatible and inconsistent with "conceptually divid[ing]" the tag ***within*** the existing CDS or TSO to create first and second tags. Ligation would have required at least one *additional* step purportedly to gain some never-specified "flexibility" but (per Petitioner) merely yield only a Ground 2 approach "entirely equivalent" to Ground 1's. And there could be no motivation to ligate a (first or) "second tag" to the CDS or TSO when, according to Ground 1 (on which Ground 2 merely builds), the CDS or TSO *already contained a first and "second tag."*

**Second**, POSITA would not have had REOS of practicing the claimed method by ligating the tag(s) to the CDS or TSO. A review of Linnarsson confirms one cannot simply ligate "an oligonucleotide comprising the tag sequences to Linnarsson's CDS or TSO" to arrive at a combination that meets claim 5, including its subsequent required steps. No tags could be ligated to the CDS, no tags ligated to the TSO would be reverse-transcribed, and no ligated tags (let alone tagged polynucleotides) would be sequenced.

**Third**, Petitioner’s additional ligation theories fail. Neither Linnarsson nor McCloskey discloses ligation of a tag to a sample polynucleotide. Further, how any ligation and subsequent steps would be implemented is entirely unclear. And Petitioner improperly relies on Hug, which **would not cure** the issues ligation would present in Petitioner’s Ground 2 combination anyway.

**Fourth**, Petitioner’s theory also fails for **failing to specify when** “after extension” any **ligation would occur**.

**A. There Is No Motivation To Modify Petitioner’s Ground 1 Combination To Add Tag(s) Via Ligation**

Petitioner’s Ground 2 fails because there is no motivation to modify the Ground 1 claim 1 combination on which Petitioner builds for Ground 2. EX2013, ¶¶81-87.

To the extent Petitioner’s theory involves modifying its Ground 1 combination by **adding one (or two)** tag(s) via ligation to the CDS and/or TSO, there is no motivation to combine.<sup>16</sup> See Pet.68 (“*instead of having the tag sequence be part of the CDS or TSO prior to extension, the tag sequences are added to the CDS or TSO after extension.*”); see *supra* §VII (discussing lack of clarity in combination); *South-Tek Sys., LLC v. Engineered Corrosion Sols., LLC*, IPR2016-00136, Pap.52, 20-23 (May 10, 2017) (finding no motivation to combine

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<sup>16</sup> *Infra*, n.20, n.23.

where the modification rendered a feature in the primary reference redundant), *aff'd* 748 F. App'x 1003, 1007 (Fed. Cir. Sept. 20, 2018) (“Given the redundant functions of Viking’s drum drip and Wood’s condensate drain, the Board found [POSITA] would not have been motivated to [combine them].”); EX2013, ¶¶85-87. Petitioner ignores that, per Petitioner’s Ground 1 arguments, its modified CDS and/or TSO from Ground 1 *already contain(s) the two tags*.<sup>17</sup> Pet.67-68. POSITA would not have been motivated to add *more* tags (and more steps) when the CDS or TSO (according to Petitioner’s theory) already contain two tags. *Id.*; EX2013, ¶¶81-83; *In re Schweickert*, 676 F. App'x 988, 995 (Fed. Cir. 2017) (non-precedential) (reversing Board’s obviousness determination where modification to prior art system that “already” performs function of proposed modification was “unnecessary” and “would do little more than add unwanted cost and complexity to the system”). Petitioner certainly provides no supported motivation for adding yet *more* tags. Pet.66-68.

To the extent Petitioner’s theory is that POSITA would have further modified its Ground 1 combination to **remove** the tag(s) from the Linnarsson/McCloskey CDS and/or TSO, “instead” ligating the tags to the CDS or TSO after extension, that, too, fails.<sup>18</sup> See Pet.68 (“instead of having the tag

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<sup>17</sup> Petitioner relies on CDSs and/or TSOs with a tag. Pet.40-41.

<sup>18</sup> *Supra*, n.17.

sequence be part of the CDS or TSO prior to extension, the tag sequences are added to the CDS or TSO after extension”). Petitioner points to no teaching and provides no explanation as to *how* POSITA would have removed the tag(s), and provides no motivation *why* POSITA would have modified Petitioner’s asserted Ground 1 combination this way. Pet.68; EX2013, ¶¶81-83.

Additionally, Petitioner’s theory fails because removing allegedly-existing tags and then ligating new tags to Ground 1’s Linnarsson-based method would fundamentally alter its principle of operation. Pet.67-68; *Plas-Pak Indus., Inc. v. Sulzer Mixpac AG*, 600 F. App’x 755, 758 (Fed. Cir. 2015) (nonprecedential) (“Such a change in a reference’s “principle of operation” is unlikely to motivate a person of ordinary skill to pursue a combination with that reference”); *see ExtractionTek*, IPR2022-00832, Pap.32, 27-29 (agreeing with patentee that switch from “continuous process” to a “batch process” would “fundamentally alter” the operation of the reference). Linnarsson is designed to generate a sequencing library of tagged cDNA by annealing CDSs and TSOs, one or both with Petitioner’s alleged cell tags, which are carried forward through the transcription process. *Supra*, §III.A. POSITA would not have been motivated to fundamentally alter that process by, *e.g.*, **removing** the functionality of those existing tags from the CDS or TSO and then adding them to the tagged fragments at some point after extension—not only because this would fail to achieve the intended purpose (*infra*,

§§VII.B, VII.D), but also because it is a fundamentally different approach that jettisons the teachings of Linnarsson that are Petitioner’s supposed starting point. EX2013, ¶84.

POSITA also would not have been motivated to change and complicate Ground 1’s Linnarsson-McCloskey method (which, per Petitioner, already has the claimed tags) only to yield what Petitioner states is an “entirely equivalent” process. Pet.68; EX2013, ¶¶85-87.<sup>19</sup> Petitioner’s Ground 2 theory requires POSITA to (1) create *another* set of tags—as well as any other materials needed for the argued ligation (such as Hug’s linker molecules and enzymes)—and add at least one additional ligation step somewhere in the process, and (2) to the extent Petitioner’s theory involves the ligated tags *replacing* any existing CDS or TSO tags (Pet.67-68), *removing* the allegedly existing tags from Linnarsson’s CDS or TSO. EX2013, ¶¶85-87. With respect to (1), POSITA would not have added a step simply for the sake of ligating tag(s) rather than using the tags Petitioner says already existed in the Ground 1 TSO or CDS. EX2013, ¶¶85-87. Indeed, this is

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<sup>19</sup> For institution purposes the Board accepted Petitioner’s theory that POSITA would have “conceptually divid[ed]” Linnarsson’s cell-tag into two portions. ID.21-22; EX1002, ¶192. This does not appear to result in any change to Linnarsson’s STRT method. *Id.*

classic hindsight: it is required only so Petitioner can argue purported coverage of claim 5. Further, litigation would likely require *not one* but *multiple* steps.

EX2013, ¶85. With respect to (2), Petitioner does not explain *how*, *when*, or *why* such removal would occur.

Petitioner's sole purported justification for this proposed modification is the conclusory assertion that "it would allow for added flexibility in selecting tag sequences during an experiment" (a statement Petitioner's expert repeats verbatim, without additional analysis or support). Pet.68 (citing EX1002, ¶243). First, Petitioner's assertion is wholly conclusory, and is only parroted with no further explanation or evidence by its expert. *Id.* Petitioner asserts Linnarsson and McCloskey each provide "tags," and neither the Petition nor Petitioner's expert ever explains how or why *ligating* tag(s) to the CDS and/or TSO would "allow for added flexibility in selecting tag sequences," how or what this "added flexibility" is, or why such "flexibility" would not already have been achieved *without* ligation. Pet.68 (citing EX1002, ¶243). Petitioner fails for this reason alone. *Markforged*, IPR2022-00679, Pap.24, 28-29 (rejecting motivation to combine where "Petitioner's statement [wa]s nothing more than an unsupported conclusory assertion regarding a possible benefit" without "providing the requisite rationale sufficient to support a conclusion of obviousness"); *ExtractionTek*, IPR2022-00832, Pap.32, 28-30 (concluding claims not unpatentable where petitioner and

expert provided conclusory assertions of combination’s “advantage”). Further, because Petitioner’s expert did not provide any further explanation or evidence for this conclusory “increased flexibility” pronouncement, his opinion should be given no weight. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15-16 (Aug. 24, 2022) (precedential) (“the cited declaration testimony is conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight”); *Xerox Corp. v. Bytemark Inc.*, IPR2022-00624, Pap.12, 5-6 (Feb. 10, 2023) (Director affirming decision on *sua sponte* review and designating Paper 9 precedential); *Apple Inc.*, IPR2022-00981, Pap.34, 37.

Additionally, Petitioner’s assertion that ligation “would be *entirely equivalent* to the method already disclosed by Linnarsson” negates any motivation to modify. Pet.68; *Schweickert*, 676 F. App’x at 995; EX2013, ¶¶85-87. This is especially true where, as here, the modification would add more steps and complexity to achieve only an “equivalent” method. Pet.68; *Weber, Inc. v. Provisur Techs., Inc.*, IPR2019-01461, Pap.36, 42-43 (Feb. 10, 2021) (finding no motivation to modify claim 1 combination to invalidate dependent claim where proposed modification doubled number of steps and added “needless complexity”) *aff’d* 2022 WL 17688071 (Fed. Cir. Dec. 15, 2022). And, in fact, Petitioner’s

Ground 2 combination would *not* be equivalent because it would be incompatible with Linnarsson’s later steps, as discussed below (*infra* §VII.B.1-2).

Petitioner’s motivation to combine assertion about ligation providing “extra flexibility” by ligating the “tag sequences” as compared to “having the tag sequence be part of the CDS or TSO” (Pet.68) is unsupported. The same tag functions Petitioner argues to add via ligation are the very ones it argues are already performed in its Ground 1 CDS or TSO. EX2013, ¶¶85-87; Pet.67-68.

For each of these reasons, there is no motivation to modify Petitioner’s Ground 1 combination to add any tag(s) by ligation.

**B. Petitioner Has Not Shown Tag(s) Can Be Successfully Added Via Ligation In Linnarsson While Still Practicing The Claimed Method**

Petitioner glosses over the complexities of Linnarsson and the Linnarsson-McCloskey combination, and asserts POSITA would have simply ligated the tag(s) to the CDS or TSO. Pet.67-68. But a review of Linnarsson and Petitioner’s Ground 1 theory (as interpreted by the Board, and on which Petitioner’s Ground 2 theory allegedly builds), belies Petitioner’s theory. And Petitioner does not assert—nor show—that there would be REOS of practicing the *rest* of claim 5 after ligation. *See Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 69 F.4th 1341, 1347-49 (Fed. Cir. 2023) (affirming claims not unpatentable where petitioner’s modifications rendered reference inoperable for intended purpose); *Intelligent Bio-*

Sys., 821 F.3d at 1367 (REOS “refers to the likelihood of success in combining references to meet the [claimed] limitations”).

### 1. Petitioner’s Proposed Ligation Of Tag(s) To The CDS Fails

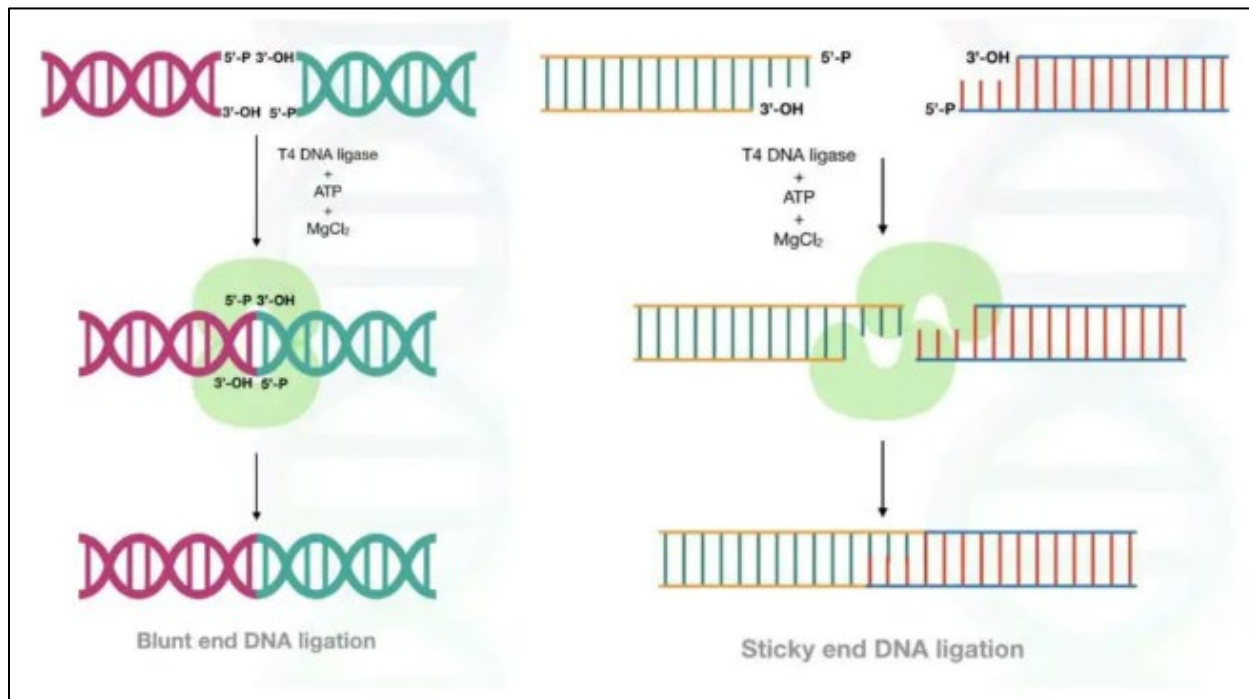
Petitioner argues tag(s) would be ligated to the CDS (Pet.67-68), but never explains precisely *how*. *Supra*, §VII. And this is not mere accident: without additional modification (which Petitioner never mentions<sup>20</sup>), it would be impossible to *ligate* tag(s) to the CDS *to achieve a method that practices claim 5*. EX2013, ¶¶88-93.

First, the biotin on the CDS’s 5’ end would block ligation of tag(s) to the CDS. EX2013, ¶89. As shown in Figure 11 and described in Examples I-II, Linnarsson’s CDS is capped by a “BIO” (biotin) molecule on its 5’ end. EX1003, Fig.11; 23:13-15 (“The sequence of STRT-T30-**BIO** (which is a CDS) is: 5’-**BIO**-AAGCAGTGGTATCAACGCAGAGT<sub>30</sub>VN-3’”); 32:19-20 (“STRT-T30-**BIO** (5’-**biotin**-AAGCAGTGGTATCAACGCAGAGT<sub>30</sub>VN-3’)”), 32:18-27 (disclosing the same CDSs and TSOs for Example II); EX2018, 23:15-25:21, 29:14-30:2. Ligation occurs when the DNA fragments’ ends are joined by the formation of

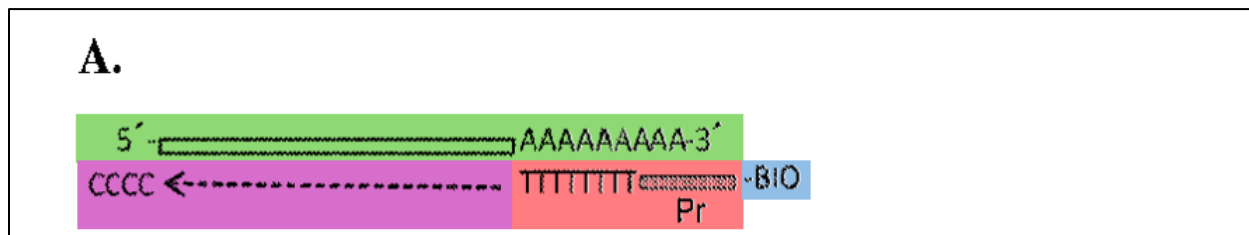
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<sup>20</sup> PO thus understands Petitioner is not asserting any further modifications to Ground 1’s Linnarsson-McCloskey combination to allow the “second tag” to be ligated “after extension” for claim 5. *Supra*, n.19; *infra*, n.23.

covalent bonds between the 3'-hydroxyl of one DNA terminus and the 5'-phosphoryl of another. EX1001, 6:15-32; EX2013, ¶89. The two forms of ligation, depicted in the picture below, both result in formation of phosphodiester bonds between adjacent nucleotides.



EX2017, 7. Linnarsson's biotin molecule is bound to the 5'-phosphoryl groups of the nucleic acids, shown below. EX1003, 23:13-14, 25:17-18, Fig.11.

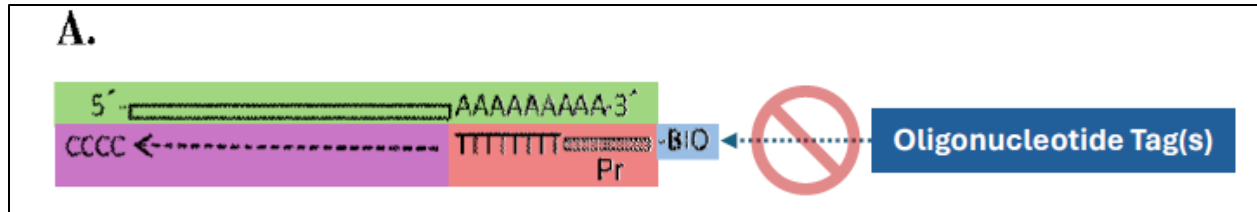


EX1003, Fig.11; EX2013, ¶¶89-90.

Once a biotin molecule is covalently bound to the end of these nucleic acids, it prevents any other molecule, including a nucleic acid tag, from being covalently bound to the end of the nucleic acid to which the biotin is already bound. EX2013, ¶89. Thus, Petitioner's tag(s) cannot be ligated to the "CDS" because a biotin is already bound to the CDS's 5' end's phosphoryl group, blocking the necessary covalent bond from being formed between the 5' end of the nucleic acid and any tag(s).<sup>21</sup> EX2013, ¶89. Petitioner's CDS theory fails. EX2013, ¶88-93.

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<sup>21</sup> Contrary to Dr. Cooper's deposition testimony that Figure 11 includes "a series of optional steps" (EX2018, 25:10-21, 31:1-22), POSITA would not have understood the biotin in Linnarsson's STRT method to be optional, and Dr. Cooper did not address any such optionality in his declaration. *See* EX2013, ¶90. Indeed, the *only examples* of Linnarsson's method include the use of biotinylated CDSs and biotinylating the "5' end" during PCR. *See* EX1003, Fig.11, Exs.I-II. And Petitioner and Dr. Cooper both expressly rely on Figure 11, which requires biotin. *E.g.*, Pet.25-26 (citing and excerpting Fig.11 with a biotinylated CDS), Pet.27 (same, and citing description of Fig.11), Pet. 29 (same), Pet.41 (same), Pet.42 (same), Pet.45-46 (same), Pet.47 (same); EX1002, ¶¶110, 113, 117, 139, 143, 153, 154, 164, 166; EX2018, 23:15-25:21, 29:14-30:2. But even if the use of biotin was eliminated from Linnarsson, this would not resolve the issues with Petitioner's



Second, even assuming, *arguendo*, that a nucleic acid could somehow bind to another nucleic acid already capped with a biotin molecule, this ligation would be incompatible with the *further* claimed steps of the combination and requirements of claim 5. These CDSs ***do not include a Bts*** sequence. EX1003, Fig.11 (Panel A); EX2013, ¶92. The Bts sequence is key to Linnarsson's method. *Id.* Therefore, these sequences (including any added tag(s)) would remain bound to the beads in Panel E and ***would not be cleaved off and sequenced***; only sequences with the Bts sequence are released by Linnarsson's disclosed BtsCI digestion, and Linnarsson never teaches releasing the CDS sequence from the beads. EX1003, 6:4-8 ("3' fragments remain stuck on the beads."), 27:6-8, Fig.11;

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theory. EX2018, 25:10-21, 31:1-22; EX2013, ¶¶90-91. Neither Dr. Cooper nor the Petition suggests eliminating biotin, or explains how Linnarsson's method would work without biotinylated cDNA. The biotin is, *e.g.*, involved in capturing the fragmented tagged cDNA, isolating it from untagged material, and then allowing those isolated sequences to be tagged with primers that permit each fragment to be sequenced. EX1003, 5:5-12; EX2013, ¶¶90-91.

EX2018, 43:21-44:22. Thus, any tag(s) allegedly ligated to the CDS would not practice the method of dependent claim 5 because these sequences would not be sequenced, as claim 1 (and dependent claim 5) requires. EX1001, Cl.1.

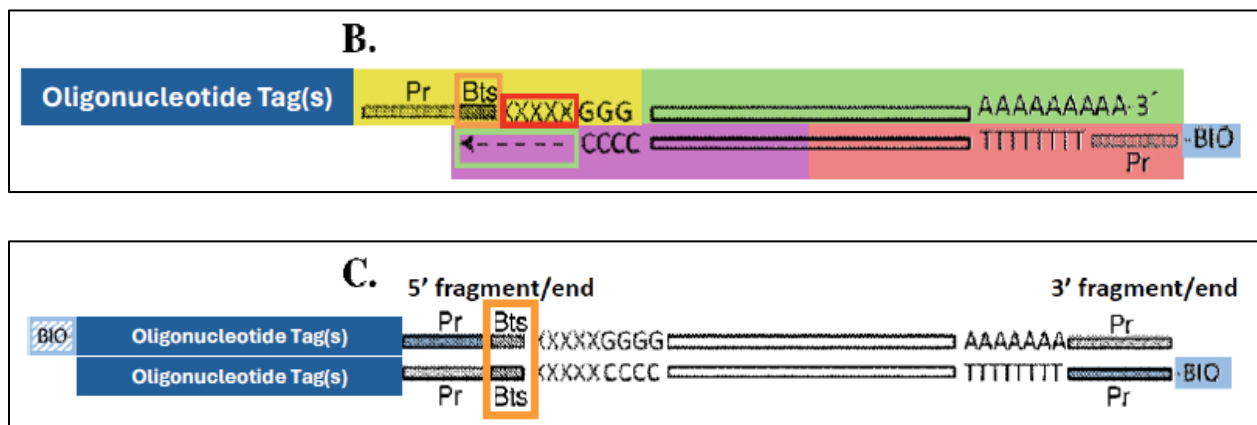
## **2. Petitioner’s Proposed Ligation Of Tag(s) To The TSO Also Fails**

The tag(s) also cannot be ligated to the TSO to arrive at a method that practices claim 5. Petitioner asserts the tag(s) would be ligated to the end of the TSO “after extension.” Pet.67-68. Ligating a tag to the TSO “after extension” would mean ligation occurs *after* the template switching step in Panel B is completed. EX2013, ¶¶94-95. At this point, the reverse-transcription of double-stranded cDNA in Linnarsson’s method is already complete. Linnarsson discloses no further extension steps, and Petitioner identifies no third “extension” step to reverse-transcribe this newly-ligated sequence to resulting cDNA. EX1003, Fig.3. In Linnarsson’s Panel A, for example, the cDNA is extended to generate a sequence complementary to the mRNA. *Supra*, §III.A. In Panel B, the cDNA is extended to include a sequence complementary to the TSO. *Supra*, §III.A.

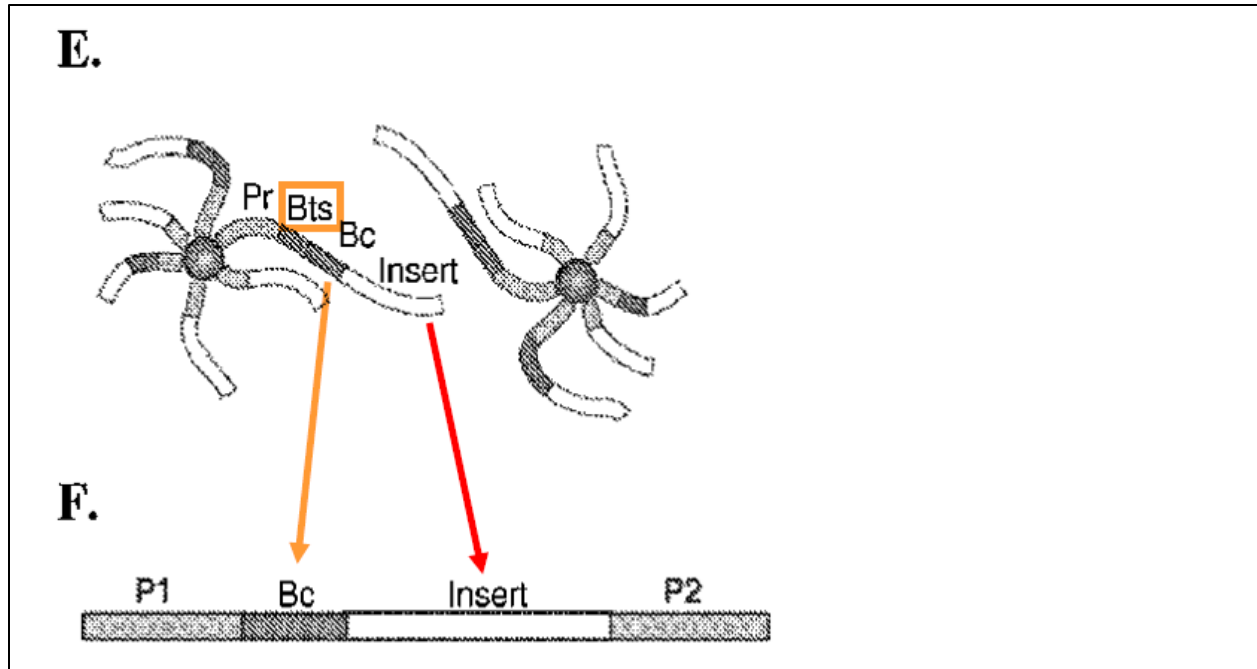
***Linnarsson discloses no third extension step to include a sequence complementary to the “second tag” in the cDNA strand if one were ligated to the TSO after extension.*** EX2013, ¶94. Nor did the Petition or Dr. Cooper discuss or posit one. Thus, Petitioner’s theory also fails because the tag(s) added via ligation would not be extended, and would therefore not be included in the cDNA that is

subsequently amplified during PCR (*e.g.*, in Panel C), and would not be part of the “tagged polynucleotide” that is sequenced (*e.g.*, in Panel F, 21:13-25). *Supra*, §III.A; EX2013, ¶94; EX2018, 21:21-32:14.

Second, even if, *arguendo*, the tag(s) were reverse-transcribed (they aren’t), the TSO theory fails for another reason. The ligated tag(s) would be located on the 5’ end of the Bts sequence,<sup>22</sup> shown in annotated Panels B and C below. EX1003, Fig.3, Fig.11; *see also id.* 27:6-7, 35:28-36:9; EX2013, ¶95. But according to Linnarsson, any sequence on the 5’ side of the Bts sequence will be *remain stuck to the bead and will not be released as part of the fragment that is sequenced*—only “*the barcode (Bc) and insert*” are “released by BtsCI digestion.” EX1003, 5:28-6:12, Fig.11 (Panel F); *see also id.* 27:6-7, 35:28-36:9; EX2013, ¶95.



<sup>22</sup> The 3’ end of the TSO is attached to the “internal” portion of the “tagged polynucleotide,” and thus no polynucleotide may be ligated to it. EX1003, Fig.11.



Thus, even if the tag(s) were ligated to the end of Linnarsson’s TSO, the ligated tag(s) would be *cleaved* from the released sample polynucleotide in Panel E *and remain stuck on the bead*. EX1003, 5:28-6:12, Fig.11; *see also id.* 27:6-7, 35:28-36:9. Once cleaved, the released polynucleotide would include no “second tag sequence,” and thus the “tagged polynucleotide” would not be sequenced—nor would it be possible to distinguish among sample polynucleotides as required by claim 1 (and, thus, claim 5). EX1001, cl.1; EX2013, ¶95.

### 3. Petitioner Does Not Assert REOS For The Claim As A Whole

Petitioner asserts there would have been “a reasonable expectation of success to introduce these tags by ligating an oligonucleotide comprising the tag sequences to Linnarsson’s CDS or TSO.” Pet.66-67. But asserting REOS of

practicing only an isolated limitation of the claim is insufficient—and Petitioner never asserts, let alone explains, how or why POSITA would have had REOS of performing the Linnarsson-McCloskey method in a manner that practices *all* of the limitations of claim 5 (including base claim 1) with this additional ligation modification. *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4<sup>th</sup> 1331, 1348 (Fed. Cir. 2021) (“it was, at all times, [petitioner’s] burden to show that the claims would have been obvious, including that a skilled artisan would have had a reasonable expectation of success in achieving the claimed invention.”); *Intelligent Bio-Sys.*, 821 F.3d at 1367-69 (“The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet ***the limitations of the claimed invention.***”); *Intelligent Bio-Sys.*, 821 F.3d at 1367-69; *Surgalign*, IPR2019-00569, Pap.73, 29-34.<sup>23</sup>

And as explained, analyzing this modification’s impact on claim 1 confirms there is no REOS for claim 5. *Supra*, §VII.C.1-2. Petitioner’s proposed ligation

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<sup>23</sup> Petitioner cannot change its theory in Reply or offer additional modifications in attempting to fix its broken combination. *In re NuVasive, Inc.*, 841 F.3d 966, 972-73 (Fed. Cir. 2016) (vacating final written decision when Board relied on factual assertion by petitioner made only after patent owner’s Response); *Intelligent Bio-Sys.*, 821 F.3d at 1369-70; *Apple Inc.*, IPR2022-00981, Pap.34, 35-36.

would fail because, as to the CDS, (1) the CDS is blocked by a biotin molecule, and (2) the “3’ fragment” containing the CDS is not sequenced (even ignoring (1)); and, as to the TSO, (1) the ligated sequence would not be transcribed if ligated to the TSO “after extension” because there is no additional extension step, and (2) if ligated to the TSO the sequence would be cleaved from the “tagged polynucleotide” prior to sequencing (even ignoring (1)). Each outcome prevents the combination from meeting claim 5’s limitations, and POSITA could thus have had no REOS in the combination. *Intelligent Bio-Sys.*, 821 F.3d at 1368-69.

### **C. Petitioner’s Other Ligation Assertions Fail**

Petitioner’s Ground 2 relies on Linnarsson and McCloskey. Pet.66. But neither teaches ligation of a “tag sequence”—nor does Petitioner assert they do. Pet.52 (“Both references describe methods... whereby polynucleotides are *annealed to oligonucleotides* comprising tag sequences (Linnarsson’s CDS and TSO; McCloskey’s encoding oligonucleotide)”), 66-68; EX2013, ¶¶96. It is unclear from Petitioner’s argument *how* the ligation and subsequent steps (such as the required amplification) are purportedly implemented in Petitioner’s asserted combination based on the addition of a “knowledge of a POSA.”<sup>24</sup> *Samsung Elecs. Co. v. Elm 3DS Innovations, LLC*, 925 F.3d 1373, 1380-81 (Fed. Cir. 2019)

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<sup>24</sup> *Supra*, n.15, n.23.

(affirming no REOS in part where petitioner failed to adequately explain how fabrication process would be changed to incorporate modification).

Petitioner’s attempt to fill this gap in its combination by relying on Hug (*not* part of its stated Ground) fails, particularly given Petitioner’s failure to explain how or why Hug’s teachings would be incorporated into the Linnarsson-McCloskey combination. *Supra*, n.8, n.15, n.23; Pet.67; *see Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1335-37 (Fed. Cir. 2020) (holding Board erred in instituting on ground outside petition); *Applied Materials, Inc. v. Demaray LLC*, IPR2021-00103, Pap.52, 36-42 (June 29, 2022) (rejecting petitioner’s argument that references evidencing POSITA’s knowledge alone “sufficiently explain how such teachings apply to [the reference’s] system”); *DSS Tech. Mgmt., Inc. v. Apple Inc.*, 885 F.3d 1367, 1374 (Fed. Cir. 2018) (identifying “three caveats” to using common sense in obviousness analysis, warning it is not “typically invoked” “to supply a missing claim limitation”); *AI-Site Corp. v. VSI Int’l, Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (“Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment.”).

And even if Petitioner’s Hug arguments could properly be considered, they fail. EX2013, ¶¶97-105. To begin, Petitioner never asserted or explained how Hug is analogous to ’981—a threshold requirement for an obviousness analysis.

*See, e.g., Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4<sup>th</sup> 1373 (Fed. Cir. 2023) (reversing Board decision for this failure). Petitioner also asserts only that Hug’s method “**could**” be used to “ligate the oligonucleotide comprising the tag sequences to Linnarsson’s CDS or TSO”—not that POSITA actually **would** have used this approach. Pet.68; *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020) (“The obviousness inquiry does not merely ask whether a skilled artisan could combine the references, but instead asks whether ‘they would have been motivated to do so.’”). And POSITA would not have looked to Hug’s fundamentally different (and theoretical) approach or been motivated to use its linker approach with Linnarsson or McCloskey. EX2013, ¶¶97-98. For example, Hug does not sequence the polynucleotides to which it adds linkers. EX2013, ¶¶97-98. Rather, the portion of Hug’s process Petitioner and Dr. Cooper cite<sup>25</sup> relies on linkers that hybridize to each other to randomly add a number of linkers to a molecule. EX1007, 7-8, Fig.3; EX2013, ¶¶97-99; EX2018, 49:8-50:9. Hug then analyzes the DNA fragments *by length* to estimate the number of molecules in a sample. EX1007, 7-8, Fig.3; EX2013, ¶¶99-100; EX2018, 49:8-50:9. This is

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<sup>25</sup> Petitioner and Dr. Cooper together cite only pages 1 and 7-9 of Hug, which correspond to the introduction (EX1007, 1) and the “Multimeric Linker Labeling” approach (EX1007, 3, 6). Pet.67-68; EX1002, ¶¶240-242.

very different from Linnarsson or McCloskey, which rely on *sequencing* molecules. EX2013, ¶¶97-100.

Petitioner also incorrectly asserts Hug’s “linker” would have “*hybridize[d] to Linnarsson’s CDS and/or TSO as well as the oligonucleotide, which could then be ligated to the CDS and/or TSO.*” Pet.68; EX2013, ¶99. Hug describes adding a BamH1 recognition site to the generated double-stranded DNA such that, when it is cut with BamH1 (a particular endonuclease), the resulting double-stranded DNA has a 5’ sticky end with a particular overhanging sequence. EX1007, 7-8, Fig.3; EX2013, ¶¶99-100. Two different sets of short linkers are subsequently added. EX1007, 7-8, Fig.3. The first set of linkers consists of the recognition site of the BamH1 restriction enzyme and an end with a short polynucleotide sequence that hybridizes to the other linker.<sup>26</sup> EX1007, 7-8, Fig.3. These linkers can form a chain. *Id.*; EX2013, ¶¶99-100; EX2018, 49:8-50:9. Hug’s second set of linkers are “Terminator Sequences” that terminate the chain because no linkers have the complementary sequence necessary to hybridize to, and thus continue, the chain. EX1007, 7-8, Fig.3; EX2013, ¶¶99-100. Petitioner, however, never acknowledges these details of Hug’s ligation method and ignores that ***Hug’s linkers are not***

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<sup>26</sup> Unlike tags that distinguish polynucleotides (EX1001, cl.1), Hug’s linkers are not unique.

*designed to link a series of random nucleotides*, like McCloskey’s barcode, *with another sequence*, like Linnarsson’s CDS or TSO. Pet.68; EX2013, ¶¶99-104.

Petitioner also does not point to the use of BamH1 in Linnarsson, which is unsurprising as Linnarsson does not use BamH1 for any purpose. Pet.67-68; EX2018, 50:22-51:4. And Petitioner proposes no modifications to Hug’s linkers, McCloskey’s barcodes, or Linnarsson’s CDSs and/or TSOs to allow these three molecules to hybridize to each other. Pet.67-68; EX2013, ¶¶99-104.

Further, even if, *arguendo*, the Petition *had* explained why and how POSITA would have looked at Hug and identified and made all modifications necessary to allow Hug’s linkers to work with McCloskey’s barcodes and Linnarsson’s CDSs and/or TSOs (it didn’t), Hug does not cure the other deficiencies PO identified in Ground 2, described above in §VII.A-B. EX2013, ¶105.

#### **D. Petitioner Fails To Explain When Any Ligation Would Occur**

Petitioner does not sufficiently explain *when* its argued ligation happens under either its CDS or TSO theory—indeed, Petitioner’s expert conceded at deposition that his declaration *did not state when it occurs*. EX2018, 54:8-21 (“I did not explicitly say a timing element there...”). As a result, Petitioner failed its burden to “fully explain how [its first reference, Linnarsson] would be modified by [its second, McCloskey].” *E.g., LinkedIn Corp. v. eBuddy Techs. B.V.*, IPR2022-

00164, Pap.40, 21-22 (June 30, 2023); *Samsung Elecs.*, IPR2022-00101, Pap.30, 28-31. Petitioner briefly asserts only that the tag would be ligated to Linnarsson’s CDS or TSOs *at some unspecified point “after extension.”* See, e.g., Pet.68 (asserting the “method would be entirely equivalent to the method already disclosed by the combination of Linnarsson and McCloskey, except that instead of having the tag sequence be part of the CDS or TSO prior to extension, the tag sequences would be added *after extension.*”). But there are *multiple* steps after extension in Linnarsson, and Petitioner never identifies where in this sequence tagging via ligation allegedly occurs. See EX1003, Figs.2, 11. Each step raises *different* issues that would prevent ligating a “second tag” in a manner that renders claim 5 obvious—and the Petition addresses *none* of them. Petitioner’s approach fails to prove how its combination renders claim 5 obvious, as required, and instead attempts to require *PO* to prove how ligating a “second tag” would fail at all steps. This is improper burden shifting.

In attempting to explain away his failure to specify when ligation occurs, Dr. Cooper, when redirected by Petitioner’s counsel in deposition, asserted this timing is not required by the claims. EX2018, 54:8-21; EX2013, ¶106. Not so. While not *PO*’s burden, the discussions above provide examples showing why ligation would fail if performed after Linnarsson’s first or second extension steps but *before* PCR. E.g., *supra*, §VII.B.1-2; EX2018, 18:19-21:1. And, as another

example, if the “second tag” were added *after* PCR (*e.g.*, Fig.11C after the extension steps in Fig.11A-B), this would fail to meet claim 1, on which claim 5 depends. Limitation [1I] requires that the “second tag” be able to “correlate [an] identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived.” EX1001, 30:18-47. In other words, after amplification and sequencing, the “second tag sequence” must be able to identify the endogenous polynucleotide from which an identified polynucleotide was derived (*e.g.*, amplified from)—enabling, *e.g.*, identification of the number of each polynucleotide present prior to tagging and amplification. EX1001, Cl.1. But tags added *after* PCR cannot identify the original polynucleotide from which any polynucleotide in the result may have been amplified, as required—instead, this would give every post-PCR polynucleotide its own unique sequence, failing claim 1. EX2013, ¶106; EX2018, 61:8-62:5. Moreover, if added after ligation, Petitioner’s combination would fail to solve Linnarsson’s amplification bias problem—the purported motivation driving Petitioner’s argued combination. Pet.53-56; EX2013, ¶106.

By including these and other scenarios within its proposed combination but failing to address any of them (or their flaws), Petitioner failed its burden.

**VIII. Grounds 1 and 2: Petitioner Fails to Allege—Let Alone Establish—That Its References Are Analogous Art *To '981***

Nowhere does Petitioner assert—let alone attempt to show—that either of the two references named in its grounds (primary reference Linnarsson and secondary reference McCloskey) is analogous art *to '981*. See Pet.52-53. A petitioner ***cannot meet its burden*** when it “argue[s] that [a prior art reference] is analogous to another prior art reference *and not the challenged patent*.” *Sanofi-Aventis*, 66 F.4<sup>th</sup> at 1380. “[A] patent challenger must compare the reference *to the challenged patent*.” *Id.* Petitioner here cannot meet its burden because the Petition failed to perform the required analogous art analysis by addressing whether its relied-upon art is analogous *to the challenged patent*; it only asserts that McCloskey, Petitioner’s secondary obviousness reference, is analogous to Linnarsson, its primary obviousness reference. Pet.52-53; EX1002, ¶187. Thus, because Petitioner’s grounds rely entirely on obviousness and Petitioner was therefore required to establish that its obviousness art is analogous to the challenged patent as a threshold issue, Grounds 1 and 2 must both be rejected because Petitioner cannot meet its burden to establish obviousness as a matter of law. *Sanofi-Aventis*, 66 F.4<sup>th</sup> at 1380. Petitioner cannot cure this issue in reply as it unambiguously asserted the references were analogous only to each other,

without any reference to '981.<sup>27</sup> *Cf. Corephotonics, Ltd. v. Apple Inc.*, 84 F.4<sup>th</sup> 990, 1003-08 (Fed. Cir. 2023) (allowing petitioner to clarify its analogous art argument in reply where the petitions were “ambiguous” as to whether petitioner was stating the references “are in the same field of endeavor as the Challenged Patents or... one another”); PTAB Consolidated Patent Trial Practice Guide (Nov. 21, 2019), available at <https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf>, 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”).

## **IX. Conclusion**

As detailed above, Petitioner has failed to meet its burden to show any of the Challenged Claims unpatentable.

Respectfully submitted by:

Dated: January 5, 2024

/J. Steven Baughman/

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<sup>27</sup> *Supra*, n.8, n.23.

**CERTIFICATE OF WORD COUNT**

The undersigned certifies that the foregoing PATENT OWNER'S  
RESPONSE complies with the type-volume limitation in 37 C.F.R. §42.24(b)(1).  
According to the word-processing system's word count, the brief contains 13,875  
words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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**CERTIFICATE OF SERVICE**

The undersigned hereby certifies that a copy of PATENT OWNER'S RESPONSE has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

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