

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

10X GENOMICS, INC.,
Patent Owner

Case IPR2023-00955
Patent 10,240,197

PATENT OWNER'S RESPONSE

LIST OF EXHIBITS

Exhibit	Description
EX2001	File History of U.S. App. No. 15/677,957
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., IPR2023-00876, Pap.1 (May 25, 2023)
EX2009	File History of U.S. App. No. 14/172,694
EX2010	Declaration of Sayem Osman
EX2011	Declaration of Sayem Osman
EX2012	<i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-00876, EX1002 (Apr. 20, 2023) (Declaration of Gregory Cooper, Ph.D.)
EX2013	Declaration of Dr. John Quackenbush
EX2014	Bruce Alberts, et al., <i>Molecular Biology of the Cell</i> , Garland Science (4th ed. 2002)
EX2015	S. Guan, A. Blanchard, P. Zhang, & Z. Zhu, <i>Alteration of Sequence Specificity of the Type IIS Restriction Endonuclease BtsI</i> , (July 26, 2010)
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) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6391780/#:~:text=Considering%20a%20mean%20weight%20in,units%2Fcarat.htm)
EX2017	T. Chauhan, <i>T4 DNA Ligase: Introduction, Functions, Applications, and Protocol</i> , (available at https://geneticeducation.co.in/t4-dna-ligase/)
EX2018	IPR2023-00876 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)
EX2020	IPR2023-00955 Deposition Transcript of Gregory Cooper, Ph.D.

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I. Introduction

U.S. Pat. No. 10,240,197's (the "'197 Patent"/"'197") Claims 1-26 (the "Challenged Claims") are directed to innovative methods of counting nucleic acids from a plurality of cells that *differentiate among the different polynucleotides* in an overall sample and *track from which particular cell* each polynucleotide originated.¹ EX1001, 6:33-7:22, 15:7-50, Cl.1 (30:16-39). Nobel Laureate Sydney Brenner and team—'197's inventors—unlocked high-resolution single cell analysis. Petitioner's perfunctory arguments fail 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, *as Petitioner argues*, that Linnarsson sequences "the *entire* tagged polynucleotide." The disclosures on which Petitioner relies confirm that only the "5' fragments" of "the tagged polynucleotides" are sequenced—Petitioner fails to address that Linnarsson never

¹ Unless stated, statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates, internal citations omitted, and emphases/annotations are added.

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’s purported motivation to combine and reasonable expectation of success (“REOS”) fail. These arguments rest, *inter alia*, on Petitioner’s premise that McCloskey stamps “*each* sample polynucleotide” in Petitioner’s combination. Pet.41-42, 55. But Petitioner fails to prove this premise is true (and McCloskey shows it is not). McCloskey’s barcode, as relied on by Petitioner in its Ground 1 combination, is only seven nucleotides long and can thus distinguish among, *at most*, 16,384 sample polynucleotides. That is facially insufficient to tag the mRNA molecules present in the cells Petitioner argues 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.

Third, Petitioner inconsistently maps the claimed “first tag sequence” in its Ground 1—mapping it at times to Linnarsson’s cell tag, but at others to McCloskey’s batch-stamp. 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.

Petitioner's **Ground 2**, which is directed to various claims that depend from claim 1 (Ground 1) based on a hodgepodge of different theories, should be rejected. The theories are insufficiently detailed, and they improperly rely on art not listed in the Grounds to supply missing limitations from the Ground 1 combination (which itself fails for the reasons noted above). Ground 2 fails for additional reasons for various claims, including claim 5, which requires *ligating* a "tag sequence" to the cDNA synthesis primer ("CDS") or template switching oligonucleotide ("TSO"). Petitioner's motivation to combine fails. For example Petitioner's sole justification for the Ground 2 combination is that it would provide "added flexibility"—but Petitioner never identifies what that would be or why that flexibility would not be achieved without ligation. Petitioner also fails to show its proposal of ligating a tag to Linnarsson's CDS or TSO would work. With respect to ligating a tag to 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. With respect to ligating to 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 being sequenced.

Petitioner's **Ground 3**, directed to various other claims depending from claim 1, first fails to address how claim 1's limitations are covered in connection with its Ground 3 theories. Even assuming Petitioner's intent was to build on its Ground 1 claim 1 combination, Petitioner's motivation to modify in further view of McCloskey II fails. Petitioner argues for incorporating a longer second tag using the teachings of McCloskey II, but Petitioner's asserted Ground 3 motivation is the same as its Ground 1 motivation (and thus does not explain this *further* change). Indeed, according to Petitioner, the problem the Ground 3 modification would allegedly solve is, according to Petitioner, *already resolved in Ground 1*. Thus, according to Petitioner's own arguments, there could be no remaining motivation to further modify Ground 1 in the way Petitioner proposes.

Finally, Petitioner entirely fails to assert or analyze whether its references are analogous art to '197 (instead discussing only whether they are analogous to one another). This failure requires rejection of Grounds 1-3, as the Federal Circuit recently confirmed.

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

'197's Challenged Claims are directed to innovative methods of counting nucleic acids from a plurality of cells that allow the user *not only to differentiate*

among the different polynucleotides (including, *e.g.*, mRNA) 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 (30:16-39).² The patent describes using *two tag sequences*: “a *first* tag sequence associated with the single cell from which the sample polynucleotide is derived” (cell-specific tags) and “a *second* tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same cell” (polynucleotide-specific tags). EX1001, Cl.1 (30:16-39); EX1001, 14:8-14; EX2013, ¶28.

Until '197's inventions, “bulk analysis” was primarily used to analyze polynucleotides in a sample of cells. EX1003, 2; EX1006, 2. This provided insight into the polynucleotides in the sample's population of cells but failed to capture critical differences among *individual* cells. Pet.8; EX2013, ¶29. For example, overexpression of the HER2 gene was associated with an aggressive form of cancer, but in the cancer's early stages only a few cancerous cells might be

²'197, like many patents, discloses multiple inventions. EX1001, 1:50-62.

Another disclosed invention is the “reflex method,” which involves a novel method of tagging and fragmenting polynucleotides to ensure they are short enough to be sequenced while enabling the user to track the origin of each fragment. *Id.*, 1:25-62.

captured amongst numerous cells in a tissue sample. EX2013, ¶29. Averaged across the entire sample population, it would not be possible to determine whether a small subset of the cells was overexpressing HER2 because the overexpression of HER2 in cancerous cells 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.

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 users to do what had not previously been possible: to determine the quantity of *each polynucleotide present* in a cell within a sample *on a cell-by-cell basis*, which Linnarsson, McCloskey, and McCloskey II do not. EX1001, 6:33-7:22, Cl.1 (30:16-39); EX1002, ¶¶68-70.

III. Petitioner's References³

A. Linnarsson (EX1003)

Petitioner relies on Linnarsson's disclosures relating to "*single-cell tagged reverse transcription (STRT)...*" Pet.16-21, 30-31, 34-37, 49 (each citing Fig.11); EX1002, ¶¶105, 108, 112, 137-138, 141, 150-151, 196, 199, 200 (same); *see also* EX1003, 5:10-11, 23:1-4, 37:31-32, Fig.11. This **STRT method** involves preparing a cDNA library (defined in Linnarsson as "a collection of cloned complementary DNA (cDNA) fragments") by reverse-transcribing mRNA produced by genes expressed in the sampled cells. EX1003, 1 (Abstract), 3:25-4:2, 12:4-8; *see also* Pet.17; EX2013, ¶33-47. According to Petitioner, "[s]ingle cells useful in the methods described herein can be obtained from a tissue of interest, or from a biopsy, blood sample, or cell culture." Pet.28; EX1003, 13:11-16; EX2013, ¶34. As part of this process, "single cells are placed in separate wells of a 96-well plate and lysed...." EX1003, 4:8-13; Pet.28. Each lysed cell "contain[s] a plurality of mRNA molecules." EX1003, 3:26-30; Pet.28-29; EX2013, ¶33; EX1054, Abstract; EX1002, ¶255. Following lysis, Linnarsson adds CDSs and

³ Petitioner (apparently hoping to evade its word limit) improperly incorporates by reference the 6-page "technical background sections" in a separate petition (and the supporting expert declaration). Pet.5-6 (citing EX2008, §IV); *see* Pet.77.

TSOs, which are then incorporated into cDNA during reverse transcription from mRNA. EX1003, 18:32-33; *see also* Pet.19-20; EX2013, ¶33.

The CDSs are designed to anneal⁴ to mRNA molecules with a poly-A tail. According to Petitioner, “Linnarsson discloses a cDNA synthesis primer... that includes a sequence of thymines....” Pet.17. 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.49, 17; EX1002, ¶138; EX1003, 24:13-20, Fig.2, Fig.11; *see also* Pet.67. Thus, these CDSs are able to anneal to any mRNA molecule with a poly-A tail in a well. EX1003, 18:27-30; Pet.17, 55; EX2013, ¶34. Petitioner admits that “the purpose of Linnarsson’s method is gene expression analysis, which a POSA would have understood *contemplates the analysis of substantially all mRNA molecules of a cell....*” Pet.55.

The TSOs are designed to anneal to newly-synthesized single-stranded reverse-transcribed cDNA with a poly-C sequence. EX1003, 16:18-17:2; 18:19-26; Pet.18-19; EX2013, ¶35. In the process of reverse-transcribing mRNA into cDNA, Linnarsson describes a reverse transcriptase that causes two to five cytosines to be added to one end of the single-stranded cDNA. EX1003, 16:18-31;

⁴ “Annealing” is the joining of two complementary strands of nucleic acids through hydrogen bonding. EX1002, ¶¶56, 86; EX1003, 13:3-10; EX1009, 1.

Pet.18-19. 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.18-19; EX1003, 18:19-23. The TSO annealing to cDNA causes "the reverse transcriptase to switch 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[s]" are sequenced. EX1003, 18:27-19:11; Pet.19-20; EX2013, ¶35.

Linnarsson provides only two examples of the STRT method—Examples I and II. Example I employs a biotinylated CDS and a TSO with a restriction enzyme (Bts) cut site on the 5' end of the cell-tag. EX1003, 23:9-19; EX2013, ¶¶36-37. Figures 2-4 depict aspects of the Example I STRT method. *See* EX2013, ¶¶36-37, 45-47. Figure 2 is a generic overview demonstrating how the CDS anneals to mRNA with a poly-A tail, and TSO anneals to a poly-C sequence of reverse-transcribed cDNA. EX2013, ¶36. Figures 3 and 4 show a "typical" TSO and CDS sequence used in Figure 2. *Id.* Figure 2 includes no explanation or depiction of purification, sequencing, or any of the other steps POSITA would recognize as necessary to prepare and subsequently analyze a cDNA library. EX1003, 4:14, 51; EX2013, ¶36. Moreover, POSITA would have understood that the black lines extending from the CDS and TSO in Figure 2 represent STRT

method features, including the disclosed TSO and CDS used in Example I, which include the amplification primer sequence (“APS”)⁵ and Bts cut site for the TSO, and at least the APS and biotin for the CDS. EX2013, ¶36.

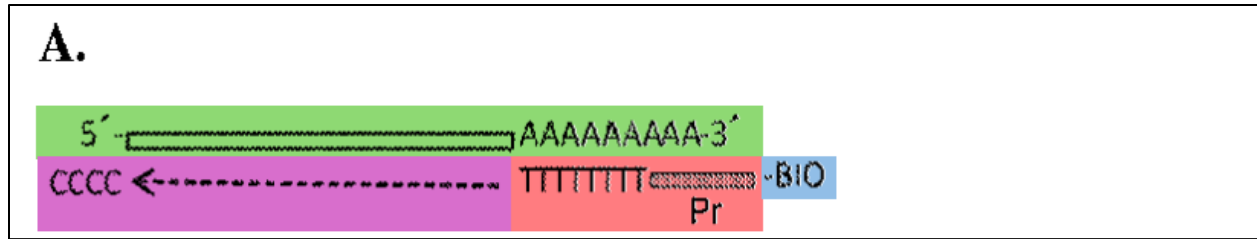
Example II describes another example of the STRT method. EX1003, 31:3-32:10. Example II also employs a biotinylated CDS and a restriction enzyme (Bts) cut site on the 5’ of the reverse transcribed DNA. EX1003, 32:10-27. Figure 11 is discussed with and depicts steps of a method used in Example II (which are the same methods used in Example I), and includes details of the process in Panels A-F, which are summarized here. EX1003, 37:31-32, 5:28-6:12; Pet.16-21; EX2013, ¶33.⁶

⁵ The APS allows the first strand of cDNA to be amplified by PCR. EX1003, 19:18-23.

⁶ The Fig.11 disclosures are also consistent with the disclosures in Example I. As in Example I, Figure 11 uses a biotinylated CDS and a TSO with a cell-tag and a Bts cut site to generate a 5’-end fragment cDNA library to analyze gene expression of a cell. EX1003, 5:28-6:12, Fig.11.

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, 23:21-25:21.⁷ 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.18-21; EX2018, 23:21-25:21; EX2013, ¶38. A cell-tag (according to Petitioner) is optionally incorporated between the primer and the poly-T tail. Pet.18 (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 annealed structure and reverse transcribes the mRNA to create 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, ¶38.

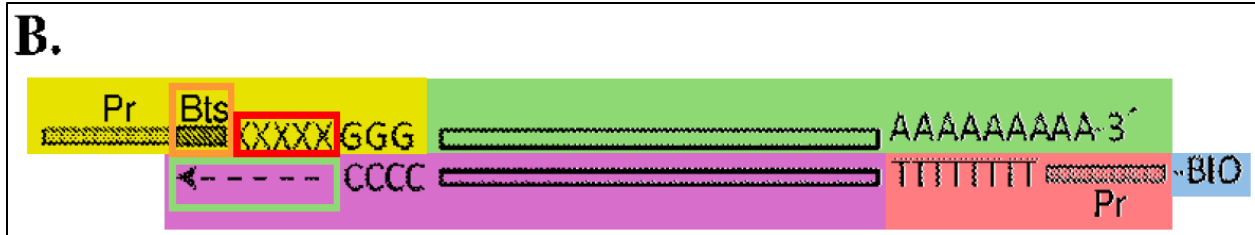
⁷ The admissions of Dr. Cooper in EX2018, his deposition transcript from an IPR on the related '981 Patent, are relevant here. As Petitioner argues, "the claims of the '197 Patent at issue here are highly similar to those of the '981 and '013 Patents." Pet.5; Pap.8, 1 (arguing that the claims of '981 "are substantially the same as those at issue here" and include "virtually identical arguments").



Panel B: To continue cDNA synthesis, Linnarsson uses a TSO (yellow).⁸ 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 TSO (yellow) as a template, which adds the cell-tag and Bts to the 3' end of the cDNA (depicted by the dotted arrow boxed in green). EX1003, 5:31-33, Fig.11 (Panel B); EX2013, ¶39.⁹

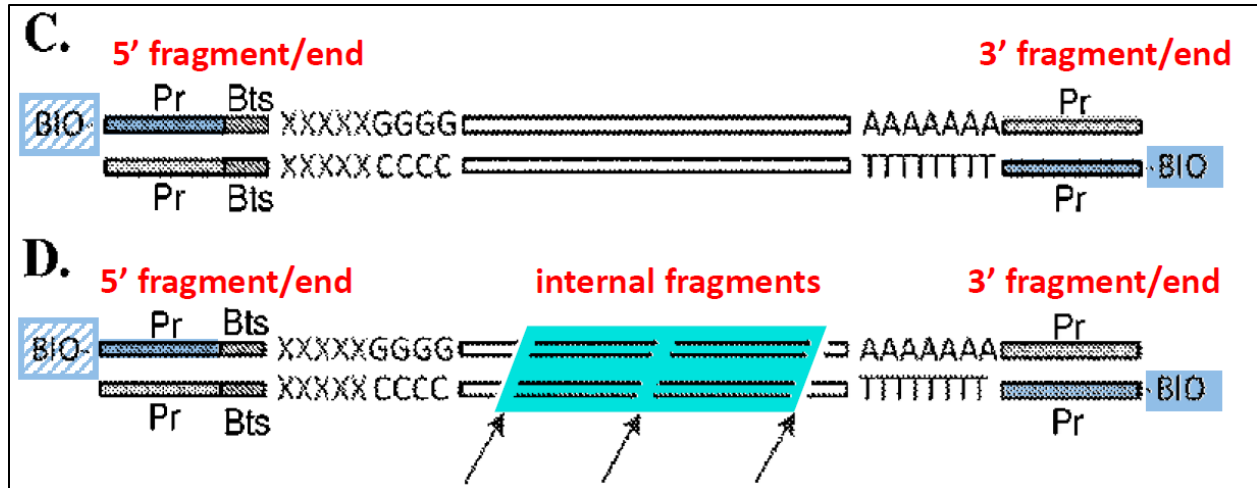
⁸ While Dr. Cooper's declaration describes Panel B's top strand as the second strand of cDNA and not as mRNA (EX1002, ¶112), in his '981 deposition Dr. Cooper said the figure is "unclear" and admitted the top strand could either be mRNA, consistent with 10x's description above, or cDNA. EX2018, 26:13-27:12.

⁹ Linnarsson describes using RNase to digest the mRNA molecule. EX1003, 16:10-17.



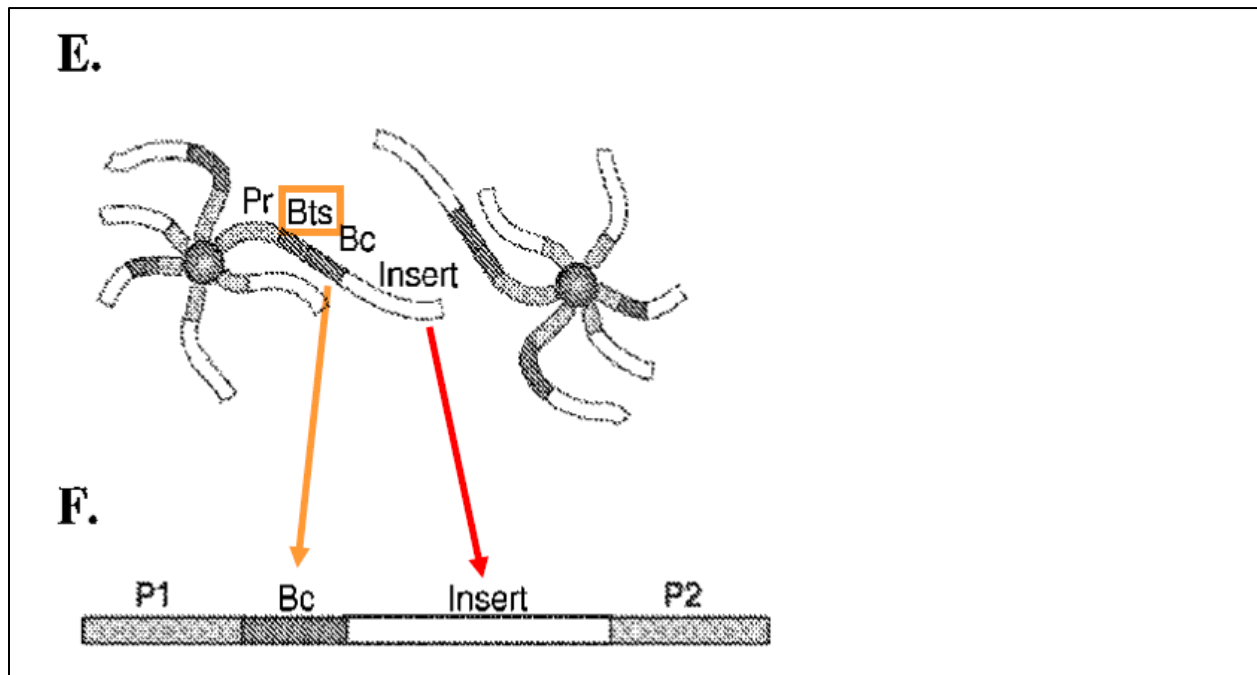
Panels C-D: The cDNA sequences generated in Panels A-B are then amplified via PCR, at which point a biotin (shaded blue) is added to all double-stranded cDNA on their “5’ ends,” resulting in the eventual “5’ fragments” having biotinylated ends.¹⁰ EX1003, 25:17-20, Fig.11 (Panel C); EX2018, 28:19-29:7. Following PCR, the sequences undergo a “fragmentation step” using a DNase enzyme. EX1003, 6:3-4, Fig.11 (Panel D), 12:4-8; EX2018, 29:8-13. Panel D’s “internal fragments” (teal) are “washed away” (and are therefore never sequenced). EX1003, 6:3-4, 26:26-26; EX2013, ¶40.

¹⁰ Each single stranded nucleic acid (whether *single*-stranded RNA, or an *individual* strand of double-stranded DNA), has a 5’ and 3’ end. EX1002, ¶57. 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.

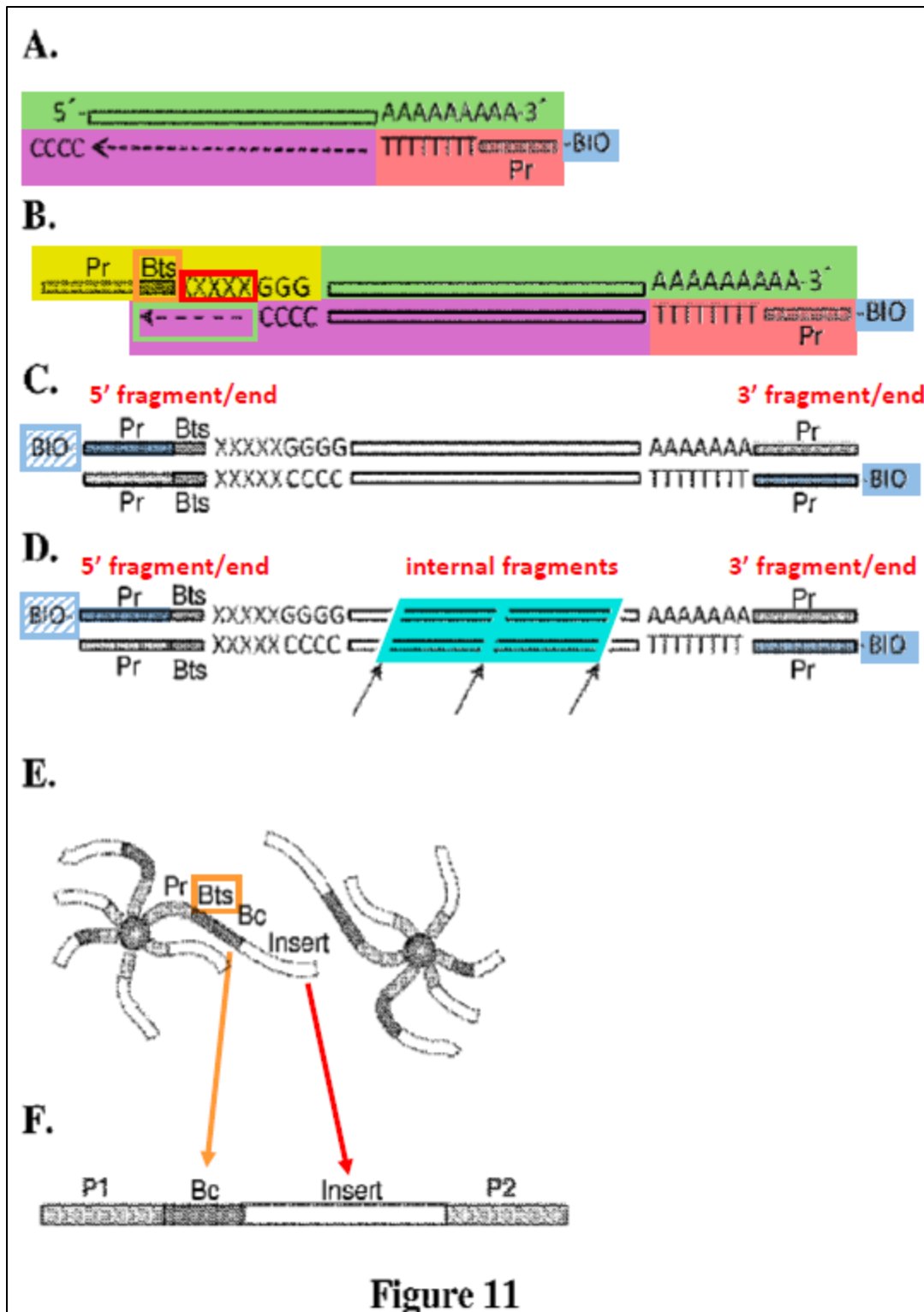


Panels E-F: The remaining biotinylated and fragmented DNA segments—the “5’ fragments” with “barcode (Br) and BtsCI site (Bts)” and the “3’ fragments” (which do not have a Bts site) from Panel D—are then bound to beads. EX1003, 6:5-6, 23:13-16, 26:21-26 32:18-27, Fig.11 (Panels D-E); EX2018, 31:12-22; *see also* EX1003, 21:13-25, 27:6-28:2, 35:23-36:9; EX1002, ¶175; EX2018, 43:21-44:22; EX2013, ¶¶42-43. 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, ¶42; 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” (Panel F) so that those fragments may be

further processed for next-generation sequencing. EX1003, 6:9-12; EX2018, 32:7-14.



These described steps are depicted together below.



POSITA would have understood that after the cDNA library is generated, as shown in Examples I-II and Figure 11, further processing steps (after, *e.g.*, Figure

11 Panel F) are contemplated to prepare it for sequencing, including in NGS. *E.g.*, EX1003, 21:13-25, 48:9-10 (Claim 27); EX2013, ¶45. For example, Linnarsson discloses that the cDNA library can be further fragmented, such as for use in shotgun sequencing or to bring the fragments to an optimal size for the particular sequencing approach being employed. EX1003, 21:13-25 (“The method of preparing a cDNA library described herein can further comprise processing the cDNA library to obtain a library suitable for sequencing...”), 22:5-21; EX2020, 57:4-20; EX2013, ¶45.

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, ¶46. 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, ¶46.

Examples I (including Figures 2-4) and II (including Figure 11)—Linnarsson’s only provided examples—both affirmatively use CDS and/or TSO, biotin, a restriction site (*e.g.*, the Bts cut site), and fragmentation, all of which are essential features of Linnarsson’s methods. EX2013, ¶47; EX1003, Figs. 2-4, 11, Examples I-II. Figure 4, for example, depicts a polynucleotide sequence with an APS, a cell-tag, a poly-dT RCS, and a Bts cut site. EX1003, Fig.4; EX2015, 1.

POSITA would understand Figure 4 as illustrating additional sequence details of a typical CDS used in Figure 2, and not as attempting to illustrate other molecules (like biotin), which the text confirms are part of the Example I process. EX2013, ¶¶36, 47. The CDS is designed to target the mRNA molecules in the cell, and triggers reverse transcription to generate the strand of cDNA with the poly-C tail. EX1003, 5:30-31, 15:1-11, 25:2-22, Figs.2, 11. The TSO then binds and triggers the generation of the rest of the strand of cDNA. EX1003, 16:18-17:2, 18:19-26, Figs.2, 11. Together, these two reverse transcription steps ensure the tags and PCR primers are added. EX1003, Figs.2, 11. And the biotin ensures the tagged fragments are bound to the beads, and not washed away with the internal fragments and untagged polynucleotides the researcher is not interested in sequencing (*e.g.*, DNA in Linnarsson's method). EX1003, 21:13-25, 35:23-36:9. This is how Linnarsson discloses purifying its sequences that will become the cDNA library. EX2013, ¶47. The Bts cut site located on the 5' fragments is then recognized by the Bts enzyme, and when cut releases the 5' fragments for clean-up and sequencing following purification. *See* EX1003, 12:4-8 (defining "cDNA library" as "DNA (cDNA) fragments."). This is further confirmed by the absence of any alternative approaches in Linnarsson for performing the STRT method. EX2013, ¶47.

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.22; EX2013, ¶¶48-52. 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 to be barcoded prior to amplification. EX1004, 2; Pet.22. The encoding oligonucleotide (with 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 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.22; EX2013, ¶49.¹¹ McCloskey’s random barcode is composed of nucleotides, where each nucleotide is one of the four deoxyribonucleotides.¹² EX1004, 4; *see also* Pap.9 (“RD”) at 16-18;

¹¹ Alleles are different versions of the same gene. EX2003, 3; EX1002, ¶60.

¹² “Deoxyribonucleotides” are nucleotides that have a deoxyribose as their sugar component. EX1002, ¶¶55-56; EX2014, 31; EX1001, 7:23-48. The four natural

EX1002, ¶76. McCloskey uses “seven nucleotides for the barcode, giving 16,384 possible 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; EX2013, ¶49; EX1002, ¶60. McCloskey’s method involves lysing the cells and combining their contents (including the DNA) before tagging the copies of a particular gene to determine the presence of alleles. *See* EX1004, 2, 5; EX2013, ¶50. 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.

According to McCloskey, incorporation of its oligonucleotides into the amplified DNA for the particular gene of interest allows researchers to identify and remove contaminant sequences (that do not include the particular batch stamp) 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.*

deoxyribonucleotides are adenine (A), guanine (G), cytosine (C), and thymine (T).

EX1002, ¶¶55-56; EX2014, 31.

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, ¶50 (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 any alleles or mutations of the target gene were present *in the sample when it was tagged (but not any particular cell in the multi-cell sample)*. EX2013, ¶¶51, 68-71; EX1004, 2, 5. And unlike Linnarsson, McCloskey’s disclosures are not focused on mRNA. EX1003, 1; EX1004, 4; EX2013, ¶52.

2. Petitioner Failed To Establish McCloskey Is Prior Art

Petitioner failed to establish McCloskey is, in fact, prior art to ’197. *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); *Liquidia Techs., Inc. v. United Therapeutics Corp.*, IPR2020-00770, Pap.45, 56-57 (Oct. 8, 2021) (similar,

rejecting Petitioner’s “cavalier attitude” to “self-help” by attempting to cure a defective declaration by filing a new declaration without authorization). 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.*

C. McCloskey II (EX1055)

U.S. Patent Publication 2007/0020640 (McCloskey II), titled “Molecular Encoding Of Nucleic Acid Templates for PCR And Other Forms Of Sequence Analysis,” is a sister patent application of McCloskey. Pet.25-26. Petitioner relies on McCloskey II only in Ground 3 (for claims 13-19) for the “addition[al]” teaching that the “barcode sequence may comprise up to 30 nucleotides.” Pet.4-5, 26. As with McCloskey, McCloskey II does not allow a user to determine the cell from which a polynucleotide originated in a multi-cell sample.

IV. Level Of Ordinary Skill In The Art Of ’197

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.13-14; EX2013, ¶¶25-26.

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 definition for “sample.” Pet.26.

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 primary theory¹³ is apparently that

¹³ Petitioner's expert, Dr. Cooper, provides this theory about what the combination would be in EX1002, ¶168, which the Board cited repeatedly at institution (although Petitioner's precise Ground 1 combination is unclear, especially based on the Petition itself). RD.14 (explaining Petitioner's theory and citing EX1002, ¶168), 17; Pap.8 (Rehearing Request), 15 (referring to Board's institution decision in IPR2023-00876 and stating “Petitioner's proposed combination and rationale... with respect to the '981 Patent are the same as... the '197 Patent”); *see also Parse Biosciences v. 10x Genomics, Inc.*, IPR2023-00876, Pap.7, 21-22 (Oct. 13, 2023)

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-stamp, and seven of those nucleotides as a second tag that performs the function of McCloskey’s barcode. Pet.43 (citing EX1002, ¶168); RD.14, 17 (citing EX1002, ¶168); Pap.8, 14-15. Petitioner also includes a conclusory “alternativ[e]” theory where, instead of “conceptually divid[ing]” Linnarsson’s cell-tag, the TSO and CDS would both

(citing ’981 EX1002, ¶192). 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).

be used, one to identify the cell of origin and the other to distinguish tagged polynucleotides. Pet.43.¹⁴ Petitioner's theories fail.

First, Petitioner fails to explain how Linnarsson meets the requirement of sequencing "the tagged polynucleotide." *See infra* §VI.A. **Second**, Petitioner's

¹⁴ PO understands this alternative theory to be based on Linnarsson and McCloskey, consistent with the remainder of Ground 1 and limitation [1F]. Pet.37. Consistent with this understanding and Petitioner's reliance on McCloskey only for its seven-nucleotide barcode, PO understands Petitioner's alternative theory to be that Linnarsson's cell-tag would be in the CDS and McCloskey's seven-nucleotide long barcode would be in the TSO or vice versa. *See* Pet.43 (stating only that "such a method would be identical to Linnarsson's method, except that one of the CDS tag or the TSO tag is modified to be different for each tagged cDNA" without explaining why a POSITA would have been motivated to make such a modification, how it would have been done for either the CDS tag or the TSO tag, or why a POSITA would have had REOS in doing so) (citing EX1002, ¶170 (simply parroting Petition with no added explanation)). Any other theory would be even more unsupported and unexplained, including as to what McCloskey is being used for, why POSITA would have been motivated to combine Linnarsson and McCloskey, and whether there is REOS.

various arguments that POSITA would have been motivated to combine Linnarsson and McCloskey fail. *See infra* §VI.B. For example, 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.B.1. **Third**, 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. *See infra* §VI.C. **Fourth**, to the extent Petitioner relies on McCloskey for the first tag sequence, Petitioner fails to show its combination results in the claimed “first tag sequence.” *See infra* §VI.D.

A. Petitioner Fails To Show Linnarsson Teaches “Sequencing The Tagged Polynucleotide” [1G]

Petitioner argues limitation [1G] is met because Linnarsson discloses “sequencing is performed *on the entire tagged polynucleotide*, which includes the sample sequence and both tag sequences.” Pet.44; EX2013, ¶¶59-65. However, Petitioner failed to prove this is so. Petitioner ignores Linnarsson’s intermediary steps and bases its conclusion merely on vague references to sequencing. Pet.44. But as discussed below, Petitioner ignores that Linnarsson’s disclosed STRT method (the process on which Petitioner relies, *supra*, 6-7) sequences only the “5’ fragment” and fails to address whether or how “sequencing is [or would be] performed on the *entire* tagged polynucleotide,” or whether or how sequencing

only the “5’ fragment” (*i.e.*, what Linnarsson actually discloses) is sufficient to satisfy Petitioner’s argument for meeting the claim element. EX1001, Cl.1; EX2013, ¶59.

Petitioner’s own citations fail to show Linnarsson discloses sequencing the “entire tagged polynucleotide” as Petitioner argues. Pet.44 (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” and simply says “sequencing is performed,” but does not provide details or specify what or how much is sequenced. EX1003, 4:8-13; EX2013, ¶63. Petitioner’s second and third citations confirm Linnarsson does ***not*** sequence the “entire tagged polynucleotide,” as Petitioner’s theory requires. EX1003, 19:28-32, 21:13-25; EX2013, ¶63. Petitioner’s second citation explains that the “5’ APS can be designed to facilitate downstream processing of the ***cDNA library***.” EX1003, 19:28-32. It says nothing about sequencing, and refers only to creation of a “cDNA library”—which Linnarsson ***defines*** as “a collection of cloned complementary DNA (cDNA) ***fragments***.” EX1003, 12:4-8. Petitioner’s third citation explains that the cDNA library (created after fragmentation, as shown in, *e.g.*, Fig.11) may be further processed (including by additional fragmentation) to make it suitable for high-

throughput sequencing:¹⁵ “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, ¶63; EX1002, ¶175; EX2018, 41:10-43:20. This disclosure similarly fails to indicate the “entire tagged polynucleotide” is sequenced.

Petitioner fails to address Linnarsson’s various references to fragmenting the cDNA, including its “cDNA library” definition, and sequencing the 5’ fragment specifically. For example, Linnarsson teaches the “amplified library is *fragmented*

¹⁵ Dr. Cooper appeared to raise a new theory at deposition that Linnarsson’s disclosures of fragmenting the cDNA generated in its method was merely optional. EX2020, 49:22-50:21. This is improper. *In re NuVasive, Inc.*, 841 F.3d 966, 972-73 (Fed. Cir. 2016); *Intelligent Bio-Sys.*, 821 F.3d at 1369-70; *Apple Inc.*, IPR2022-00981, Pap.34, 35-36. It is also inconsistent with Linnarsson’s other disclosures (*supra*, §III.A), and the Petition made no attempt to meet Petitioner’s burden of showing Linnarsson discloses creating a cDNA library without fragmentation, including, e.g., in view of Linnarsson’s express definition of its “cDNA library” as “a collection of cloned DNA (cDNA) *fragments*.” EX1003, 12:4-8. *See supra*. Moreover, neither the Petition nor Dr. Cooper cite any Linnarsson disclosures that do not use fragmentation. Pet.44; EX1002, ¶¶172-176.

to 200–300 bp using controlled DNase digestion,” which creates 5’, 3’, and internal “fragments.” EX1003, 6:3-6, 21:13-25, 27:6-28:2, 35:23-36:9; *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, ¶¶60-61; *supra*, §III.A. Thus, those internal fragments are ***not sequenced***. EX2018, 41:10-44:22. Moreover, the “3’ fragment” does not contain a Bts sequence and, as a result, ***is not released from the “beads”*** to which it is 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, ¶¶60-61. Indeed, Linnarsson does not disclose sequencing the “3’ fragments” of the “tagged polynucleotide” (which includes the CDS sequence and any tag within it). *Supra*, §III.A; EX2013, ¶¶60-61; EX1002, ¶175; 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.44; EX1002, ¶175 (citing EX1003, 21:13-25); EX2018, 41:10-43:20.

In view of Linnarsson’s disclosures about fragmenting, washing away fragments, and sequencing only the “5’ fragment,” Petitioner’s bare assertion that this limitation is met because Linnarsson teaches “sequencing is performed on the

entire tagged polynucleotide” is plainly wrong. Pet.44; EX2013, ¶¶59-63; *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); *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).

Petitioner’s sequencing argument is also contradicted by Dr. Cooper’s other statements, where he admits that “NGS is a type of high-throughput sequencing technology that uses parallel sequencing of many fragments of DNA.” EX1002, ¶96; EX2020, 57:4-20. Dr. Cooper identifies the “Roche/454” and the “SOLiD System” as two such NGS technologies, admits these “platforms...generally have a common workflow to produce sequence reads starting with preparing a sequencing library,” and states that this preparation is “often accomplished by *random fragmentation of input DNA*.” EX1002, ¶¶95-97; EX2020, 57:4-20. Indeed, the Petition and Dr. Cooper argue for claims 21 and 22 that “Linnarsson used the SOLiD platform sequencing” and that it would have been obvious to use the SOLiD or Roche 454 platforms for sequencing. Pet.62 (citing EX1002, ¶243). The SOLiD platform—which “has an optimal size... on the order of a few

hundred, maybe 400 nucleotides”—uses fragmented cDNA libraries.¹⁶ EX1002, ¶¶95-97; EX2020, 57:4-20. Critically, Petitioner’s claim 21 arguments do not assert any modification of Linnarsson to introduce this fragmenting. Thus, Petitioner’s assertions are consistent with (and, indeed, assume) Linnarsson disclosing a fragmentation step.

Additionally, with respect to Petitioner’s CDS theory, where both tag sequences are included in the “conceptually divided” cell-tag located on the CDS (Pet.43), and Petitioner’s “alternative[]” theory, where one of the two tags are included in the CDS (Pet.43), both fail for the additional reason that the CDS is part of the 3’ fragment, and Petitioner identifies no teaching in Linnarsson showing the 3’ fragment is *sequenced*. EX2013, ¶64; *see* EX1003, Fig.11 (Panel E); EX1003, 6:8; EX2018, 43:21-44:22; *cf.* Pet.44 (Petitioner’s arguments premised on Linnarsson disclosing sequencing “the entire tagged polynucleotide, which includes the sample sequence *and both tag sequences*”). Petitioner identifies no disclosure indicating these fragments are *ever released* for sequencing. Pet.44. Indeed, as Petitioner’s expert admits, nowhere does Linnarsson describe releasing

¹⁶ Dr. Cooper recognizes it also requires biotinylated polynucleotides: “The SOLiD System *utilizes a biotin-streptavidin interaction* to immobilize the sample polynucleotides to the bead.” EX1002, ¶241.

any “3’ fragment” from the bead or sequencing it. EX2013, ¶¶64; EX2018, 43:21-44:22.¹⁷ Thus, Petitioner’s CDS theory fails for Ground 1.

Petitioner’s sequencing arguments fail under its “alternativ[e]” theory for another reason. Pet.43. Even if the 3’ fragment were somehow released and sequenced, the 5’ and 3’ fragments would be *separate* fragments. EX2013, ¶¶47, 64. Petitioners identify no disclosures of associating the 3’ fragment (containing the first tag or some part thereof) with the 5’ fragment (containing the second tag or some part thereof) and the sample polynucleotide with which the tags are meant to be associated.

B. Petitioner’s Claim 1 Motivation To Combine Fails

1. McCloskey’s Tags Are Insufficient To Tag “Each Polynucleotide” In Linnarsson’s Gene Expression Analysis

Both of Petitioner’s Ground 1 theories rely on incorporating McCloskey’s barcode teachings into Linnarsson’s method. Pet.43 (citing EX1002, ¶170).

¹⁷ Nor does Petitioner offer any explanation of how or why, in light of Linnarsson’s disclosures above, this limitation would be disclosed or obviated by its alternative argument about using “both tag sequences in Linnarsson’s TSO and CDS...in combination, wherein one is used to identify the single-cell origin of the tagged polynucleotide, and the other is used to distinguish tagged polynucleotides originating from the same cell.” *See* Pet.43.

Petitioner asserts there is a motivation to combine Linnarsson with McCloskey because McCloskey “provides the exact solution” to Linnarsson’s alleged amplification bias problem “[b]y incorporating a second tag in an oligonucleotide that uniquely identifies *each sample polynucleotide* prior to amplification.”¹⁸ Pet.41-42; *see also* Pet.52 (“the combination...teaches attaching unique molecule-tag sequences...to each sample polynucleotide...”); Pap.8, 5 (“each tag has its own unique sequence that is random”), 9, 10, 11 (“Petitioner’s proposal associates each sample polynucleotide with a *different and unique* random sequence...”)(emphasis original), 13, 15. According to Petitioner, Linnarsson teaches “tagg[ing]” “substantially all mRNA molecules of [each] cell,” and “a POSA would have understood that [Linnarsson’s] method was designed to be applied to substantially all mRNA molecules of a given cell.” Pet.54-55; EX1002, ¶222 (“the released mRNA sample comprises substantially all mRNA molecules of said cell... this method would provide associating a tag with substantially every sample

¹⁸ This is, again, the Petition’s argued-for motivation, and Petitioner is the master of its own Petition. *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1367 (Fed. Cir. 2023).

mRNA molecule”).¹⁹ Thus, *per Petitioner’s argued-for understanding of Linnarsson*, substantially all mRNA in a cell is tagged (not just a subset of it). Pet.54-55 (“the purpose of Linnarsson’s method is gene expression analysis, which a POSA would have understood contemplates the analysis of substantially all mRNA molecules of a cell”; “Because [Linnarsson’s] mRNA is indiscriminately released from each single cell without any elimination or filtration, the released mRNA sample that is tagged, amplified, and sequenced comprises substantially all mRNA molecules of said cell”); EX1002, ¶¶222, 166, 91 (“To solve this problem [of amplification bias].... Every sample and the polynucleotides within every given sample are first uniquely tagged before being amplified...”).

However, Petitioner’s citations to McCloskey show that *McCloskey does not have enough barcodes to tag each mRNA molecule of Linnarsson*, as Petitioner’s theory requires. 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. 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,

¹⁹ Petitioner offers no additional modifications of its combination to satisfy claim 25, which is part of Ground 1. See Pet.54-55. Thus, Petitioner’s claim 25 understanding applies equally to claim 1.

3-5; EX1002, ¶60. Petitioner invokes McCloskey’s teachings of a 7-nucleotide barcode and maps these barcodes to the “second tag” (to uniquely identify each polynucleotide). Pet.42-44 (citing EX1002, ¶168); EX1004, 4 (“16,384 possible barcodes”); EX2013, ¶¶77-83; *see* Pet.54-55.

While Petitioner’s theory requires that “each,” “every,” and “substantially all” mRNA be uniquely tagged, 16,384 barcodes would not be enough to tag each mRNA molecule in Linnarsson based on Petitioner’s own numbers. 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 a mammalian cell (as identified in the Petition). EX1002, ¶168; RD.14 (explaining Petitioner’s theory and citing EX1002, ¶168), 17; Pet.41 (citing EX1002, ¶166 (“By incorporating a second tag in an oligonucleotide that uniquely identifies each sample polynucleotide prior to amplification, McCloskey’s method is able to uniquely account for each individual sample polynucleotide and ‘solve’ amplification bias.”)), 42 (citing EX1002, ¶167 (explaining that Linnarsson “tag[s] each sample polynucleotide uniquely”), ¶91 (“every sample and the polynucleotides within every given sample are first uniquely tagged... uniquely tagging the sample...results in addressing amplification bias...”)), 67 (providing estimate for number of mRNA molecules in mammalian cell); EX1002, ¶222 (“Linnarsson

describes a method which is designed to be applied to substantially all mRNA molecules of a given cell.”)); EX1004, 4; EX1054, Abstract; *see also* n.13. Indeed, as Petitioner argued and POSITA would have known, uniquely tagging all target nucleic acids, such as mRNA, would have required many more tags than the number of nucleic acids being targeted for tagging.²⁰ EX1002, ¶77; Pet.65-67 (acknowledging that “e.g., *at least 100 times [more unique tags] than the number of sample polynucleotides*” are required to ensure “that each sample polynucleotide is uniquely tagged.”) (citing EX1002, ¶254); 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.”); EX2013, ¶¶77-80. POSITA would thus not have been motivated to modify Linnarsson’s method to tag “each sample polynucleotide” (Pet.41-42) 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.²¹

²⁰ *According to Petitioner’s arguments*, tagging each mRNA molecule in a typical mammalian cell would require a minimum of 5,000,000-30,000,000 unique sequences. *See* Pet.66-67; EX1002, ¶255.

²¹ Because Petitioner has argued that “each,” “every,” or “substantially all” mRNA molecule(s) is/are tagged uniquely, Petitioner cannot argue on Reply that tagging a

EX2013, ¶¶80-83; *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 Grounds 2-3, which rely on Ground 1) fails. *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]”).

small subset of the sample’s mRNA molecules with a second tag somehow satisfies its Petition theory (Pet.40-42) and resolves amplification bias (EX1002, ¶¶91, ¶166); and, as a factual matter, this is wrong. EX2013, ¶82; *infra*, §VII.

Tagging only some of the mRNA molecules would not allow POSITA to determine the number of molecules in the sample, which, as Petitioner argues, would have been understood to be substantially all the mRNA in the sample (Pet.55; EX1002, ¶222), because many of the sample molecules would remain *untagged*. EX2013, ¶82. Thus, as argued by the Petition, this would alter Linnarsson’s method and fail to satisfy its objective of analyzing substantially all of a cell’s mRNA. Pet.55; EX1002, ¶222.

2. McCloskey Does Not Describe Single Cell Analysis

Petitioner asserts that POSITA would have combined Linnarsson and McCloskey because both describe single cell analysis. Pet.38-39. 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.

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. EX1002, ¶68; EX2013, ¶¶69-71. McCloskey discloses the possibility of tagging (for detecting contamination) *when the sample consists of a “single cell.”* EX1004, Abstract, 7; EX2013, ¶¶67-71; EX2018, 38:6-39:17. In ’197, 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, ¶¶68-70. 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, ¶¶67-71.

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, ¶71. 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, ¶71; 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 disclose such an isolation step*, nor did he explain why such a step be useful in McCloskey’s method. EX1002, ¶71.

Even if, *arguendo*, McCloskey’s reference to “single cell” or “single-cell samples” *did* refer to “single cell analysis,” 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 all “single cell analyses.” EX2013, ¶¶84-85; 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*, §IX. 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.1-2; *infra* §VI.D), it clearly is not. EX1004, 4; EX1003, 1; EX2013, ¶¶84-85.

C. Petitioner’s Ground 1 REOS Fails

Petitioner’s REOS argument also fails for its Ground 1 theories, 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.41-42. 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.B.1; EX2013, ¶86; *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.41-42. 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.

D. Petitioner Fails To Show A “First Tag Sequence” Is Obvious

Petitioner’s attempt to show the claimed “first tag sequence” is obvious also fails in connection with at least its “conceptually divided” tag theory. First, Petitioner maps “first tag sequence” 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 [1E] and [1H]* to Linnarsson’s “cell-tag.” Pet.36-37, 44-46. For example, Petitioner states “Linnarsson discloses that the tag [*sic*] polynucleotide comprises a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein that first tag sequence distinguishes the sample polynucleotide from sample polynucleotides from other cells.” Pet.36. But then, in attempting to establish obviousness of *element [1F]*, Petitioner and its expert improperly *abandon* their relied-on *existing* Linnarsson cell-tag (the Petition’s “first tag” for elements [1E] and [1H]) and rely instead on a *modified* version that *functions like McCloskey’s batch-stamp* as the “first tag

sequence.”²² Pet.36-38, 42-44 (citing EX1002, ¶168); RD.13 (“For limitations [1A]-[1E]... Petitioner relies on Linnarsson alone.”). Dr. Cooper explains: “POSA

²² Paragraph 168 of Dr. Cooper’s declaration is inconsistent with other aspects of Dr. Cooper’s opinions (*e.g.*, EX1002, ¶¶153-156 (relying on Linnarsson *alone* 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, ¶¶169, 171. And Dr. Cooper inconsistently testified between his deposition on the ’981 and ’197 Patents, despite there being “virtually identical” theories relying on the same references. *Supra*, n.7. For example, Dr. Cooper admitted in the ’981 deposition that his ligation arguments “did not explicitly [state] a timing element” (EX2018, 54:8-21), but in the ’197 Dr. Cooper claimed that the timing was “explicitly there” (EX2020, 39:10-11). Dr. Cooper testified inconsistently elsewhere, too. *Compare* EX2018:21-22:12 (admitting Figure 11 discloses “some of the – the key steps” of Linnarsson’s method) *with* EX2020, 9:20-10:1 (“So I don’t think it uses the word “key.” It has steps that are used, that can be used. It describes it as optionally usable in the STRT method.”); *compare* EX2018, 43:21-44:25 (testifying that he did not recall citing anything in Linnarsson where the 3’ fragment was released from the bead or sequenced) *with* EX2020, 25:22-27:13

could 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....*" EX1002, ¶168; *see also* RD.17-18.

Petitioner cannot rely on disclosure in one reference to cover a limitation, and then *reverse course* and modify that same disclosure using *another* reference in a subsequent limitation. *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*, and petitioner cites no McCloskey disclosure for this limitation. *See* Pet.38-44; EX2013, ¶¶66-71. ***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 cells"); EX2013,

(testifying that Linnarsson's embodiments that do not depict beads disclose the 3' fragment being sequenced). 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").

¶¶67-71; *supra*, §VI.B.2. McCloskey's batch-stamp 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, ¶¶67-71. This is how McCloskey's batch-stamps confirm a sequence is not from a **contaminant**. EX1004, 4. 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; EX1002, ¶¶153-156. 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.

Third, even if McCloskey's batch stamp could serve as the "first tag," Petitioner's motivation to modify Linnarsson's tag to implement the first 6-8 nucleotides to perform the function of **McCloskey's 'batch-stamp'** fails. EX1002, ¶168; Pet.42-43; *supra*, §VI.B.1. 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, ¶¶72-76. 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, ¶¶72-76. 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 and prevents data being misattributed from a first cell to a second cell. But McCloskey’s batch-stamp 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, ¶¶74-75.

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, ¶¶157-171; EX2013, ¶76. 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. *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*, IPR2019-00569, Pap.73, 29-34.

E. Petitioner’s Claim 8 Argument Fails For Additional Reasons

Petitioner argues claim 8 is met and relies on only Linnarsson’s CDS as the “oligonucleotide tag” that hybridizes to the sample polynucleotide to generate the tagged polynucleotides, *not its TSO*. Pet.49; EX1002, ¶200. This is incompatible with Petitioner’s primary theory to the extent it relies on the “conceptually divided” tag being inserted into Linnarsson’s TSO, and Petitioner’s “alternativ[e]” theory, which requires there be a tag in *both* the CDS and TSO. Pet.43.

F. Petitioner’s Claim 23-25 Arguments Fail For Additional Reasons

Petitioner argues claims 23 and 24 are met because Ground 1 “teaches attaching unique molecule-tag sequences (i.e., ‘second tag sequences’) to each sample polynucleotide during the process of generating tagged polynucleotides....Because a unique molecule-tag is attached to each sample polynucleotide...the number of sample polynucleotides can be determined...”. Pet.52-54. In arguing claim 25 is rendered obvious, Petitioner similarly points to its claim 1 arguments and asserts “it would have been obvious to tag substantially every sample polynucleotides from a cell. Thus, the tagged, amplified, and sequenced samples necessarily comprise substantially all mRNA molecules from a cell.” Pet.55. As explained above, Petitioner’s combination does not provide

enough second tags to tag “each” or “substantially every” mRNA molecule in the cells Petitioner identifies. *Supra*, §VI.B.1.²³

VII. Ground 2: Petitioner’s Conclusory Combination Fails

According to Petitioner, Ground 2 builds from Ground 1’s obviousness combination for claim 1. *See* Pet.§IX.1.f.ii (addressing independent claim 1). Ground 2 fails for at least the reasons set forth above (§VI), and also (to the extent PO can divine Petitioner’s potential theories) for the reasons discussed below. Petitioner’s grab-bag of Ground 2 theories are insufficiently detailed; arguing a particular element of a claim was known in the art is insufficient to establish obviousness of the claim, which requires an explanation as to what the argued modification of prior art is and whether, why, and how the modification would be implemented in the argued combination. Pet.55-65; *Samsung Elecs. Co. v. Lynk Lab’ys, 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

²³ Petitioner limits its arguments for certain dependent claims, *e.g.*, Claim 6, to the “conceptually divided” theory and not their alternative theory. *See* Pet.47. Indeed, Claim 6, could not be met by the alternative theory, where the tags would be found on different ends of any tagged polynucleotide. Pet.43; EX1002, ¶170.

(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”). Indeed, 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 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); *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 296 (2016) (Alito J., concurring in-part).

Further, Petitioner’s Ground 2 combinations improperly rely on art not listed in the Grounds to supply limitations in the dependent claims and modify the Ground 1 Linnarsson-McCloskey combination. *See* Pet.58 (claim 5, referencing Hug), Pet.59-63 (claims 21-22, referencing Roche 454), Pet.63-65 (claim 26, relying on Albert); *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.”). Finally, various of Petitioner’s arguments regarding particular Ground 2 claims fail for additional reasons discussed below.

A. Petitioner’s Claim 5 Arguments Fail

1. Petitioner’s Motivation To Add A Tag Via Ligation Fails

Claim 5 requires “generat[ing] through at least one ligation reaction” “the plurality of tagged polynucleotides.” EX1001, Cl.5. Petitioner’s claim 5 argument fails because it provide a sufficient motivations to ligate a tag. EX2013, ¶¶88-94. Petitioner’s ligation theory is unclear, and while it could be understood to involve adding additional tags to the Linnarsson-McCloskey combination of Claim 1 (which Petitioner asserts contains two tags already) (*see* Pet.56-58), or *removing* tags from the Linnarsson-McCloskey combination of claim 1, Dr. Cooper testified that neither of these is his theory.²⁴ EX2020, 41:22-44:20.

Petitioner’s sole purported justification for the Ground 2 combination is the conclusory assertion that “it would allow for added flexibility in selecting tag

²⁴ The first theory would fail because the additional tags would be redundant.

sequences during an experiment.” Pet.58 (citing EX1002, ¶230). First, this conclusory assertion is only parroted verbatim 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* a tag 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.58 (citing EX1002, ¶230). Petitioner fails for this reason alone. *Markforged*, IPR2022-

South-Tek Sys., LLC v. Engineered Corrosion Sols., LLC, IPR2016-00136, Pap.52, 20-23 (May 10, 2017) (finding no motivation to combine where the modification rendered a feature in the primary reference redundant), *aff’d* 748 F. App’x 1003, 1007 (Fed. Cir. Sept. 20, 2018); *In re Schweickert*, 676 F. App’x 988, 995 (Fed. Cir. 2017) (non-precedential); EX2013, ¶¶92-94. With respect to the second theory, Petitioner points to no teaching and provides no explanation as to *how* POSITA would have removed the tag, and provides no motivation *why* POSITA would have modified Petitioner’s asserted Ground 1 combination this way. Pet.58; EX2013, ¶¶88-90. Petitioner’s claim 5 theory would also be incompatible with its Ground 1 “alternative theory,” which requires that the CDS and TSO each contain the first or second tag.

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”). Second, 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”), *aff’d, id.*, Pap.12 (*sua sponte* Director review); *Apple Inc.*, IPR2022-00981, Pap.34, 37. Third, 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, ¶¶92-94; Pet.57-58; *supra*, n.24.

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

2. Petitioner Has Not Shown A Tag Can Be Successfully Added Via Ligation In Linnarsson While Still Practicing The Claimed Method

Petitioner glosses over the actual complexities of the Linnarsson method that it relies on in the Linnarsson-McCloskey combination, and asserts POSITA would have simply ligated the tag to the CDS or TSO. Pet.57-58. Petitioner relies heavily on the fact that “ligation” itself was a known, conventional technique as of the priority date, and points to ’197’s admission as support. Pet.56. This misapprehends the law. A claim is not obvious because each element was previously known. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”). Moreover, whether ligation is, as a general proposition, a well-known technique does not mean it can be successfully used in any method, as confirmed by the fact that ligation of the second tag would fail to practice claim 5. *Intel Corp. v. Koninklijke Philips N.V.*, 2024 WL 725243, at *1 (Fed. Cir. Feb. 22, 2024) (nonprecedential) (affirming Board’s non-obviousness holding where petitioner’s references were “incompatible” and petitioner failed to “reconcile the conflict” between the references).

Other than ligation itself, Petitioner asserts no further modifications to Ground 1’s Linnarsson-McCloskey combination to allow the “second tag” to be

ligated “after extension” for claim 5. *Infra*, n.29. And Petitioner does not assert, let alone 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”).

(a) Petitioner’s Proposed Ligation Of A Tag To The CDS Fails

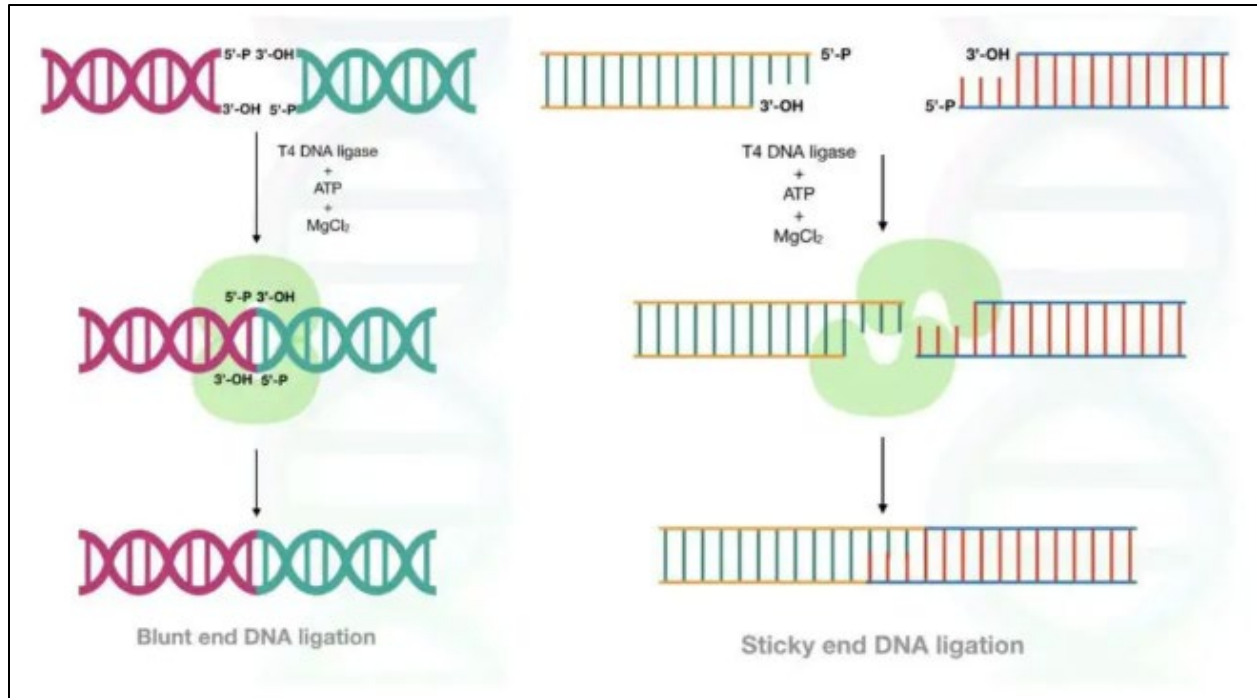
Petitioner argues a tag would be ligated to the CDS (Pet.57-58; EX2020, 32:18-33:5), but never explains precisely *how*. *Supra*, §VII.A.1. And this is not mere accident: without additional modification (which Petitioner never mentions, let alone explains²⁵), Petitioner has not shown it would be possible to ***ligate*** a tag to the CDS ***to achieve a method that practices claim 5*** based on its combination. EX2013, ¶¶95-100.

First, the biotin on the CDS’s 5’ end would block ligation of a tag to the CDS. EX2013, ¶96. As shown in Figure 11 and described in Examples I-II,

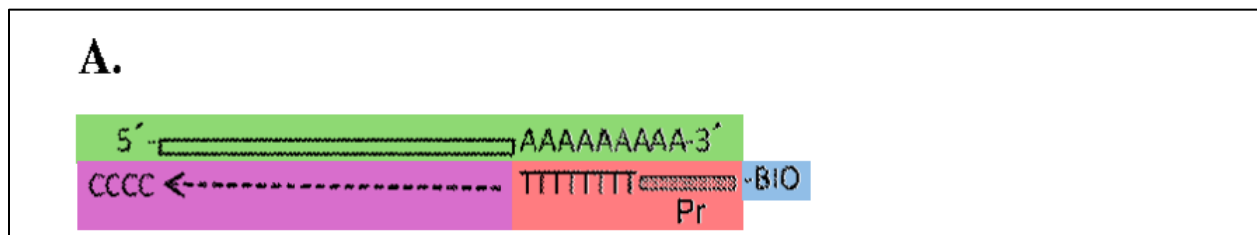
²⁵ PO thus understands Petitioner is not asserting any further modifications to Ground 1’s Linnarsson-McCloskey combination to allow the “second tag” to be ligated “after extension” for claim 5. *Supra*, n.13.

Linnarsson's CDS in its STRT method 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**-AAGCAGTGGTATCAACGCAGAGT₃₀VN-3'"); 32:19-20 ("STRT-T30-**BIO** (5'-**biotin**-AAGCAGTGGTATCAACGCAGAGT₃₀VN-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 covalent bonds between the 3'-hydroxyl of one DNA terminus and the 5'-phosphoryl of another. EX1001, 6:15-32; EX2013, ¶96. 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, 32:18-25, Fig.11.



EX1003, Fig.11; EX2013, ¶¶96-97.

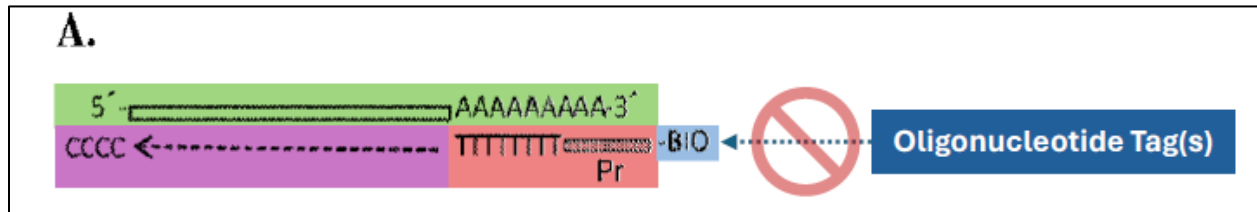
Once a biotin molecule is covalently bound to the end of these nucleic acids, as it is in Linnarsson, the biotin prevents any other molecule, including a nucleic acid tag, from being covalently bound to the end of the nucleic acid to which the biotin is already bound. EX2013, ¶96. Thus, Petitioner's tag 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. EX2013, ¶96. Petitioner's CDS theory fails. EX2013, ¶¶95-100.

Contrary to Dr. Cooper's improper new suggestion at deposition that the biotin in Linnarsson's Figure 11 is optional (EX2020, 10:19-11:1),²⁶ POSITA would not have understood the biotin in Linnarsson's STRT method to be optional, and Dr. Cooper's declaration never addressed any such optionality. *See* EX2013, ¶97. Indeed, the *only examples* of Linnarsson's method (Examples I and II) 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 (disclosed in the context of Example II), which POSITA would have understood requires biotin. *E.g.*, Pet.17-18 (citing description of and excerpting Fig.11 with a biotinylated CDS), Pet.19, 21, 30-31, 34-36, 48-49 (same); EX1002, ¶¶105, 108, 112, 137, 138, 141, 150, 151, 196, 199, 200 (same); EX2018, 23:15-25:21, 29:14-30:2; EX2013, ¶47. But even if Linnarsson's use of biotin were eliminated, this would not resolve the issues with Petitioner's theory. EX2018, 25:10-21, 31:1-22; EX2013, ¶¶97-98. Neither Dr. Cooper nor the Petition suggests eliminating biotin, or explains how Linnarsson's method would work *without*

²⁶ *Supra*, n.13, n.15.

biotinylated cDNA.²⁷ 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, ¶¶97-98.



Second, even assuming, *arguendo*, that a nucleic acid could somehow be ligated to another biotinylated nucleic acid, this ligation would be incompatible with the *further* claimed steps of the combination and requirements of claim 5. Petitioner's mapping points to no disclosure of Linnarsson releasing the CDS sequence from the beads. *Cf.* EX1003, 6:4-8 ("3' fragments remain stuck on the

²⁷ At deposition Dr. Cooper conceded he relied on what he considers multiple embodiments, but never explains how and why POSITA would mix and match across them. EX2020, 12:7-13:11; *Markforged*, IPR2022-00679, Pap.24, 14-15 ("Pointing to disparate embodiments without providing a sufficient motivation to combine them is not enough to establish the obviousness of [the claim] as a whole.").

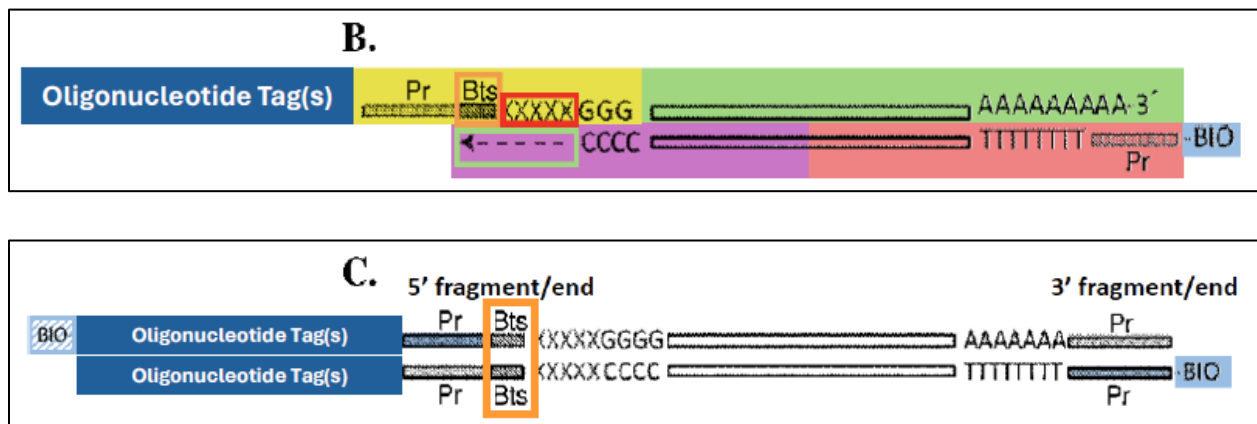
beads.”), 27:6-8, Fig.11; EX2018, 43:21-44:22. Thus, any tag allegedly ligated to the CDS would not practice the method of dependent claim 5 because Petitioner has not shown Linnarsson teaches these sequences being sequenced, as claim 1 (and dependent claim 5) requires. EX1001, Cl.1.

(b) Petitioner’s Proposed Ligation Of A Tag To The TSO Also Fails

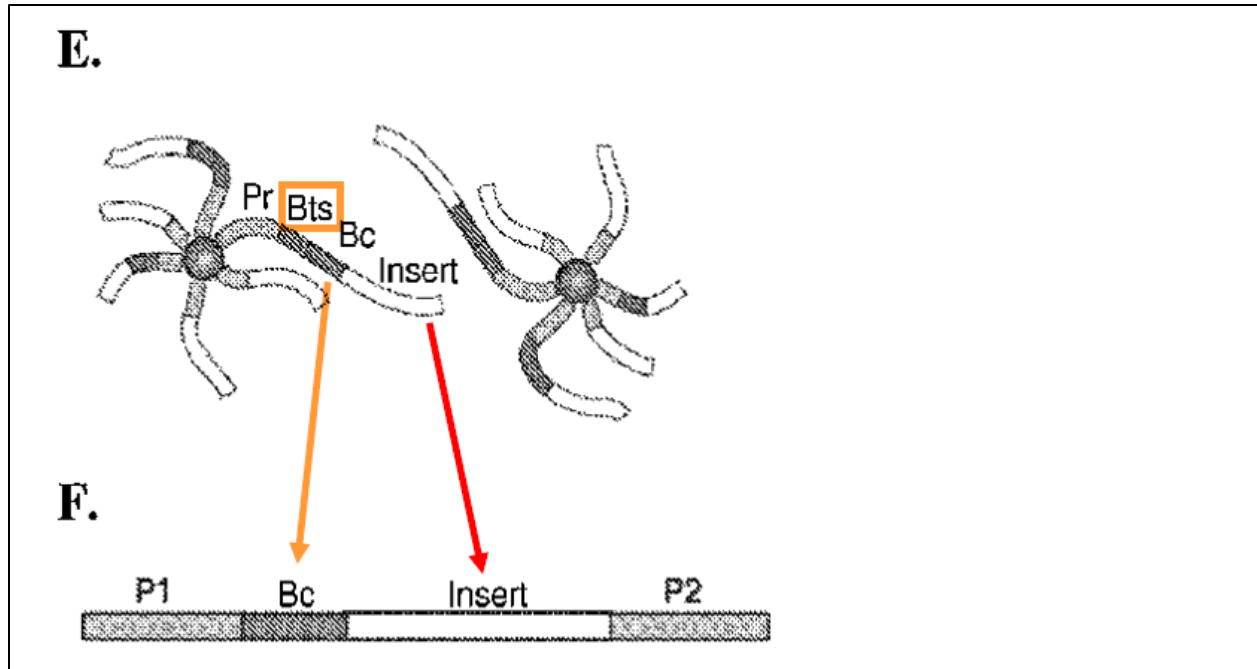
Petitioner also failed to show a tag can be ligated to the TSO to arrive at a method that practices claim 5. Petitioner asserts the tag would be ligated to the end of the TSO “after extension.” Pet.57-58. Ligating a tag to the TSO “after extension” would mean ligation occurs *after* the template switching step in Panel B is completed. EX2013, ¶¶101-102. At this point, the reverse-transcription of double-stranded cDNA in Linnarsson’s method is already complete. 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 (and Petitioner identifies) 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, ¶101. Nor did the Petition or Dr. Cooper discuss or posit one. Thus, Petitioner’s theory also fails because the tag 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, ¶101; EX2018, 21:21-32:14.

Second, even if, *arguendo*, the tag were reverse-transcribed (it isn’t), the TSO theory fails because the ligated tag would be located on the 5’ end of the Bts sequence,²⁸ shown in annotated Panels B and C below. EX1003, Fig.3, Fig.11; *see also id.* 27:6-7, 35:28-36:9; EX2013, ¶102. According to Linnarsson, any sequence on the 5’ side of the Bts sequence will ***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, ¶102.



²⁸ 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 were ligated to the end of Linnarsson's TSO, the ligated tag would *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, ¶102.

(c) 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.56. 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.4th 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.***”); *Surgalign*, IPR2019-00569, Pap.73, 29-34.²⁹

And as explained (§VII.A.2.a-b), Petitioner’s proposed ligation 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

²⁹ Petitioner cannot change its theory in Reply or offer additional modifications in attempting to fix its broken combination. *Supra*, n.13.

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.

3. Petitioner's Other Ligation Assertions Fail

Petitioner's Ground 2 relies on Linnarsson and McCloskey, but Petitioner does not assert either reference teaches ligation, let alone ligation of a "tag sequence." Pet.39 ("Both references describe methods... whereby polynucleotides are *annealed to oligonucleotides* comprising tag sequences (Linnarsson's CDS and TSO; McCloskey's encoding oligonucleotide)"), 56-58; EX2013, ¶103. 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."³⁰ *Samsung Elecs. Co. v. Elm 3DS Innovations, LLC*, 925 F.3d 1373, 1380-81 (Fed. Cir. 2019) (affirming no REOS in part where petitioner failed to adequately explain how fabrication process would be changed to incorporate modification); *Applied*, IPR2021-00103, Pap.52, 36-42; *DSS Tech.*, 885 F.3d at 1374; *AI-Site Corp.* 174 F.3d at 1324.

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

³⁰ *Supra*, n.24, §VII.

how or why Hug’s teachings would be incorporated into the Linnarsson-McCloskey combination. *Supra*, n.13, §VII; Pet.57.

And even if Petitioner’s Hug arguments could properly be considered, they fail. EX2013, ¶¶104-112. To begin, Petitioner never asserted or explained how Hug is analogous to ’197—a threshold requirement for an obviousness analysis. *See, e.g., Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 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.58; *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, ¶¶104-105. For example, Hug does not sequence the polynucleotides to which it adds linkers. EX2013, ¶¶104-105. Rather, the portion of Hug’s process Petitioner and Dr.

Cooper cite³¹ relies on linkers that hybridize to each other to randomly add a number of identical linkers to a molecule. EX1007, 7-8, Fig.3; EX2013, ¶¶104-106; EX2018, 49:8-50:9. Hug then analyzes the DNA fragments *by length* to estimate the number of sample molecules. EX1007, 7-8, Fig.3; EX2013, ¶¶106-107; EX2018, 49:8-50:9. This is different from Linnarsson or McCloskey, which *sequence* molecules. EX2013, ¶¶104-107.

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.58; EX2013, ¶106. 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, ¶¶106-107. Two different sets of short linkers are subsequently added. EX1007, 7-8, Fig.3. The first set consists of the recognition site of the BamH1 restriction enzyme and an end with a short polynucleotide sequence that hybridizes

³¹ Petitioner and Dr. Cooper together cite only pages 1-2 and 7-9 of Hug, which correspond to the introduction (EX1007, 1-2) and the “Multimeric Linker Labeling” approach (EX1007, 3, 6). Pet.57-58; EX1002, ¶¶227-229.

to the other linker.³² EX1007, 7-8, Fig.3. These linkers can form a chain. *Id.*; EX2013, ¶¶106-107; EX2018, 49:8-50:9. Hug's second set 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, ¶¶106-107. Petitioner, however, never acknowledges these details of Hug's ligation method and ignores that ***Hug's linkers are not designed to link a series of random nucleotides***, like McCloskey's barcode, ***with another sequence***, like Linnarsson's CDS or TSO. Pet.58; EX2013, ¶¶106-111. Petitioner also identifies no use of BamH1 in Linnarsson, which is unsurprising as Linnarsson does not use BamH1 for any purpose. Pet.57-58; 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.57-58; EX2013, ¶¶106-111.

Further, even if, *arguendo*, the Petition *had* explained why POSITA would have looked at Hug and identified and made the 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 Ground 2's other deficiencies, described above

³² Unlike tags that distinguish polynucleotides (EX1001, cl.1), Hug's linkers are ***not unique***. EX2013, ¶105 n.19.

in §VII.A.1-2. EX2013, ¶112.

4. 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—nor does Petitioner’s expert’s declaration *state when it occurs*. *See also* EX2018, 54:8-21 (testifying in deposition on related ’981 patent with a verbatim declaration in relevant part that “I did not explicitly say a timing element there...”); *compare* EX1002, ¶¶223-231 *with* EX2012, ¶¶235-244. 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.58 (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 first testified this timing is not required by the claims.³³ EX2018, 54:8-21; EX2013, ¶113. 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.A.2.a-b; 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 [11] requires that the “second tag” be able to “count a number of sample polynucleotides in said plurality of sample polynucleotides of said cell.” EX1001, 30:16-39. In other words, after amplification and sequencing, the “second tag sequence” must be able to count *endogenous* polynucleotide from which a polynucleotide was derived (*e.g.*,

³³ Dr. Cooper’s new testimony (*supra*, n.22) that this timing was “explicitly” identified in Paragraph 231 of his declaration. EX2020, 37:11-39:11. Not so. Tagged polynucleotides are generated in later steps, such as PCR. EX2013, ¶114.

amplified from)—enabling, *e.g.*, counting 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, ¶113; 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.40-44; EX2013, ¶113.

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

B. Petitioner’s Claims 12 And 26 Arguments Fail

Claim 12 additionally fails as the motivation Petitioner provides to modify the Linnarsson-McCloskey combination is directed to solving an alleged problem Petitioner claims is *already solved* by the Ground 1 combination. Thus, there would be no motivation to *further* modify Ground 1. *Compare* Pet. 40-43, 54-55 *with* Pet.59-60; *see also* Pet.65-66. Claim 26 additionally fails because the claim requires that a “subset of polynucleotides of said cell hav[e] the same sequence.” EX1001, Cl.26. In other words, here, Petitioner needed to show that a cell had multiple mRNA molecules with the same sequence. But Petitioner did not: its

analysis is directed, instead, to an entirely different concept. Pet.63-65.

Petitioner's arguments for claims 12 and 26 fail for these additional reasons.

VIII. Ground 3: Petitioner's Conclusory Combination Fails

Petitioner fails to address how claim 1 is satisfied in its arguments about the dependent claims in Ground 3. This failure is sufficient to reject this ground.

Microsoft Corp. v. Biscotti Inc., IPR2014-01457, Pap.59, 26-27 (Mar. 17, 2016).

Even assuming the Ground 1 claim 1 analysis is relied on for Ground 3 (which is not articulated anywhere in the Petition), Ground 3 fails for the reasons articulated above (*see supra*, §VI) and the reasons below.

Petitioner's motivation to combine for Ground 1 is based on its assertion that "each" and "substantially all" sample polynucleotides are uniquely tagged in Ground 1, and that this unique tagging solves the alleged amplification bias issue in Linnarsson. *See* Pet.40-43 ("Linnarsson... could be modified... to incorporate a second tag sequence to uniquely identify each sample polynucleotide according to McCloskey's teachings..."), Pet.54-55 ("POSA would have understood that [Linnarsson's] method was designed to be applied to substantially all mRNA molecules of a given cell"); *see also id.* ("Also, as explained in Section IX.B.2., it would have been obvious to tag substantially every sample polynucleotides [sic] from a cell"); EX1002, ¶¶91, 166, 222. Petitioner *repeats this motivation as its Ground 3 motivation*. Pet.65. However, there can be no motivation to further

modify the Ground 1 combination in accordance with Ground 3 if, as Petitioner argues, Ground 1 itself *already* uniquely tags each molecule, as its supposed motivation for this additional Ground 3 modification would have *already been accomplished*. *In re Schweickert*, 676 F. App'x at 995. Thus, Petitioner has failed to show that claims 13-19—challenged only in Ground 3—are unpatentable.

IX. Grounds 1-3: Petitioner Fails to Allege—Let Alone Establish—That Its References Are Analogous Art *To '197*

Nowhere does Petitioner assert—let alone attempt to show—that any of the three references named in its grounds (primary reference Linnarsson and secondary references McCloskey and McCloskey II) is analogous art *to '197*. *See* Pet.38-40, 65-67. 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.4th 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.38-40; EX1002, ¶163. Petitioner does not even make this (insufficient) assertion for McCloskey II. Pet.65-67. 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 1-3 must each be rejected because Petitioner cannot meet its burden to establish obviousness as a matter of law. *Sanofi-Aventis*, 66 F.4th 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 '197.³⁴ *Cf. Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 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.”).

³⁴ *Supra*, n.13.

X. Conclusion

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

Respectfully submitted by:

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The undersigned certifies that the foregoing PATENT OWNER'S
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