

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

10X GENOMICS, INC.,
Patent Owner

Case IPR2023-00958
Patent 10,697,013

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	INTENTIONALLY OMITTED
EX2020	IPR2023-00958 Deposition Transcript of Gregory Cooper, Ph.D.
EX2021	Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00955, Pap.1 (May 25, 2023)
EX2022	<i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-00955, EX1002 (Apr. 20, 2023) (Declaration of Gregory Cooper, Ph.D.)

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I. Introduction

Claims 1-28 (the “Challenged Claims”) of U.S. Pat. No. 10,697,013 (the “’013 Patent”/“’013”) are directed to innovative methods of analyzing polynucleotides from a plurality of single cells that *differentiate among the different polynucleotides* in an overall sample and *track from which particular cell* each polynucleotide originated.¹ EX1001, 6:41-7:30, 15:16-58, Cl.1 (30:38-31:9). Nobel Laureate Sydney Brenner and team—’013’s inventors—unlocked the ability to do high-resolution single cell analysis. Petitioner’s perfunctory analysis fails to establish any Challenged Claim is obvious. As laid out below, Petitioner’s Linnarsson-McCloskey combination fails to disclose the limitations of claim 1 and is forced together through hindsight—skilled artisans would not have been motivated to stitch these references together.

Petitioner’s **Ground 1** has multiple failings. First, there is no motivation to modify Linnarsson to add any tags via *ligation*, as all of the Challenged Claims require. Petitioner’s argued modifications of its prior art references to add “tag sequences” via ligation would have required *additional* steps to gain some never-specified “flexibility” but, per Petitioner, merely yield an approach “*entirely*

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.

equivalent” to the Linnarsson-McCloskey combination. This is nonsensical and confirms only that Petitioner’s modifications are driven entirely by improper hindsight: Petitioner does not, *inter alia*, explain in substance how or why skilled artisans would actually find them beneficial, but Petitioner still *needs* these changes to argue (incorrectly) that the claims are obvious.

Further, Petitioner’s ligation arguments are conclusory and fail to confront the actual details of Linnarsson’s method (on which Petitioner relies). These details confirm that ligating “tag sequences” to the CDS or TSO would not render claim 1 obvious for multiple reasons. For the CDS, (1) a biotin molecule blocks the CDS’s 5’ end, which prevents any nucleic acid from being ligated to it, and (2) any sequence that is somehow ligated to the CDS would be on the “3’ fragment”, which “remain[s] stuck on the bead” and is not sequenced. For the TSO, (1) any sequence that is ligated to Linnarsson’s TSO “after extension” would not be reverse-transcribed into cDNA, and (2) even if reverse-transcribed, any sequence would be on the 5’ end of the TSO’s Bts sequence and thus would be *cleaved off* of the nucleic acid prior to the sequencing step. Finally, Petitioner fails to explain how the ligation and subsequent steps are implemented—and Petitioner’s improper reliance on Hug only creates additional incompatibilities with Petitioner’s ligation theory.

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

Third, Petitioner’s combination lacks the particularly required for 10x to adequately respond. Petitioner’s arguments rest, *inter alia*, on the premise that incorporating McCloskey’s barcode will remove amplification bias in Linnarsson. To remove amplification bias, Dr. Cooper argues that every polynucleotide within a sample must be tagged uniquely. But Petitioner never identifies the length of McCloskey’s barcode used in its combination, or explains how it would be sufficient to achieve Petitioner’s argued-for motivation. Without this information, 10x is unable to frame a meaningful response to Petitioner’s arguments and is thus deprived of basic due process.

Petitioner’s **Ground 2** argues POSITA would have been motivated to *modify* its Ground 1 combination to uniquely tag each sample polynucleotide. But, to the extent Petitioner’s Ground 1 arguments are credited, this need was *already*

resolved in Petitioner’s Ground 1 combination, and Petitioner identifies no motivation to modify McCloskey’s barcode further.

Finally, Petitioner entirely fails to assert or analyze whether its references are analogous art to ’013 (instead discussing only whether they are analogous to one another). This failure requires rejection of Grounds 1 and 2, as the Federal Circuit recently confirmed.

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

’013’s Challenged Claims are directed to innovative methods of counting polynucleotides from a plurality of cells that allow the user *not only to differentiate among the different polynucleotides* in an overall sample (including, *e.g.*, mRNA), *but also to track from which particular cell* each polynucleotide originated. EX1001, 6:41-7:30, 15:16-58, Cl.1 (30:38-31:9).

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 (30:38-31:9) EX1001, 14:16-22; EX2013, ¶28.

Until '013's inventions,² "bulk analysis" was primarily used to analyze polynucleotides in a sample of multiple cells. EX1003, 2; EX1006, 2. This provided insight into the polynucleotides in the overall population of cells in the sample but failed to capture critical differences among *individual* cells. Pet.7; EX2013, ¶29. For example, overexpression of the HER2 gene was associated with an aggressive form of cancer, but in the early stages of cancer only a few cancerous cells might be captured amongst numerous cells in a tissue sample to be analyzed. EX2013, ¶29. Averaged across the entire sample population, it would not be possible to determine whether a small subset of the cells 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*,

² The Challenged Claims are directed to the innovative use of these two tags, but '013, like many patents, discloses multiple inventions. EX1001, 1:63-2:6.

Another invention disclosed in '013 is the "reflex method," which, using the MID, fragments polynucleotides to ensure they are short enough to be sequenced while enabling the user to track the origin of each fragment. *Id.*, 1:38-2:6.

respectively), provides a “correlation between a polynucleotide and its source.”

EX1001, 6:52-53. 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, 6:41-7:30, Cl.1 (30:38-31:9); EX1002, ¶¶67-69.

III. Petitioner’s References³

A. Linnarsson (EX1003)

Petitioner relies on Linnarsson’s disclosures relating to “*single-cell tagged reverse transcription (STRT)...*” Pet.17-22, 32-33, 41-42 (each citing Fig.11); EX1002, ¶¶101, 104, 108, 135, 136, 139, 155, 156, 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

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.

from a biopsy, blood sample, or cell culture.” Pet.28; EX1003, 13:11-16. As part of this process, “single cells are placed in separate wells of a 96-well plate and lysed....” EX1003, 4:8-13; Pet.29. Each lysed cell “contain[s] a plurality of mRNA molecules.” EX1003, 3:26-30; Pet.29-30; EX2013, ¶33; EX1054, Abstract; EX1002, ¶125. Following lysis, Linnarsson adds CDSs and TSOs, which are then incorporated into cDNA during reverse transcription from mRNA. EX1003, 18:32-33; *see also* Pet.18; 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.18-19. 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.31, 18-19; EX1002, ¶136; EX1003, 24:13-20, Fig.2, Fig.11. Thus, these CDSs are able to anneal to any mRNA molecule with a poly-A tail in a well. EX1003, 18:27-30; Pet.18; EX2013, ¶34. Petitioner and its expert admit that “the purpose of Linnarsson’s method is gene expression

⁴ “Annealing” is the joining of two complementary strands of nucleic acids through hydrogen bonding. EX1002, ¶¶55, 82; EX1003, 13:3-10; EX1009, 2 (“Denaturation separates the complementary strands of DNA....”).

analysis, which a POSA would have understood *contemplates the analysis of substantially all mRNA molecules of a cell....*” EX2021, 55; EX2022, ¶222.

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.18-20; 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; Pet.18-20. 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.18-20; 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.21; 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. Figures 2-4 depict aspects of the Example I STRT method. *See id.*, 23:1-25:4. 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. 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. 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-

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

F, which are summarized here. EX1003, 37:31-32, 5:28-6:12; Pet.17-18; EX2013, ¶33.⁶

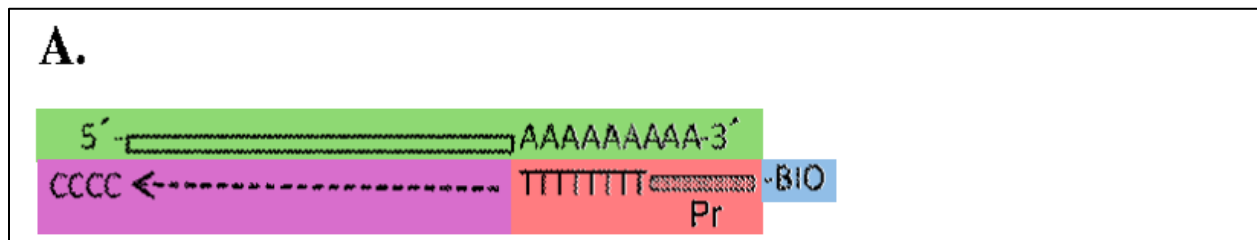
Panel A: The CDS (red) includes a poly-T tail, which hybridizes to the mRNA molecule's (green) poly-A tail. EX1003, 5:28-31; EX2018, 23:21-25:21.⁷ The CDS's primer sequence (Pr) is located on the CDS's 5' end, outside the poly-T tail, which is then capped by a biotin molecule (blue). EX1003, Fig.11 (Panel A), 23:13-19; Pet.20-22; 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.19 (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

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.

⁷ The admissions of Dr. Cooper in EX2018, the transcript of his deposition from an IPR on the related '981 Patent, are relevant here because, 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 that the arguments were "virtually identical").

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.

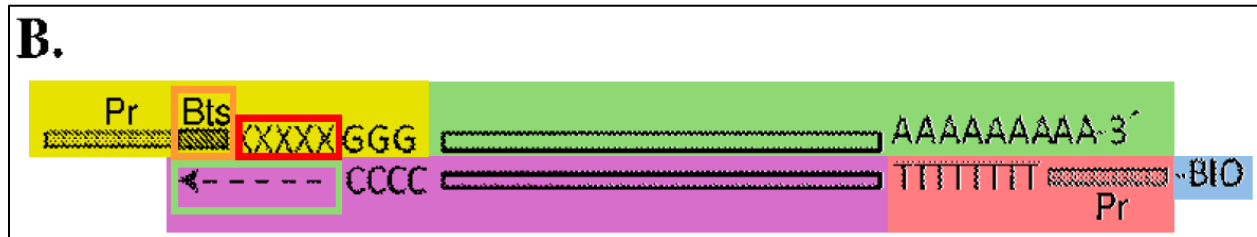


Panel B: To continue cDNA synthesis, Linnarsson uses a TSO (yellow).⁸ EX1003, 5:31-6:1. The TSO’s poly-G tail hybridizes to the poly-C tail of the cDNA created in Panel A. EX1003, 5:31-33, Fig.11 (Panel B); EX2018, 25:22-26:12. The TSO includes a cell tag (red box), a Bts sequence (orange box), and a 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 yellow highlighted TSO as a template, which adds the cell-tag and Bts to the 3’

⁸ While Dr. Cooper’s declaration describes Panel B’s top strand as the second strand of cDNA and not as mRNA (EX1002, ¶108), 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.

end of the cDNA (depicted by the dotted arrow boxed in green). EX1003, 5:31-33,

Fig.11 (Panel B); EX2013, ¶39.⁹

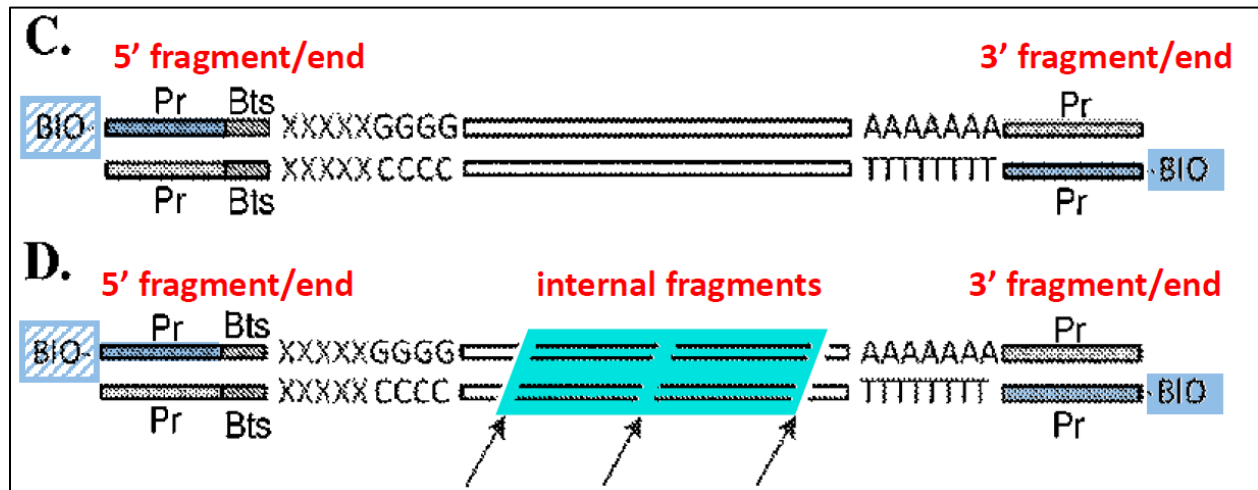


Panels C and D: The cDNA sequences generated in Panels A and B are then amplified via PCR, at which point a biotin (shaded blue) is added to all double-stranded cDNA on their “5’ ends,” resulting in the eventual “5’ fragments” having a biotin on their ends.¹⁰ EX1003, 25:17-20, Fig.11 (Panel C); EX2018, 28:19-29:7. Following PCR, the sequences are subjected to a “fragmentation step”

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

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, ¶56. 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.

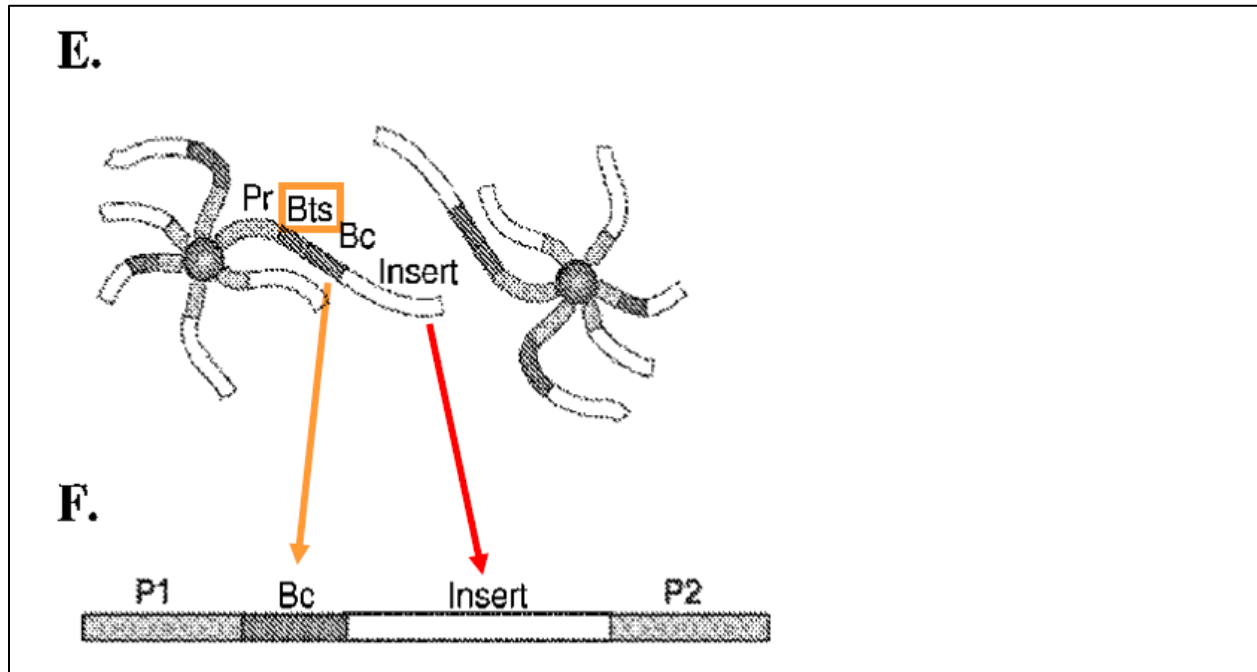
using a DNase enzyme. EX1003, 6:3-4, Fig.11 (Panel D), 12:4-8; EX2018, 29:8-13. The “internal fragments” (teal) from Panel D are “washed away” (and are therefore never sequenced). EX1003, 6:3-4, 26:26-26; EX2013, ¶40.



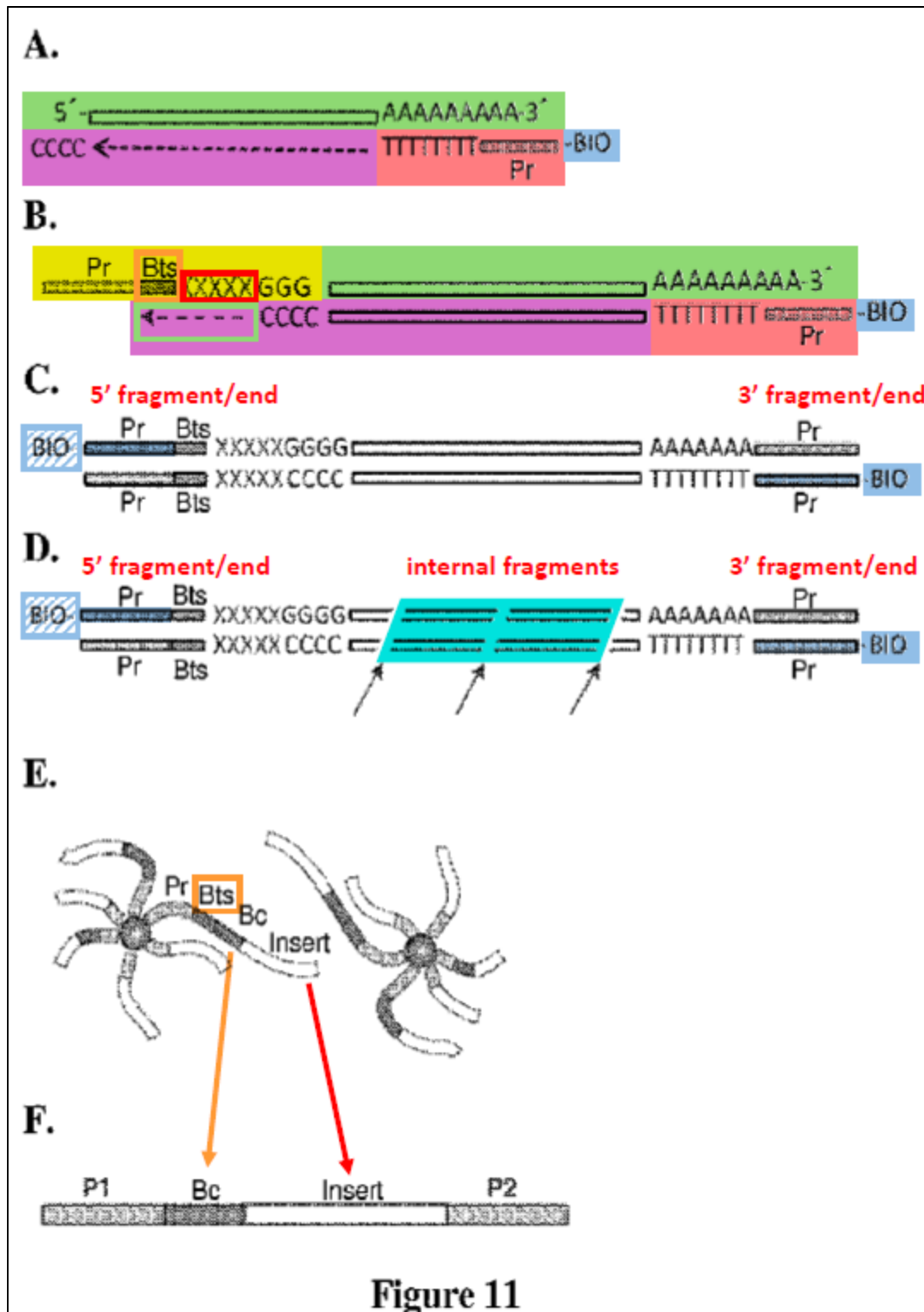
Panels E and F: The remaining biotinylated and fragmented DNA segments—the “5’ fragments” with “barcode (Br) and BtsCI site (Bts)” and the “3’ fragments” (which do not have a Bts site) from Panel D—are then bound to beads. EX1003, 6:5-6, 23:13-16, 26:21-26 32:18-27, Fig.11 (Panels D-E); EX2018, 31:12-22; *see also* EX1003, 21:13-25, 27:6-28:2, 35:23-36:9; EX1002, ¶186; EX2018, 43:21-44:22; EX2013, ¶¶41-43. 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 and 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, ¶¶36-47; 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 (Panel A). 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 (Panel B). Together, these two reverse transcription steps ensure the tags and PCR primers are added. EX1003, Figs.2, 11 (Panel C). 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.22-23; 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 on the chromosomal DNA to be barcoded prior to amplification. EX1004, 2; Pet.22-23. 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 left over from a prior analysis)* and the barcode distinguishes between *copies of an allele for a particular gene in the sample (without identifying the particular cell of origin)*. EX1004, 2-4; Pet.22-23; EX2013, ¶49.¹¹ McCloskey's random barcode is composed of nucleotides, where each nucleotide is one of the four deoxyribonucleotides.¹²

¹¹ Alleles are different versions of the same gene. EX2003, 3; EX1002, ¶59.

¹² "Deoxyribonucleotides" are nucleotides that have a deoxyribose as their sugar component. EX1002, ¶¶54-55; EX2014, 31; EX1001, 7:31-56. The four natural

EX1004, 4; *see also* Pap.9 (“RD”) at 16-18; EX1002, ¶176. 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, ¶59. McCloskey’s method involves lysing the cells and combining their contents (including the DNA) before tagging the copies of a particular gene within this combined material to determine the presence of alleles. *See* EX1004, 2, 5; EX2013, ¶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, the 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*

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

EX1002, ¶¶54-55; EX2014, 31.

target allele are tagged with a sequence that tracks an allele to its cell of origin.

EX1004, 3. Indeed, McCloskey pools the nucleic acids from all of the cells in the sample *prior to tagging*, such that the cell of origin for the nucleic acid cannot be tracked. EX1004, 2, 5 (“Human genomic DNA (2.71 µg)... Digested genomic DNA (0.27 µg)”); EX2013, ¶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 the target gene was present, including whether there were any alleles or mutations present, *in the sample when it was tagged (but not any particular cell in the multi-cell sample)*. EX2013, ¶51. 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 ’013. *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.26. Petitioner relies on McCloskey II only in Ground 2, and only for the “addition[al]” teaching that the “barcode sequence may comprise up to 30 nucleotides.” *E.g.*, Pet.5, 26. As with McCloskey, McCloskey II does not allow a user to determine the cell from which a polynucleotide originated in a sample comprised of multiple cells.

IV. Level Of Ordinary Skill In The Art Of ’013

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.14-15; 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.27.

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).

First, POSITA would not have been motivated to complicate Linnarsson's existing method by adding the “second tag sequence” through ligation, only to achieve an “equivalent method” to Linnarsson. *See infra* §VI.A.1. Even if POSITA were so motivated, Petitioner's combination fails: Petitioner fails to show how a molecule tag can be ligated to Linnarsson's CDS or TSO. *See infra* §VI.A.2.

Second, Petitioner fails to explain how Linnarsson meets the requirement of sequencing “said plurality of amplified polynucleotides.” *See infra* §VI.B. Petitioner maps the “tagged polynucleotides” to the cDNA generated through the two extension steps. But Petitioner relies on Linnarsson disclosures showing that

portions of the tagged polynucleotides are fragmented and the “internal fragments” are washed away. Relatedly, the “3’ fragments” remain bound to the beads and *are not sequenced*. See EX1003 6:8 (“3’ fragments remain stuck on the beads”). Thus, the *only* portion of Linnarsson’s “tagged polynucleotide[s]” (which are the polynucleotides that are amplified)—that is sequenced is the “5’ fragment.” Petitioner fails to address whether sequencing just a *portion* of the “tagged polynucleotide” meets claim 1’s requirement of “sequencing the... tagged polynucleotides.”

Third, Petitioner’s failure to identify the length of the barcode being ligated to Linnarsson’s CDS or TSO with particularity is an independent reason Petitioner failed to meet its burden. See *infra* §VI.C. Petitioner’s motivation to combine requires that every polynucleotide in the sample is tagged uniquely, yet Petitioner did not identify how many nucleotides comprise its “second tag” sequence. Without knowing this information, 10x is unable to respond to Petitioner’s arguments.

A. Petitioner’s Claim 1 Motivation To Combine Fails

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

Petitioner’s Ground 1 fails because there is no motivation to modify Linnarsson to add a tag via ligation. EX2013, ¶¶58-61.

Petitioner has failed to show why POSITA would have been motivated to

change and complicate Linnarsson’s method by adding ligation only to yield what Petitioner’s Dr. Cooper opines is an approach “POSA would have understood” to be “*entirely equivalent*” to the method disclosed by the combination of Linnarsson and McCloskey. The only difference is in the timing: with the combination of Linnarsson and McCloskey... the tag sequence is part of the CDS or TSO prior to extension whereas by using ligation, the tag sequence is added after extension.” EX1002, ¶149; Pet.39 (relying on EX1002, ¶149¹³); EX2013, ¶¶58-61.¹⁴ As Dr. Quackenbush here explains, Petitioner’s Ground 1 theory requires POSITA to create *another* set of tags—as well as any other unexplained preparations for or

¹³ While the Petition appears to articulate this argument differently than Dr. Cooper (suggesting “the second tag sequence is added to the CDS or TSO after extension” “instead of having the tag sequence be part of the CDS or TSO prior to extension”), this formulation is mere attorney argument: the only evidence Petitioner relies on for this proposition is Dr. Cooper’s testimony in EX1002, ¶149. *See* Pet.39.

¹⁴ Petitioner only argued-for modifications to Linnarsson’s STRT method are to add a second set of tags by ligation. *Id.* PO thus understands Petitioner is not asserting any further modifications to its Linnarsson-McCloskey combination to allow the “second tag” to be ligated “after extension.”

materials needed for the argued ligation (such as Hug’s linker molecules and enzymes)—and add at least one additional ligation step somewhere in Linnarsson’s process. EX2013, ¶¶59-60. But Petitioner has failed to show why POSITA would have added such a step (and any unaddressed requirements for further preparations and materials) simply for the sake of ligating a separate tag, rather than (as Dr. Cooper explains and as Petitioner has argued elsewhere) including a “second tag sequence” in the tags Petitioner says already existed in the TSO or CDS. EX1002, ¶149 (“with the combination of Linnarsson and McCloskey discussed above... the tag sequence *is part of the CDS or TSO*”); EX2008, 66-69; EX2021, 55-59; EX2013, ¶¶59-60. This is, of course, classic hindsight: it is required only so Petitioner can argue purported coverage of claim 1. Further, ligation would likely require *not one* but *multiple* steps. EX2013, ¶59.

Additionally, Petitioner, through Dr. Cooper, asserts that further modifying Petitioner’s argued Linnarsson-McCloskey combination to include such ligation “would have been *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 second tag sequence is added to the CDS or TSO after extension. EX1002, ¶149; *see also* Pet.39 (citing EX1002, ¶149). This negates any motivation to modify: the argued combination *already addressed this problem* before any additional modification to add ligation

after extension. *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).; EX2013, ¶¶59-61.

This is especially true where, as here, the modification would add more steps and complexity to achieve only an “equivalent” method. Pet.39; *Weber, Inc. v. Provisur Techs., Inc.*, IPR2019-01461, Pap.36, 42-43 (Feb. 10, 2021) (finding no motivation to modify claim 1 combination to invalidate dependent claim where proposed modification doubled number of steps and added “needless complexity”) *aff'd* 2022 WL 17688071 (Fed. Cir. Dec. 15, 2022). And, in fact, Petitioner’s Ground 1 combination would *not* be equivalent because it would be incompatible with Linnarsson’s later steps, as discussed below (*infra* §VI.A.2).

Finally, Petitioner’s sole purported justification for this proposed modification is the conclusory assertion that “it would allow for added flexibility in selecting tag sequences during an experiment.” Pet.39 (citing EX1002, ¶149). First, Petitioner’s assertion is wholly conclusory, and 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 (*e.g.*, if the tags were included in the CDS or TSO as Petitioner argued in other proceedings). Pet.39 (citing EX1002, ¶149); EX2008, 66-69; EX2021, 55-59. Petitioner fails for this reason alone. *Markforged*, IPR2022-00679, Pap.24, 28-29 (rejecting motivation to combine where “Petitioner’s statement [wa]s nothing more than an unsupported conclusory assertion regarding a possible benefit” without “providing the requisite rationale sufficient to support a conclusion of obviousness”); *ExtractionTek*, IPR2022-00832, Pap.32, 28-30 (concluding claims not unpatentable where petitioner and expert provided conclusory assertions of combination’s “advantage”). Further, because Petitioner’s expert did not provide any further explanation or evidence for this conclusory “increased flexibility” pronouncement, his opinion should be given no weight. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15-16 (Aug. 24, 2022) (precedential) (“the cited declaration testimony is conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight”); *Xerox Corp. v. Bytemark Inc.*, IPR2022-00624, Pap.12, 5-6 (Feb. 10, 2023) (Director affirming decision on *sua sponte* review and designating Paper 9 precedential); *Apple Inc. v Smart Mobile Tech. LLC.*, IPR2022-00981, Pap.34, 37 (Nov. 7, 2023).

For each of these reasons, there is no motivation to modify Linnarsson 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.38-39. But a review of Linnarsson belies Petitioner’s theory. And Petitioner does not assert—nor show—that there would be REOS of practicing the *rest* of claim 1 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., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359,1367 (Fed. Cir. 2016) (REOS “refers to the likelihood of success in combining references to meet the [claimed] limitations”); *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 the petitioner's references were "incompatible" and the petitioner failed to "reconcile the conflict" between the references).

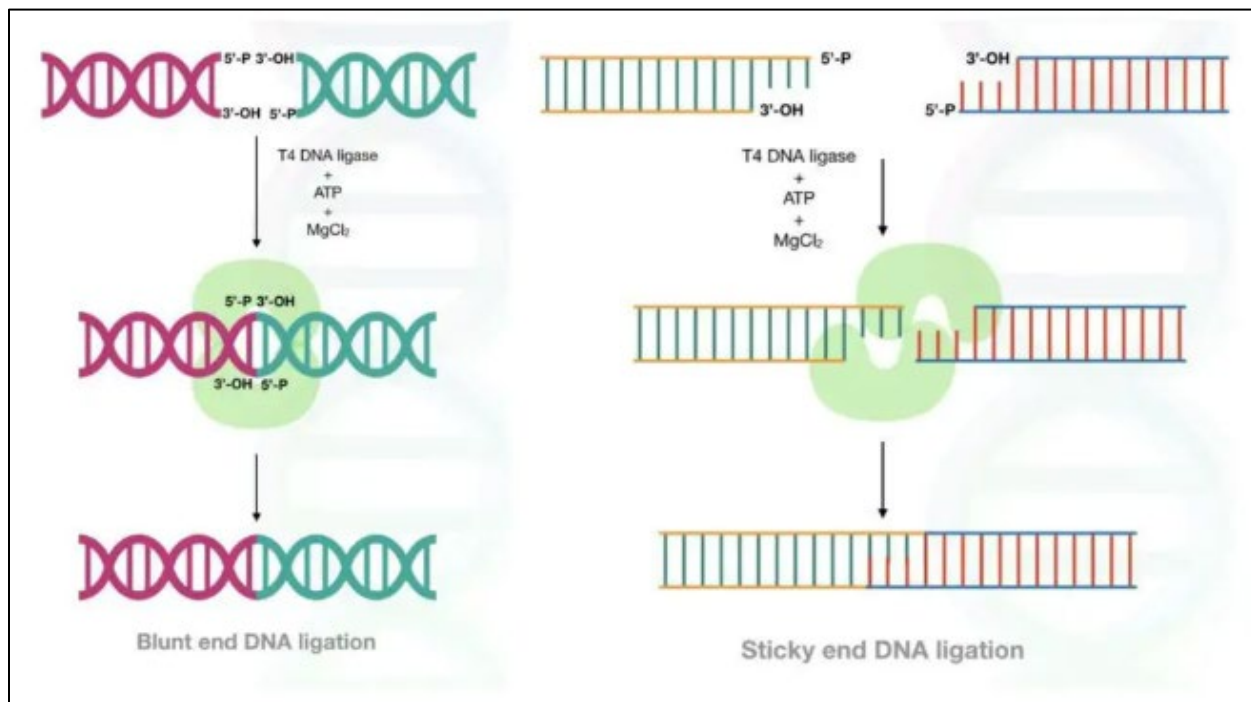
(a) Petitioner's Proposed Ligation Of A Tag To The CDS Fails

Petitioner argues a tag would be ligated to the CDS (Pet.38-39; EX2020, 32:18-33:5), but never explains precisely *how*. And this is not mere accident: without additional modification (which Petitioner never mentions, let alone explains¹⁵), Petitioner has not shown it would be possible to *ligate a* tag to the CDS *to achieve a method that practices claim 1* based on its combination. EX2013, ¶¶62-67.

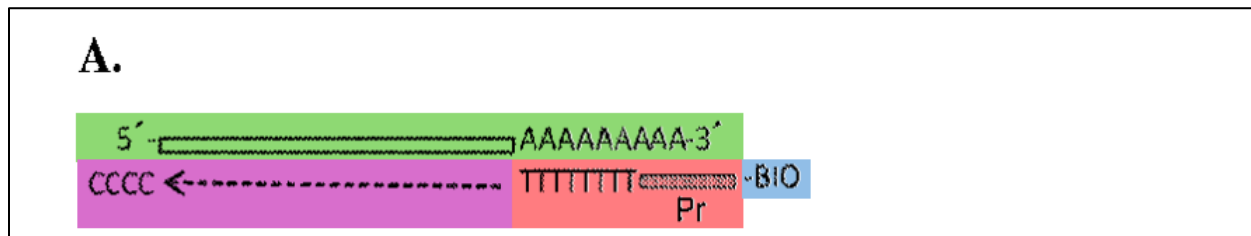
First, the biotin on the CDS's 5' end would block ligation of a tag to the CDS. EX2013, ¶63. As shown in Figure 11 and described in Examples I-II, Linnarsson's CDS in its STRT method is capped by a "BIO" (biotin) molecule on its 5' end. EX1003, Fig.11; 23:13-15 ("The sequence of STRT-T30-**BIO** (which 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

¹⁵ *Supra*, n.14.

and the 5'-phosphoryl of another. EX1001, 6:23-40; EX2013, ¶63. 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, ¶¶63-64.

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, ¶63. 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, ¶63. Petitioner's CDS theory fails. EX2013, ¶62-67.

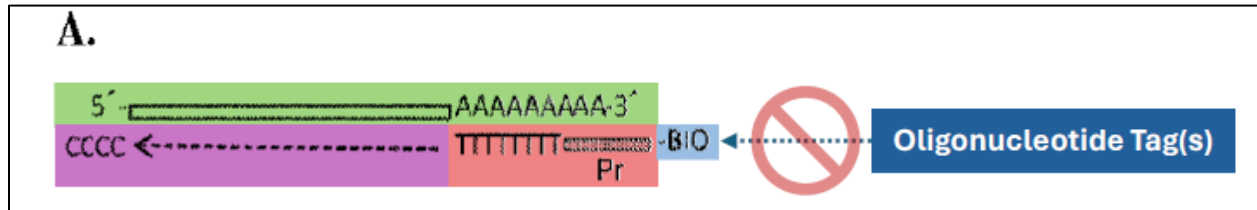
Contrary to Dr. Cooper's improper new suggestion at deposition that the biotin in Linnarsson's Figure 11 is optional (EX2020, 10:20-11:2),¹⁶ POSITA

¹⁶ 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. *NuVasive, Inc.*, 841 F.3d at 972-73; *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.

would not have understood the biotin in Linnarsson's STRT method to be optional, and Dr. Cooper never addressed any such optionality in his declaration. *See* EX2013, ¶64. 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.17-19 (citing description of and excerpting Fig.11 with a biotinylated CDS), Pet. 20-22 (same), Pet.31-34 (same), Pet.41-42 (same); EX1002, ¶¶101, 104, 108, 135, 136, 139, 155, 156, 199, 200; EX2018, 23:15-25:21, 29:14-30:2; EX2013, ¶¶47, 64. But even if the use of biotin were eliminated from Linnarsson, this would not resolve the issues with Petitioner's theory. EX2018, 25:10-21, 31:1-22; EX2013, ¶¶64-65. Neither Dr. Cooper nor the Petition suggests eliminating biotin, or explains how Linnarsson's method would work *without* biotinylated cDNA.¹⁷ The biotin is, *e.g.*, involved in

¹⁷ 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

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, ¶¶64-65.



Second, even assuming, *arguendo*, that a nucleic acid could somehow be ligated to another nucleic acid already capped with a biotin molecule, this ligation would be incompatible with the *further* claimed steps of the combination and requirements of claim 1. 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 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 claim 1 because Petitioner has not shown Linnarsson teaches these sequences being sequenced, as claim 1 requires. EX1001, Cl.1.

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

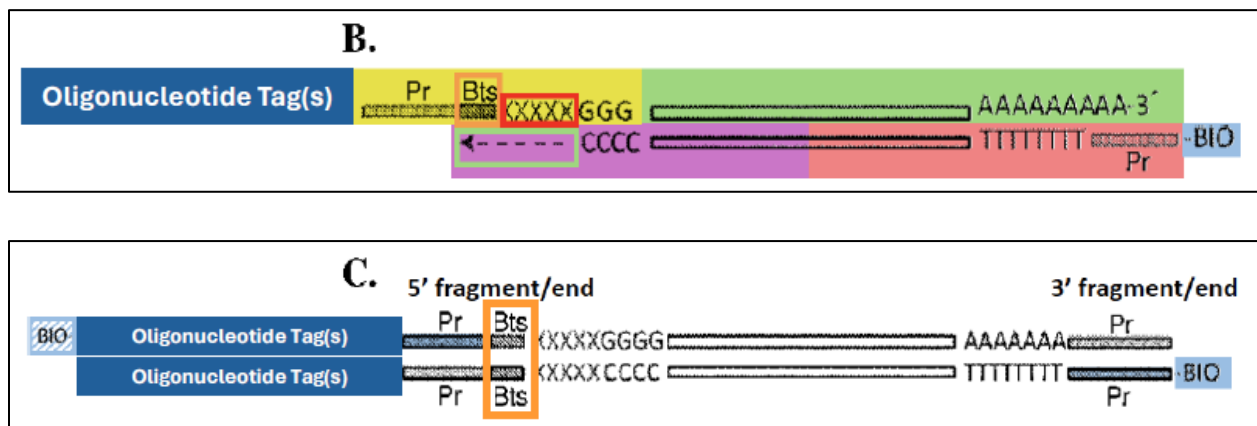
The tag also cannot be ligated to the TSO to arrive at a method that practices

combine them is not enough to establish the obviousness of [the claim] as a whole.").

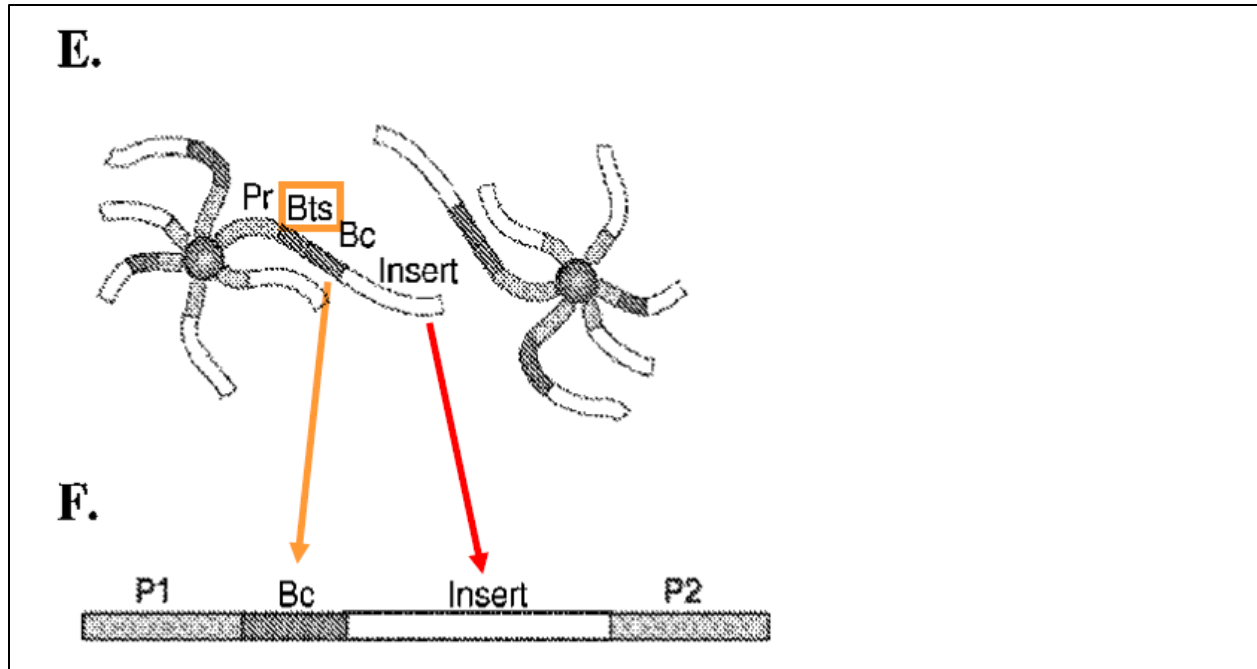
claim 1. Petitioner asserts the tag would be ligated to the end of the TSO “after extension.” Pet.39. Ligating a tag to the TSO “after extension” would mean ligation occurs *after* the template switching step in Panel B is completed. EX2013, ¶¶68-69. At this point, the reverse-transcription of double-stranded 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, ¶68. 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, ¶68; EX2018, 21:21-32:14.

Second, even if, *arguendo*, the tag were reverse-transcribed (it is not), the TSO theory fails because the ligated tag would be located on the 5’ end of the Bts

sequence,¹⁸ shown in annotated Panels B and C below. EX1003, Fig.3, Fig.11; *see also id.* 27:6-7, 35:28-36:9; EX2013, ¶69. 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, ¶69.



¹⁸ 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 be *cleaved* from the released sample polynucleotide in Panel E *and remain stuck on the bead*. EX1003, 5:28-6:12, Fig.11; *see also id.* 27:6-7, 35:28-36:9.

Once cleaved, the released polynucleotide would include no "second tag sequence," and thus the "tagged polynucleotide" would not be sequenced—nor would it be possible to distinguish among sample polynucleotides as required by claim 1. EX1001, cl.1; EX2013, ¶69.

(c) Petitioner Does Not Assert REOS For The Claim As A Whole

Petitioner asserts "POSA would have had a reasonable expectation of success in ligating a second sequence to Linnarsson's CDS or TSO." Pet.38. But asserting REOS of practicing only an isolated portion of a 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 1 with this 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, 29-34.¹⁹

And as explained, analyzing this modification’s impact on claim 1 confirms there is no REOS. *Supra*, §VI. 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

¹⁹ Petitioner cannot change its theory in Reply or offer additional modifications in attempting to fix its broken combination. *In re NuVasive, Inc.*, 841 F.3d 966, 972-73 (Fed. Cir. 2016) (vacating final written decision when Board relied on factual assertion by petitioner made only after patent owner’s Response); *Intelligent Bio-Sys.*, 821 F.3d at 1369-70; *Apple Inc.*, IPR2022-00981, Pap.34, 35-36.

TSO, (1) the ligated sequence would not be transcribed if ligated to the TSO “after extension” because there is no additional extension step, and (2) if ligated to the TSO the sequence would be cleaved from the “tagged polynucleotide” prior to sequencing (even ignoring (1)). Each outcome prevents the combination from meeting claim 1’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 1 relies on “Linnarsson, McCloskey, and the knowledge of a POSA.” Pet.27. Petitioner does not assert either reference teaches ligation, let alone ligation of a “tag sequence.”²⁰ Pet.35 (“Both references describe methods... whereby polynucleotides are *annealed to oligonucleotides* comprising tag sequences (Linnarsson’s CDS and TSO; McCloskey’s encoding oligonucleotide)”), 35-39; EX2013, ¶¶70-71. It is unclear from Petitioner’s argument *how* the ligation and subsequent steps (such as the required

²⁰ Petitioner confusingly argues “[t]o the extent Linnarsson does not teach ligating a second oligonucleotide tag to the claimed ‘extension product,’ this would have been obvious in view of McCloskey and the knowledge of a POSA.” Pet.34.

Petitioner neither explains nor asserts that Linnarsson discloses ligation of a second tag, and Petitioner cannot do so on Reply. *Supra*, n.19.

amplification) are purportedly implemented in Petitioner’s asserted combination based on the addition of a “knowledge of a POSA.” *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).

Petitioner’s attempt to fill this gap in its combination by relying on Hug (*not* part of its stated Ground) fails, particularly given Petitioner’s failure to explain how or why Hug’s teachings would be incorporated into the Linnarsson-McCloskey combination. *Supra*, n.19; Pet.38; *see Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1335-37 (Fed. Cir. 2020) (holding Board erred in instituting on ground outside petition); *Applied Materials, Inc. v. Demaray LLC*, IPR2021-00103, Pap.52, 36-42 (June 29, 2022) (rejecting petitioner’s argument that references evidencing POSITA’s knowledge alone “sufficiently explain how such teachings apply to [the reference’s] system”); *DSS Tech. Mgmt., Inc. v. Apple Inc.*, 885 F.3d 1367, 1374 (Fed. Cir. 2018) (identifying “three caveats” to using common sense in obviousness analysis, warning it is not “typically invoked” “to supply a missing claim limitation”); *AI-Site Corp. v. VSI Int’l, Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (“Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment.”).

And even if Petitioner’s Hug arguments could properly be considered, they fail. EX2013, ¶¶71-79. To begin, Petitioner never asserted or explained how Hug is analogous to ’013—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.39; *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, ¶¶71-79. For example, Hug does not sequence the polynucleotides to which it adds linkers. EX2013, ¶¶72-73. Rather, the portion of Hug’s process Petitioner and Dr. Cooper cite²¹ relies on linkers that hybridize to each other to randomly add a number of identical

²¹ Petitioner and Dr. Cooper together cite only pages 1-2 and 7-9 of Hug, which correspond to the introduction (EX1007, 1) and the “Multimeric Linker Labeling” approach (EX1007, 3, 6). Pet.38-39; EX1002, ¶¶146-148.

linkers to a molecule. EX1007, 7-8, Fig.3; EX2013, ¶¶71-73; EX2018, 49:8-50:9.

Hug then analyzes the DNA fragments *by length* to estimate the number of molecules in a sample. EX1007, 7-8, Fig.3; EX2013, ¶¶72-73; EX2018, 49:8-50:9. This is very different from Linnarsson or McCloskey, which rely on *sequencing* molecules. EX2013, ¶¶71-74.

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.39; EX2013, ¶73. 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, ¶¶73-74. Two different sets of short linkers are subsequently added. EX1007, 7-8, Fig.3. The first set of linkers consists of the recognition site of the BamH1 restriction enzyme and an end with a short polynucleotide sequence that hybridizes to the other linker.²² EX1007, 7-8, Fig.3. These linkers can form a chain. *Id.*; EX2013, ¶¶73-74; EX2018, 49:8-50:9. Hug’s second set of linkers are “Terminator Sequences” that terminate the chain because no linkers have the

²² Unlike tags that distinguish polynucleotides (EX1001, cl.1), Hug’s linkers are not unique. EX2013, ¶72, n.12.

complementary sequence necessary to hybridize to, and thus continue, the chain.

EX1007, 7-8, Fig.3; EX2013, ¶¶73-74. 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.39; EX2013, ¶¶73-78.

Petitioner also does not point to the use of BamH1 in Linnarsson, which is unsurprising as Linnarsson does not use BamH1 for any purpose. Pet.38-39; 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.38-39; EX2013, ¶¶73-78.

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 the other deficiencies PO identified with respect to ligation, described above in §VI.A-B. EX2013, ¶79.

B. Petitioner Fails To Show Linnarsson Teaches “Sequencing Said Plurality Of Amplified Polynucleotides” [1J]

Petitioner argues Linnarsson discloses limitation [1J] because Linnarsson refers to sequencing. Pet.44. Petitioner fails to meet its burden to show Linnarsson sequences the claimed “plurality of tagged polynucleotides.” Pet.44; EX2013, ¶¶80-86.

Petitioner identifies the “tagged polynucleotides” in Linnarsson as the complete cDNA molecules generated during reverse transcription. Pet.30-40 (“Linnarsson teaches generating a plurality of tagged polynucleotides (*i.e.*, tagged double-stranded cDNA [and/or amplified copies]) from the plurality of sample polynucleotides (*i.e.*, sample mRNA)...”); EX2013, ¶80. Petitioner then ignores the intermediary steps of Linnarsson and argues that Linnarsson sequences *the plurality of tagged polynucleotides* in their entirety based simply on vague references to sequencing. Pet.44. As discussed below, Petitioner ignores that its Linnarsson mapping sequences only the “5’ fragment” and fails to address whether or how sequencing only the “5’ fragment” is sufficient to meet the claim element. EX1001, Cl.1; EX2013, ¶80.

Petitioner’s own citations fail to show Linnarsson discloses sequencing the entirety of the “tagged polynucleotide” as Petitioner argues. Pet.43 (citing EX1003, 4:8-13). Petitioner’s first citation is to a description of Linnarsson’s Figure 1, which is an “overview of a method” that simply says, “sequencing is performed,” but does not provide details or specify what or how much is sequenced. EX1003, 4:8-13; EX2013, ¶84. Petitioner’s second and third citations confirm Linnarsson does *not* sequence the entirety of the “tagged polynucleotide” as Petitioner’s theory requires. 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:²³ “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, ¶84; EX1002, ¶186; 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 definition of cDNA library, and sequencing the 5’ fragment specifically. For example, the Figure 11 embodiment of Linnarsson—relied on by Petitioner throughout its claim 1 mapping—teaches the “amplified library is *fragmented* to 200–300 bp using controlled DNase digestion,” which creates 5’, 3’, and internal “fragments.” EX1003, 6:3-6, 21:13-25, 27:6-28:2, 35:23-36:9; *supra*, §III.A; Pet.32-33 (citing Fig.11 in mapping of limitation [1D]), Pet.30 (citing to limitation [1D] mapping for limitation [1C]), Pet.41-42 (citing Fig.11 in

²³ *Supra*, n.16.

mapping of limitation [1F]). 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, ¶¶81-83; *supra*, §III.A. Thus, those internal fragments are not sequenced. EX2018, 41:10-44:22. Moreover, those "3' fragments" do not contain a Bts sequence and, as a result, *are not released from the "beads"* to which they are bound. EX1003, 6:3-8; *id.* at Figs.11 (Panels C-E), 35:28-31 ("5' fragments containing barcodes and cDNA inserts were released from the beads by BtsCI digestion..."); EX2018, 41:10-44:22; EX2013, ¶¶81-83. 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, ¶¶81-83; EX1002, ¶186; 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 [1J]. Pet.42-43; EX1002, ¶186 (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 entirety of the "tagged polynucleotide" is plainly wrong. Pet.35-36; EX2013,

¶¶80-84; *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). Indeed, Petitioner has not addressed whether or how sequencing just the “5’ fragment” is sufficient to have sequenced “the tagged polynucleotide,” nor has Petitioner presented any argument or claim construction addressing how much of a “5’ fragment” would be needed to sequence “the tagged polynucleotide.” Pet.44. For this reason alone, Petitioner’s Ground 1 fails (and, with it, Ground 2, which relies on Ground 1). EX2013, ¶¶80-84.

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, ¶92. 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, ¶¶91-93. Indeed, the Petition and Dr. Cooper argue for claims 20 and 21 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.53; EX1002, ¶¶228-230). The SOLiD platform—which “has an optimal size... on the order of a few hundred, maybe 400 nucleotides”—uses fragmented cDNA libraries.²⁴ EX1002, ¶¶91-93; EX2020, 57:4-20. Critically, Petitioner’s claim 20 arguments do not assert any modification of Linnarsson to introduce fragmenting. Thus, Petitioner’s assertions are consistent with Linnarsson disclosing a fragmentation step.

Additionally, Petitioner’s CDS theory fails for the further reason the CDS is part of the 3’ fragment, and Petitioner identifies no teaching in Linnarsson showing the 3’ fragment is *sequenced*. EX2013, ¶85. Petitioner’s theory, which apparently relies on incorporating McCloskey’s encoding oligonucleotide teachings, including its barcode teachings, and ligating McCloskey’s molecule tag to Linnarsson’s CDS, fails for this reason, too. The “3’ fragment” (the end of the double stranded cDNA with the CDS) is *not sequenced*. EX2013, ¶85; *see* EX1003, Fig.11 (Panel

²⁴ It also requires the polynucleotides be biotinylated, as Dr. Cooper recognizes: “The SOLiD System *utilizes a biotin-streptavidin interaction* to immobilize the sample polynucleotides to the bead.” EX1002, ¶228.

E); EX1003, 6:8; EX2018, 43:21-44:22. 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 any "3' fragment" from the bead or sequencing it. EX2013, ¶85; EX2018, 43:21-44:22. Thus, Petitioner's CDS theory also fails for Ground 1 for this additional reason.

C. Petitioner's "Second Tag" Argument Lacks the Required Particularity

Petitioner's lack of particularity leaves PO unable to evaluate or frame a meaningful response to Petitioner's motivation to combine or reasonable expectation of success arguments—failing the particularity requirements for any IPR petition and depriving PO of basic due process—and its Ground 1 thus also fails for this further reason. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)); *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 296 (2016) (Alito J., concurring in-part). Petitioner argues that POSITA would have "been motivated to combine Linnarsson's use of a cell tag with McCloskey's molecule tag to distinguish individual molecules within a sample." Pet.35-36. But Petitioner never identifies *what* precisely is being added (as "McCloskey's molecule tag") to the CDS or TSO via ligation. Pet.34-39. Neither does Dr. Cooper. EX1002, ¶¶143-150. All we know is *something* from McCloskey is ligated to the CDS or TSO in some unspecified manner. Pet.34-39;

EX1002, ¶¶143-150, 162-177; *supra*, §VI.A.2-3. Petitioner does not even identify the length²⁵ (*i.e.*, the number of nucleotides) of the “second tag” sequence that is being ligated to the CDS or TSO, which determines the number of unique tag sequences available. EX1004, 4. But this missing information is material—indeed, central—to Petitioner’s argument. Petitioner’s motivation to combine Linnarsson and McCloskey is premised on McCloskey’s barcode “remov[ing] amplification bias,” which according to Petitioner requires that “[e]very sample and the polynucleotides within every given sample [be] uniquely tagged.” EX1002, ¶¶174, 87. Without the Petition identifying the length of the “molecule tag” it purports to import from McCloskey, 10x is unable to evaluate or respond to Petitioner’s purported combination.²⁶ Petitioner’s Ground 1 fails for this additional reason.

²⁵ Unlike its failure for Ground 1, Petitioner did identify this information for other claims in Ground 2. Pet.62.

²⁶ In Petitions on patents related to ’013, Petitioner stated that McCloskey’s 7-nucleotide barcode was to be combined with Linnarsson. EX2021, ¶¶39-43 (citing EX2022, ¶168); Pet.39-43 (citing EX2022, ¶168). Petitioner has not made that same argument here, and it is too late for Petitioner to do so now. But, even if Petitioner’s 7-nucleotide barcode theory were applied here, Petitioner’s Ground 1

VII. Ground 2: Petitioner’s Conclusory Combination Fails

Petitioner fails to address how claim 1 is satisfied in its arguments about the dependent claims in Ground 2. 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 2 (which is not articulated anywhere in the Petition), Ground 2 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 the sample polynucleotides in Ground 1—all mRNA molecules in Linnarsson’s sample—are tagged with a tag that distinguishes individual molecules in the sample (*i.e.*, each is uniquely tagged), and that this unique tagging solves the alleged amplification bias issue in Linnarsson. *See* Pet.35-36 (Linnarsson could be modified to incorporate “McCloskey’s molecule tag to distinguish individual molecules within a sample because this approach addresses the amplification bias issue set forth in Linnarsson.”), 45 (“As discussed above in Sections IX.A.1.d-e

also fails because a barcode of that length would not provide enough unique tags to satisfy Petitioner’s argued-for motivation. EX2013, ¶¶87-94. And Petitioner has entirely failed to address this issue in its Ground 1 arguments despite recognizing it as an issue in Ground 2.

and g-h, the combination of Linnarsson and McCloskey discloses and renders obvious using a first tag to identify the single-cell origin of tagged polynucleotides, and using a second tag to uniquely identify each tagged polynucleotide.”); EX1002, ¶¶75, 87, 173; EX2021, 44-45 (“POSA would have understood that [Linnarsson’s] method was designed to be applied to substantially all mRNA molecules of a given cell”); EX2022, ¶¶91, 222. Petitioner *repeats this motivation as its motivation in Ground 2*. Pet.60 (“POSA would have been motivated to tag each sample polynucleotide with a unique second tag sequence.”). However, there can be no motivation to *further* modify the Ground 1 combination in accordance with Ground 2 if, as Petitioner argues, Ground 1 itself *already* uniquely tags each molecule, as its supposed motivation for this additional Ground 2 modification would have *already been accomplished*. *In re Schweickert*, 676 F. App’x at 995; EX2013, ¶¶95-96. Thus, Petitioner has failed to show that claims 13-18 (which are challenged only in Ground 2) are unpatentable.

VIII. Grounds 1-2: Petitioner Fails to Allege—Let Alone Establish—That Its References Are Analogous Art *To* ’013

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* ’013. *See* Pet.35-36, 60-62. 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.35-36; EX1002, ¶170. Petitioner does not even make this (insufficient) assertion for McCloskey II. Pet.60-62. Thus, because Petitioner’s grounds rely entirely on obviousness and Petitioner was therefore required to establish that its obviousness art is analogous to the challenged patent as a threshold issue, Grounds 1 and 2 must both be rejected because Petitioner cannot meet its burden to establish obviousness as a matter of law. *Sanofi-Aventis*, 66 F.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 ’013.²⁷ *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

²⁷ *Supra*, n.19.

<https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf>, 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”).

IX. Conclusion

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

Respectfully submitted by:

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The undersigned certifies that the foregoing PATENT OWNER'S
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According to the word-processing system's word count, the brief contains 11,461
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