

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 PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

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, (April 20, 2023)
EX2009	File History of U.S. App. No. 14/172,694
EX2010	Declaration of Sayem Osman

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I. Introduction

Patent Owner 10x Genomics, Inc. (“PO”) submits this §42.107¹ Preliminary Response to the above-captioned Petition (“Petition”/“Pet.”). While Petitioner asserts the methods of Claims 1-28 (the “Challenged Claims”) of U.S. Pat. No. 10,697,013 (the “’013 Patent”/“’013”) are, in the specification, “described as nothing but mere prior art techniques” (Pet.1), its Petition advances no §102 ground, and argues only that ’013’s revolutionary method—which unlocked the ability to do high-resolution single-cell analysis—was somehow obvious. The Board should deny the Petition because Petitioner’s inadequate obviousness arguments are fatally deficient.

To begin with, the Petition presents the classic case for discretionary denial under §325(d). The Petition’s two grounds assert obviousness based on three recycled references (**Linnarsson**, **McCloskey**, and **McCloskey II**) whose substance was already thoroughly considered by the Office. **Linnarsson**, Petitioner’s primary reference (EX1003), was the explicit basis of rejection during prosecution, was distinguished and overcome, and featured prominently in the initial Notice of Allowance of U.S. Patent No. 10,155,981 (the “’981

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

Patent”/“’981”) —against which ’013 is terminally disclaimed. EX2001, 238.

McCloskey, Petitioner’s Ground 1 secondary reference (EX1004), is a less detailed version of “US20070020640” to McCloskey *et al.* (“McCloskey II”) (EX1055), Petitioner’s other secondary reference. ***McCloskey II was also asserted by the Office, substantively considered, and then overcome*** in the applications leading to ’013. *See, e.g.*, EX2002, 335-336, 372-373. Petitioner either misunderstands or simply ignores the relevance of the prosecution history of related patents to §325(d).

And Petitioner identifies no cognizable error that would let it escape discretionary denial in this textbook §325(d) fact pattern. Instead, the only “error” Petitioner suggests—that the Examiner overlooked, and never acknowledged, the teachings of Linnarsson, McCloskey, and McCloskey II—is palpably ***false***: Linnarsson and McCloskey II (of which McCloskey is cumulative) were ***substantively considered*** in ’013’s priority applications, including ’981. This is exactly the case §325(d) was meant to prevent.

Further, Petitioner fails to assert or analyze whether its references are analogous art to ’013—instead discussing only whether they are analogous to one another (and only in Ground 1, so McCloskey II is never discussed). This failure impacts both Grounds and requires denial. *See, e.g., Sanofi-Aventis Deutschland*

GmbH v. Mylan Pharms. Inc., 66 F.4th 1373 (Fed. Cir. 2023) (reversing a Final Written Decision for this failure).

Additionally, Petitioner fails to clearly identify the art in its combinations. Although Petitioner names only Linnarsson and McCloskey (and, for Ground 2, McCloskey II), Petitioner also seems to rely on one or more additional references, making it unclear what Petitioner's grounds really are, and without providing the required obviousness analysis for those references.

Even setting aside these fatal threshold errors, Petitioner's purported motivation to combine with a reasonable expectation of success ("REOS") also fails. It is not clear if Petitioner argues the claimed "second tag" is *added to* or *replaces* Linnarsson's "tags." It is also unclear *where* the argued second tag is added or substituted, *when* in Linnarsson's reverse transcription process it is added, and *how* exactly Petitioner argues it is ligated. Petitioner also recognizes that *neither* Linnarsson nor McCloskey teaches *ligating* a tag, and fails to identify which part of McCloskey's "encoding polynucleotide" Petitioner argues is incorporated in its combination.

Additionally, on their face, Linnarsson and McCloskey have key differences and incompatibilities that Petitioner simply ignores. Linnarsson is focused on gene *expression* and tagging *all* of the mRNA transcribed from expressed genes. *See* EX1003, 1 (Abstract). In contrast, McCloskey is about stamping only copies of a

particular gene. McCloskey uses a batch-stamp that identifies the sample from which cells originated in order to identify contamination (*i.e.*, to identify sequences originating from a *different* sample leftover from a prior analysis) and a barcode that distinguishes between *copies of a particular allele in the sample* (without identifying the cell of origin).

Petitioner also fails to establish any motivation to combine, admitting its added ligation step would be “entirely equivalent” to Linnarsson’s method. Even Petitioner’s assertion about the combination providing “added flexibility” is not supported by any detail or explanation, particularly in view of Petitioner’s assertion about the two methods’ “equivalen[ce.]”

In addition, Petitioner argues motivation to combine based on its assertion that McCloskey addresses an amplification bias issue in Linnarsson. Petitioner attempts to sidestep the fact that Linnarsson *already addresses* amplification bias, but fails to explain how any amplification bias “solution” in McCloskey would actually improve Linnarsson’s process. Further, Petitioner bases its REOS argument on *each* sample nucleotide being tagged, but fails to explain how that would actually occur in the Linnarsson-McCloskey combination. These claim 1 failures permeate all claims of both Grounds.

Finally, Petitioner suggests the Challenged Claims lack written description or are somehow invalid because PO made §101 arguments about unrelated patents

in an unrelated proceeding (Pet.11-14). Petitioner is incorrect as to each, but, more importantly, its arguments are irrelevant in an *inter partes* review proceeding.

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

'013, "Methods For Analyzing Nucleic Acids From Single Cells," claims priority to an August 20, 2009 provisional. EX1001, 1; Pet.6. '013's Challenged Claims are directed to innovative methods of analyzing polynucleotides from a plurality of single cells that allow the user *not only to differentiate among the different polynucleotides in an overall sample, but also to track from which particular cell each polynucleotide originated.* EX1001, 6:41-7:30, cl.1 (30:38-31:9). This is achieved by using a multiplex identifier ("MID"), which comprises a tag or combination of tags. EX1001, 6:41-7:30. The claims of '013 require *two tag sequences*: "a *first* tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells" and "a *second* tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell." *Id.* In other words, the claimed method simultaneously employs (1) *cell-specific tags* and (2) *polynucleotide-specific tags*. EX1001, cl.1 (30:38-31:9). *Id.* Indeed, the innovative methods claimed in '013 allowed users to do what had not previously been possible: to determine the quantity of *each polynucleotide present in a cell on a cell-by-cell basis*, which Linnarsson, McCloskey, and McCloskey II cannot. EX1001, 6:41-7:30, cl.1 (30:38-31:9). The specification

explains that combinatorially tagging a polynucleotide with this first and second tag sequence provides a “correlation between a polynucleotide and its source” so that researchers can know, for example, how many individual polynucleotides are in each single cell within a sample. EX1001, 6:46-59. As discussed below, the claims were allowed because of their novel tagging of nucleotides, with each nucleotide being tagged with a cell-specific and polynucleotide-specific tag.²

² The Challenged Claims are directed to the innovative MID and its use, but ’013 discloses multiple inventions. EX1001, 1:60-2:6. Another disclosed invention is the “reflex method,” which, using the MID, allows a user to fragment polynucleotides to ensure they are short enough for the entire fragment to be sequenced while enabling the user to track each fragment’s origin. *Id.*, 1:38-2:6.

III. Petitioner's Recycled References³

A. Linnarsson (EX1003)

Linnarsson, a patent publication identifying Sten Linnarsson as sole inventor (EX1003 (“Linnarsson”), 1), is cited on ’013’s face and was the basis of multiple rejections by the Office in Application No. 15/677,957 (“’957 application”), which issued as ’981, as well as ’981’s parent Application No. 14/792,094 (“’094 application”). EX1001, 2; EX2001, 153-156; EX2004, 1085-1087.

Linnarsson discloses a method of preparing a cDNA library for sequencing by reverse-transcribing cDNA from mRNA initially produced by transcription of genes being expressed in the analyzed cells. EX1003, 1 (Abstract), 3:25-4:2; *see also* Pet.17-18. 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 of those cells “contain[s] a plurality of mRNA molecules.” EX1003, 3:26-30; Pet.29.

Linnarsson then adds cDNA synthesis primers (“CDSs”) and/or template switching

³ Petitioner purports to incorporate by reference six pages of “technical background” from Petitioner’s separate petition on a related patent (as well as the supporting expert declaration). Pet.5-6. This is improper, and these six pages *far* exceed (by more than 1,000 words) the 83 words Petitioner says remain below its 14,000-word limit. *See* Pet.77; Pet.5 (citing EX2008, §IV).

oligonucleotides (“TSOs”), which are then incorporated into cDNA during reverse transcription from mRNA. EX1003, 18:32-33; *see also* Pet.18. The CDSs and/or TSOs identify the cell from which a tagged polynucleotide originated. EX1003, 19:4-7; Pet.18-20.

According to Petitioner, “Linnarsson discloses a cDNA synthesis primer... that includes a sequence of thymines....” Pet.18. Because every mRNA molecule has a poly-A tail, “a sequence of thymines... hybridiz[e] with a sequence of adenines making up a poly-A tail... of an mRNA strand.” Pet.18; EX1003, 24:13-20, Fig.2. Thus, such CDSs are able to anneal to *every mRNA molecule in a well*.

Similarly, TSOs have a poly-guanosine sequence. Pet.19-20; EX1003, 18:19-21. In the process of reverse-transcribing mRNA into cDNA, reverse transcriptase typically causes two to five cytosines to be added to one end of the cDNA. EX1003, 16:18-31; Pet.19-20. The poly-guanosine sequence in TSOs then “‘anneals transiently’ to th[is] series of cytosine nucleotides at the end of [a] newly-synthesized strand.” Pet.19-20; EX1003, 18:19-23. The TSO annealing to cDNA causes “the reverse transcriptase to switch template and continue to synthesis [sic] a strand complementary to the TSO.” EX1003, 18:23-24. After the tags are added during reverse transcription, the cDNA (which includes a CDS and/or TSO) from each well is pooled, and a cDNA library is created. EX1003, 18:27-19:11.

Linnarsson's method results in all the mRNA extracted from a single cell being tagged with the same barcode as it is reverse transcribed into DNA. Thus, after amplification and sequencing of the reverse-transcribed DNA, it is impossible to distinguish among the multiple copies of polynucleotides (*e.g.*, multiple copies of mRNA resulting from overexpression of a particular gene) and determine how many instances of that particular polynucleotide existed *in a particular cell* before amplification. *See* EX1003, 22:22-28.

B. McCloskey (EX1004)

Petitioner's EX1004, "Encoding PCR Products with Batch-stamps and Barcodes," by Megan L. McCloskey, Reinhard Stöger, R. Scott Hansen, and Charles D. Laird, purports to address a "source-uncertainty" problem that arises when pooled DNA samples are amplified. EX1004 ("McCloskey"), 1, 2. To address this problem, McCloskey adds an "encoding oligonucleotide" with a batch-stamp and barcode via primer extension as part of the DNA amplification process. EX1004, 2-4; Pet.22-24. The batch-stamp identifies the batch sample from which the cells originated to identify contamination (*i.e.*, to identify sequences originating from a *different* patient or sample left over from a prior analysis); 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.22-23.⁴

McCloskey's oligonucleotide sequence includes, *inter alia*, (1) a batch-stamp; and (2) a random barcode that distinguishes alleles of the same gene with (3) a genomic target-binding site that targets the specific gene to be barcoded prior to amplification. EX1004, 2; Pet.22-24.

McCloskey's method involves lysing the cells and combining the contents (including the DNA) of those cells before tagging the copies of a particular gene within this combined material to determine the presence of alleles. EX1004, 2, 5. Copies of a particular gene (including any alleles or mutations) are tagged by annealing the genomic target-binding site of the oligonucleotide to the complimentary DNA sequence found on one end of the target gene. EX1004, 5. Because the oligonucleotide has a sequence that *anneals only to a specific sequence of the target gene* (which is subsequently amplified), it **does not tag other genes** (which, in McCloskey's process, are not amplified). EX1004, 2, 4-5.

McCloskey discloses that its incorporation of oligonucleotides into the amplified DNA for the particular gene of interest allows researchers to identify and remove contaminated sequences (from different batch samples) and redundant sequences (amplified copies containing the same random barcode) after the gene of

⁴ Alleles are different versions of the same gene. EX2003, 3.

interest is amplified. EX1004, 3 (Fig. 1), 7. However, McCloskey's method does not allow a user to determine, *e.g.*, whether or which copy of a particular allele (or mutation) is present in a given cell because *no copies of the target allele are tagged with a sequence that tracks an allele to its cell of origin*. EX1004, 3. 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. Id.*

C. McCloskey II (EX1055)

Petitioner's EX1055 is, as Petitioner admits, "a sister application that goes along with the McCloskey reference" and, "similar to McCloskey... discloses a method for tagging polynucleotides with 'a molecular barcode and batch-stamp....'" Pet.26. Thus, McCloskey II shares McCloskey's deficiencies. Notably, McCloskey II is relied on only in Ground 2 for the "addition[al]" teaching that the "barcode sequence may comprise up to 30 nucleotides." Pet.26, 60-62.

IV. Petitioner Ignores The Bulk Of '013's Prosecution History

Clearly hoping to lead the Board *away* from the Office's extensive analysis and consideration during prosecution of the many applications in '013's direct family tree, Petitioner myopically focuses only on the single application (16/817,461 ("461 application")) that matured directly into '013. Pet.10-11

(discussing only the '461 application); EX1005 (attaching only the '461 application's prosecution history). While Petitioner asserts that "the Examiner's decision to allow the claims was based solely on an incomplete and wholly inadequate understanding of the scope of the prior art" (Pet.11), it is actually Petitioner's treatment of the prosecution history that is "incomplete and wholly inadequate." *The twelve other applications in '013's family*—including, in particular, '981, against which '013 is terminally disclaimed, and earlier App. Nos. 13/859,450 ("'450 application") and 13/387,343 ("'343 application"), the first non-provisional application in '013's priority chain—contain extensive discussion confirming both that (1) the substantive teachings of Petitioner's three cited references (Linnarsson, McCloskey, and McCloskey II) were squarely before the Office (indeed, *the Office* raised and substantively addressed both Linnarsson and the more detailed McCloskey II in prosecution), and (2) Petitioner's regurgitation of those references and related arguments here fails to render '013's claims obvious.

A. The Examiner's "Second Tag" Art Included McCloskey II

Petitioner argues (Pet.34-39), in both of its recited Grounds, that McCloskey discloses '013's "second tag" (the *polynucleotide-specific* tag that Petitioner urges "distinguish[es]... other sample polynucleotides"). Pet.43, 34-39. But during prosecution of '013's family, the Office expressly *declined* to find a molecule-

specific tag in a more detailed version of McCloskey—along with a raft of *other* references (such as Kanda and Miner) over which McCloskey is, at best, *cumulative*. EX2002, 335-336 (distinguishing Petitioner’s EX1055 “US20070020640”).

For example, during the ’343 application’s prosecution—the first non-provisional application, which, like ’013, claimed use of a combination of tags (or a MID) “whose identity can be used to differentiate polynucleotides in the sample”—the Office initially asserted that U.S. Pub. 2007/0238113 (“Kanda”) (cited on ’013’s face) taught the “limitation of [a] broadly recited multiplex identifier because F2 *can be used as the tag to differentiate a polynucleotide* in the sample.” EX2005, 686, 728-729; EX2006; EX1001, 2, 6:41-7:30, cl.1. But the Office withdrew that rejection in view of Applicant’s arguments regarding Kanda (EX2005, 805), including that Kanda failed to teach sequencing the primer sequences (as the pending claims required), which would “distinguish[] said polynucleotide strand from other polynucleotide strands in said sample.” EX2005, 789, 793-798. The Office identified some dependent claims as allowable but issued new rejections of others, asserting they were anticipated by or rendered obvious with a publication—“*Laird*”—that is cited in McCloskey (EX1004, 2, 7) and whose lead author is also a co-author of McCloskey (EX1004, 1). EX2005, 807-817; EX2007. Specifically, the Office asserted Laird disclosed the claimed

multiplex identifier (MID) because its “sequence *can be used as the tag to differentiate the hairpin polynucleotide* in the sample.” EX2005, 809-812. But, after Applicant argued Laird failed to disclose sequencing the MID (and amended the claims to specify the length of the polynucleotide of interest (EX2005, 844-851)), the Office allowed the remaining claims. EX2005, 865-867. The Office’s “Reasons for Allowance” stated that “Laird alone or in combination with the art of record *does not disclose or make* it [sic] *obvious* the claimed method steps ‘a’ to ‘c’, wherein the polynucleotide strand comprises... *a multiplex identifier (MID) comprising a unique nucleotide sequence that distinguishes said polynucleotide strand from other polynucleotide strands in said sample*...” EX2005, 868-869. The Office further noted that “[t]he instant method has *several advantages... as compared to other extraction methods... that only use a single oligonucleotide sequence*, [including that the instant method] *allows [users] to analyze* homologous genomic locations in *a multiplexed sample (i.e., a sample having polynucleotides from different genomic samples) in which the polynucleotides are tagged with the multiplex identifier domain*.” EX2005, 868-869. Thus, the Office concluded that Laird failed to render obvious, *inter alia*, using a “(MID) comprising a unique nucleotide sequence that distinguishes said polynucleotide strand from other polynucleotide strands in said sample.” EX2005, 868-869.

During later prosecution of '343's grandchild '450 application, which issued as U.S. Patent No. 8,563,274 ("274 Patent"/"274"), the Office considered a "potential rejection" that would have addressed Laird's deficiencies using McCloskey II. EX2002, 335-336, 372-373, 383. The Office raised a number of references and, in July 24 and 26, 2013 interviews, "requested that the Applicants provide a brief summary of how the claims are distinguished from [them]." EX2002, 335-336. One reference raised and successfully distinguished was McCloskey II, which, as Applicant explained, "does not provide *segments* of a region, where each of the segments has the same MID sequence; [and] also *doesn't provide [a] composition in which all of the segments have a multiplex identifier that uniquely identifies the individual molecule of said contiguous region from which said segments originate.*" *Id.* (italics on first use of "segments" original). As Applicant summarized, the Office agreed: the "Examiner indicated that [a proposed] amendment [(replacing "fragments" with "segments" as noted below)] would likely distinguish the claims from the [cited] references for the reason outlined in the Applicants' brief comments." *Id.*, 336, 383. Per that discussion, Applicant submitted the amended language below for independent claim 21 (all emphases except italics are original):

(Currently amended) A composition comprising a mixture of:

- a) a first plurality of segments ~~fragments that have been amplified from different parts~~ of a single nucleic acid molecule of a

contiguous region locus in genomic DNA, wherein *each of said first plurality of segments fragments* is appended to a first multiplex identifier (MID) sequence; and

b) a second plurality of **segments** fragments that have been amplified from different parts of another nucleic acid molecule of said **contiguous region** locus, wherein each of said second plurality of **segments** fragments is appended to a second MID sequence and said first MID sequence and said second MID **sequence** are different,

wherein all of the segments in said composition have a multiplex identifier that uniquely identifies an individual nucleic acid molecule of said contiguous region from which said segments originate.

And in '274's Notice of Allowance—acknowledging that the Examiner and Applicant “[d]iscussed the amended claims” and that “specific claim languages were discussed to overcome the potential rejection of said amended claims over Laird... *in view of McCloskey [III]* (cited in the previous interview)” (EX2002, 372-373)—the Office indicated that while “tagging of sample or a nucleic acid of interest” was known:

“it would not have been obvious to [POSITA] to modify the references of the [sic] record... to arrive at the claimed composition... wherein... all of the segments of each of the nucleic acid molecules of the contiguous region comprises a unique MID sequence that uniquely identifies each of the nucleic acid molecules.”

EX2002, 374-375.

During prosecution of the '450's great-grandchild '957 application—which issued as '981, and against which '013 is terminally disclaimed, EX1005, 103—after Applicant overcame the Examiner's anticipation rejection using *Linnarsson* by arguing Linnarsson lacked the second tag, the Examiner concluded in a second Notice of Allowance that none of the art of record, “*including the prior art submitted in the newly filed IDS,*” reasonably suggested the claimed invention.

EX2001, 306; *infra*, §IV.B; *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Pap.8, 22-23 (Dec. 15, 2017) (precedential as to §III.C.5, first paragraph) (“*Becton*”); *Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01529, Pap.16, 15-18 (Mar. 21, 2023) (considering the prosecution histories of continuations “determined by Examiner to not be patentably distinct” from the parent application). The “newly filed IDS” noted by the Examiner was *one page* and contained just 13 references (EX2001, 285), one of which was “MINER et al., ‘Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR.’” EX2001, 285; EX1013, 1.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	TS
	B16	BRENNER, S. et al. "In vitro cloning of complex mixtures of DNA on microbeads: Physical separation of differentially expressed cDNAs" PNAS 2000 Feb. 15; 97(4):1665-70.	
	B17	HUG, H. et al. "Measurement of the number of molecules of a single mRNA species in a complex mRNA preparation" J Theor Biol. 2003 Apr 21; 221(4):615-24.	
	B18	MINER et al. "Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR" Nucleic Acids Res. 2004 Sep 30; 32(17):e135.	
	B19		

EX2001, 285. Miner, which is discussed in McCloskey as applying to “hairpin-bisulfite PCR” the same principles used in McCloskey (EX1004, 2), discloses:

“us[ing] *molecular barcoding to label each genomic DNA template with an individual sequence tag prior to PCR amplification*. In addition, *we include molecular ‘batch-stamps’ that effectively label each genomic template with a sample ID and analysis date*. This highly sensitive method identifies redundant and contaminant sequences and serves as a reliable method for positive identification of desired sequences...”

EX1013, 1 (Abstract). These are the same McCloskey teachings that Petitioner argues disclose the claimed “second tag.” Pet.34-39; EX1013, 1; EX1004, 1; EX1001, cl.1 (30:38-31:9). The Examiner allowed ’981’s claims over Linnarsson *with Miner in hand*, and ’013 was later terminally disclaimed against ’981. EX2001, 283-284.

B. The Examiner’s Reliance On Linnarsson

Petitioner’s obviousness arguments urge combining these recycled McCloskey teachings with Linnarsson as the base reference asserted to provide disclosure of ’013’s method of analyzing a plurality of cells and tagging polynucleotides within those cells with a “first” tag (the *cell-specific* tag). Pet.27-46. But this merely repeats the Office’s *previous* consideration of Linnarsson, with these same purported (but failed) “second tag” teachings in hand (*see supra*, §IV.A). The Office *raised and applied Linnarsson* in rejections during prosecution

of '981's parent and '981; but Applicant overcame Linnarsson and obtained '981's claims (against which '013's are terminally disclaimed) because Linnarsson alone *or in combination with the art of record* (see §IV.A) did not anticipate or render them obvious.

During prosecution of '981's parent ('094) application, the pending claims—like '013's—included both first and second tags (“first and second multiplex identifier (MID) sequences”). EX2004, 860. For example, an August 30, 2017 amendment added this independent claim:

56. (New) A method of analyzing nucleic acids, the method comprising:

(a) providing a plurality of nucleic acid samples, each made from single isolated cells;

(b) *tagging a plurality of segments of the nucleic acid molecules* in the samples of (a) *with first and second multiplex identifier (MID) sequences*, wherein:

(i) the *first MID sequences* associated with a segment of a nucleic acid molecule of (a) *uniquely identifies the single isolated cell from which the nucleic acid molecule is provided*; and

(ii) the *second MID sequences are all different from each other*;

(c) sequencing the tagged segments of (b) to obtain the nucleotide sequences of the plurality of nucleic acids and the attached first and second MID sequences.

EX2004, 860. In response, for the first time in the '013 family's prosecution, the Office identified and asserted Petitioner's primary Linnarsson reference (EX1003), and rejected the pending claims as anticipated. EX2004, 1084-1087. In particular, the Office found Linnarsson disclosed the *first* tag:

The cell specific tag (e.g., see figure 3) in the nucleic acid sample from each of the single cell is the first Multiplex Identifier (first MID) sequences associated with a segment of a nucleic acid molecule of (a) uniquely identifies the single isolated cell from which the nucleic acid molecule is provided.

EX2004, 1086. And the Office additionally found Linnarsson disclosed the *second* tag. EX2004, 1086 ("Different tags associated with cDNA segment of Linnarsson meets the limitation of second MID sequences [that] are different from each other.").

Prosecution then moved forward in the child ('957) application that matured into '981. The '957 application's as-filed claims included this independent claim:

1. A method of analyzing nucleic acids from a plurality of single cells, the method comprising:
 - (a) providing a sample comprising a plurality of single cells, wherein each single cell of the plurality of single cells comprises a plurality of sample polynucleotides;

(b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides, wherein each tagged polynucleotide comprises:

- (i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and
- (ii) a multiplex identifier (MID) sequence comprising:

- I. a *first tag sequence associated with the single cell from which the sample polynucleotide is derived*; and
- II. *second tag sequence distinguishing the sample polynucleotide from other pluralities of sample polynucleotides derived from the same single cell*

(c) sequencing the plurality of tagged polynucleotides to obtain a plurality of identified polynucleotide sequences;

(d) using the first tag sequence to correlate the identified polynucleotide sequence with the single cell from which the polynucleotide sequence is derived, and

(e) using the second tag sequence to correlate the identified polynucleotide sequence with the plurality of sample polynucleotides [sic] from which the polynucleotide sequence is derived.

EX2001, 64. During '981's prosecution, the Office rejected these then-pending claims as anticipated by Linnarsson (EX2001, 154), but later withdrew that rejection after further argument (EX2001, 181-182) (and an

amendment clarifying “the first tag sequence is a different sequence for different single cells in the plurality of single cells” (EX2001, 178)). As the Office correctly concluded in ’981’s initial August 28, 2018 Notice of Allowance, “[t]he closest prior art, *Linnarsson* (WO 2010/117620), ***does not teach or suggest generating a plurality of tagged polynucleotides comprising an identifier sequence*** of instant claim 1(ii). The claimed identifier sequence comprises a first tag sequence, which distinguishes each single cell in a sample of a plurality of cells, ***and a second tag sequence, which distinguishes a sample polynucleotide from other sample polynucleotides derived from a single cell, which is not taught by Linnarsson.***” EX2001, 238. The Examiner confirmed even more broadly in a second Notice of Allowance, after reviewing an additional IDS (EX2001, 283-284), that Linnarsson’s gap was not filled by the art the Office had considered: “[a] ***thorough search*** of the prior art, ***including the prior art submitted in the newly filed IDS***, filed after the Notice of Allowance mailed on 8/28/2018, ***shows no art that teaches or reasonably suggests the claimed invention.***” EX2001, 306.

As discussed above, the “newly filed IDS” was *one page* and contained just 13 references (EX2001, 285), including Miner. EX2001, 285; EX1013, 1; *supra*, §IV.A. Thus, the Examiner reviewed Miner, a reference

with the very same teachings as McCloskey, which Petitioner relies on here as disclosing the “second tag” and motivating its Linnarsson-McCloskey combination (Pet.34-39)—*after Applicant distinguished Linnarsson for lacking the “second tag”*—then allowed ’981’s claims, finding they were neither anticipated nor obvious. EX2001, 306.

After prosecution of intervening applications allowed without prior art rejections (but with various terminal disclaimers), the Office later allowed ’013’s Challenged Claims after being terminally disclaimed against, *e.g.*, ’981. EX1005, 103.

V. Institution Should Be Denied Under 35 U.S.C. §325(d)

This is the prototypical IPR that §325(d) and the Board’s two-part framework in *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH* (IPR2019-01469, Pap.6, 8-9 (Feb. 13, 2020) (precedential) (“AB”)) were meant to prevent. Petitioner fails to show any error in the Examiner’s application during prosecution of the prior art teachings Petitioner now purports to invoke from Linnarsson and McCloskey⁵ to argue claim 1 is obvious. Instead, Petitioner offers just a conclusory assertion—without support—that the “Examiner materially

⁵ McCloskey II is also recycled and used only in Ground 2 for certain dependent claims—solely to modify the length of McCloskey’s tag. Pet.60-64.

erred *by not considering the relevant teachings in Linnarsson, McCloskey, and McCloskey II.*” Pet.66. This is factually incorrect and legally insufficient to show “error.” *Becton*, 22-23; *Autel Intelligent Tech. Corp. v. Orange Elec. Co.*, IPR2021-01545, Pap.8, 26-27 (Apr. 8, 2022) (conclusory arguments fail to demonstrate Office error).

Petitioner’s secondary McCloskey reference is at best cumulative of the more detailed McCloskey II, which *was raised by the Office and substantively discussed as the basis for a potential rejection using its asserted disclosure of a polynucleotide-specific tag—the same purported teaching for which Petitioner relies on McCloskey here.* *Supra*, §IV.A. But that McCloskey II disclosure was *successfully distinguished and overcome by Applicant* in the face of the Office’s contemplated rejection. Petitioner never acknowledges that prosecution history, never disputes McCloskey is cumulative of McCloskey II, and never demonstrates any error in the Office’s prior substantive consideration of McCloskey II. And Petitioner *ignores* that its primary reference, Linnarsson, was expressly overcome during prosecution of the ’981 (against which ’013 is terminally disclaimed). The office found Linnarsson lacked this teaching of a polynucleotide-specific tag, which the Office also found (with Laird) McCloskey II was inadequate to supply. Pet.34; *see also* EX2001, 238; EX2002, 335-336, 372-373, 383. Revisiting the

same art and arguments already overcome during prosecution is a waste of the Board's limited resources and would unfairly burden PO.

A. Advanced Bionics Part One

AB part one considers whether the same or “substantially the same” art or arguments “previously were presented to the Office.” *AB*, 8. The *Becton* Factors relevant to *AB*'s part one inquiry include: “(a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination;” and “(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art.” *AB*, 9 n.10, 10; *see also Becton*, 17-18. *AB* part one is satisfied here.

First, the Office has clearly considered “the same or substantially the same prior art” before. Petitioner's Grounds rely on two recycled references to render claim 1 obvious: *Linnarsson* and *McCloskey*. *Linnarsson* was the basis of explicit rejections—both in the application that issued as '981 (which the Challenged Claims are terminally disclaimed against) and in its parent '094 application—which Applicant ultimately overcame. EX2001, 193-196; EX2004, 1085-1087; *Ivantis*, IPR2022-01529, Pap.16, 15-17. To argue claim 1 is obvious, Petitioner points now to the *same Linnarsson disclosures* previously cited by the Office, and advances the *same arguments* that the Office made in prosecution. For

example, Petitioner points to Linnarsson p.4 (Pet.28) as disclosing the preamble, Linnarsson's Fig.3 as disclosing the ("first") cell tag (Pet.33), and Linnarsson's disclosure of a "cDNA sample [with] a combination of tags" (Pet.33-34). The Office similarly pointed to Linnarsson p.4 as teaching a method where "identification of expressed genes and identification of cells from which they are originated" and its Fig.3 as disclosing a "cell-tag." EX2001, 195; EX2004, 1086 (arguing Linnarsson disclosed "[t]he cell specific tag (e.g., see figure 3)"). And the Office, like Petitioner, also asserted that Linnarsson discloses "a distinct tag or combination of tags" such that "each cDNA sample comprised 2 distinct tags." EX2001, 196; EX2004, 1086 (arguing Linnarsson disclosed "[d]ifferent tags"); Pet.33-34. Petitioner is, thus, repeating the *same* Linnarsson *prior art disclosures* and *arguments*, which the Office rejected, in hopes of reaching a different result.

The same is true for *McCloskey*. EX1004. Petitioner does not dispute McCloskey is cumulative of McCloskey II (EX1055), which is cited on '013's face and was raised and argued by the Office in prosecuting the related '450 application in '013's priority chain (Pet.65-66; EX1001, 1; EX2002, 335-336, 372-373, 383). Petitioner now argues McCloskey should be combined with Linnarsson, but those very McCloskey teachings (in the form of McCloskey II) were already raised *by the Office*, argued, and overcome during prosecution leading to '013. This alone is reason enough to find *AB* part one is met. *See, e.g., Autel*, IPR2021-01545,

Pap.8, 17, 20-23, 27 (denying institution under §325(d) where petitioner failed to “persuasively identify any specific, substantial difference between [petitioner’s reference] and the Third Reexamination’s prior art”); *Darfon Elecs. Corp. v. Shipman*, IPR2022-01008, Pap.11, 14 (Dec. 2, 2022) (denying institution under §325(d), noting “Petitioner does not address whether the proffered art is cumulative to or substantially the same as the art considered during prosecution.”); *Alarm.com, Inc. v. Vivint, Inc.*, IPR2022-00728, Pap.6, 20-22 (Nov. 1, 2022) (similar).

Indeed, Petitioner *concedes* the parallels between McCloskey and McCloskey II. Petitioner admits here:

McCloskey II is a *sister patent application that goes along with the McCloskey reference*. The subject matter of McCloskey II was invented by the authors of McCloskey. Thus, *similar to McCloskey, McCloskey II also discloses a method for tagging polynucleotides with ‘a molecular barcode and batch-stamp.’*

Pet.26. And Petitioner essentially acknowledges that McCloskey II disclosed the information Petitioner now argues is relevant by complaining the Office erred by not “discuss[ing] or cit[ing] any passage or disclosure of” McCloskey II—*not* McCloskey. *See* Pet.66-67.

Moreover, a review of both references confirms the more detailed McCloskey II raised and argued by the Office (and overcome by PO) during

prosecution of '013's related '450 application *already included the teachings on which Petitioner purports to rely*—and at minimum McCloskey is cumulative of the previously-considered McCloskey II. Petitioner relies on McCloskey solely for its method of tagging nucleotides with an oligonucleotide that has a “batch-stamp” and “barcode” sequence, which Petitioner hopes to use to satisfy '013's requirement of a “second” polynucleotide-specific tag. Pet.34-39, 45-46. But McCloskey II includes the very same teaching, as Petitioner admits (Pet.26), and includes more detail. EX1055, 1 (Abstract) (“the present invention provides methods for authenticating a nucleic acid molecule and its sequence with a molecular barcode and batch-stamp”), Figs. 4A-G, ¶¶5, 20-27, 35, 46. Indeed, Petitioner's various cited McCloskey disclosures substantially overlap with McCloskey II. *Compare, e.g.,* Pet.34-35 (citing EX1004, Fig.1) *with* EX1055, Figs.1, 3, ¶¶13, 15; Pet.9, 23 (citing EX1004, 1-2) *with* EX1055, ¶27; Pet.22-23 (citing EX1004, 2) *with* EX1055, ¶¶21, 54-63; Pet.26 (citing EX1004, 1, 5) *with* EX1055, ¶¶3, 6; Pet.36-37 (citing EX1004, Abstract) *with* EX1055, ¶5.

Thus, the prior art substance of McCloskey that Petitioner now advances was already before the Office, and McCloskey (EX1004) is, at most, cumulative of McCloskey II (EX1055) and the other art that was already considered by the Office. Indeed, this would have been the case even if McCloskey II had not been expressly discussed. *See, e.g., Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01533,

Pap.14, 13-14 (Mar. 27, 2023) (*AB* part one satisfied even where reference to which an asserted reference was cumulative was not discussed during prosecution); *Keysight Techs., Inc. v. Centripetal Networks, Inc.*, IPR2022-01421, Pap.9, 9-10 (Mar. 22, 2023) (“[*AB*] makes clear that previously presented art includes art that was provided via an [IDS].”); *cf.* Pet.67. But in fact, as detailed *supra* §IV.A, ***McCloskey II was discussed and distinguished*** to avoid a potential rejection in the prosecution leading to ’013. *Becton*, 22-23; *see Motorola Mobility LLC v. Maxell, Ltd.*, IPR2023-00110, Pap.7, 16 n.8 (June 15, 2023); *Eyenovia, Inc. v. Sydnexis*, IPR2022-00965, Pap.7, 13-14 (Nov. 7, 2022) (denying institution and considering arguments and rejections made during prosecution of related patents in §325(d) part one analysis); *see also Ivantis*, IPR2022-01529, Pap.16, 15-17. And, as detailed above (*supra*, §IV.A), the Office also expressly considered *other* references for potential disclosures of a polynucleotide-specific tag including, *e.g.*, Miner (EX1013) and Kanda (EX2006)—again confirming that Petitioner’s McCloskey (EX1004) is at best a cumulative stand-in.

Second, Petitioner’s mistaken assertion that the ***arguments*** here are new—even if credited—is irrelevant and need not be reached by the Board since the ***art*** is not new. *AB* part one is met where art ***or*** arguments were previously presented. *Microsoft Corp. v. ThroughPuter, Inc.*, IPR2022-00757, Pap.10, 20 (Nov. 1, 2022). Moreover, Petitioner’s arguments are ***not*** new.

During prosecution of the related '981, the Office initially argued the claims were anticipated by Linnarsson but then allowed the claims over those teachings and found no prior art of record taught or suggested the claimed invention. EX1003, 48; EX1004, 25. In '981's first Notice of Allowance, the Examiner concluded Linnarsson did not disclose the "claimed identifier sequence," and in the second Notice of Allowance (following an additional IDS) the Office confirmed that "[a] *thorough search of the prior art, including the prior art submitted in the newly filed IDS*, filed after the Notice of Allowance mailed on 8/28/2018, *shows no art that teaches or reasonably suggests the claimed invention.*" EX2001, 238, 306. This prior art already of record included McCloskey II, and the "newly filed IDS" included Miner, which, *using terminology identical to McCloskey*, disclosed using an oligonucleotide containing a batch-stamp and barcode to identify contamination and redundant sequences in PCR. EX1003, 2-3; EX1013, 1-2 ("we include molecular 'batch stamps' that effectively label each genomic template with a sample ID and analysis date. This highly sensitive method identifies redundant and contaminant sequences... In addition to adding the random barcode, we 'batch-stamped' molecules...").

The Examiner thus expressly considered whether the claims were obvious over the prior art of record—including **Linnarsson**, **McCloskey II**, and **Miner**—and determined the '981's claims (which '013 is terminally disclaimed against)

were not rendered obvious. In doing so, the Office specifically considered and rejected alleged prior art disclosure of the “second” polynucleotide-specific tag sequence, which Petitioner now reprises with McCloskey. *E.g.*, EX2001, 238, 306. And as detailed above (§IV.A), in prosecution of ’013’s related ’450 application, McCloskey II’s oligonucleotide was specifically distinguished from the claimed MID to overcome a potential rejection: “US20070020640 [McCloskey II]... does not provide *segments* of a region, where each of the segments has the same MID sequence; [and] also *doesn’t provide [a] composition in which all of the segments have a multiplex identifier that uniquely identifies the individual molecule of said contiguous region from which said segments originate.*” EX2002, 335 (italics on first use of “segments” original). Petitioner here simply rehashes these same rejected teachings now from the less detailed, summary McCloskey article (EX1004). Thus, Petitioner’s assertion that “*no arguments* were made during examination with respect to any of these references” is wrong—and, indeed, strains credulity.⁶ Pet.65 (emphasis original).

⁶ Petitioner is well aware of the ’981’s prosecution history, having filed a Petition seeking *inter partes* review of ’981 weeks before the present Petition was filed. EX2008, 17-19. Petitioner nonetheless failed to acknowledge (let alone address) that prosecution history, which is undisputedly relevant as confirmed by, *e.g.*,

Petitioner’s outdated, pre-*AB* cases—*3Shape A/S v. Align Tech., Inc.*, IPR2019-00160, Pap.9, 39-42 (June 11, 2019) and *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00486, Pap.10, 15 (July 15, 2015)—do not yield a different outcome. First, while pre-*AB* panels in *3Shape* and *Microsoft* focused on whether references were the *basis of a specific rejection*, *AB* part one is satisfied if the references were ***of record***. *AB*, 7-8. Moreover, even in this respect Petitioner’s cases are not on point: Petitioner ***ignores*** that both *Linnarsson* and *McCloskey II* (a more detailed version of *McCloskey* (EX1004)) ***were*** substantively considered during the prosecution of ’013’s related applications.

In fact, the Office *explicitly* considered obviousness combinations for both *Linnarsson* and *McCloskey II* in those applications. The Office asserted ***Linnarsson*** in an obviousness-type double patenting rejection in combination with PO’s ’149 patent during ’981’s prosecution (EX2001, 157), and considered ***McCloskey II*** in a potential obviousness combination with *Laird* in another related application. EX2002, 372-373 (“specific claim languages were discussed to

Petitioner’s *Becton* case. Pet.64-65 (citing informative *Becton* decision, which considered the prosecution history of the parent application); *see Becton*, 22 (“[the references] were substantively considered... ***during prosecution of the parent application*** from which the [challenged] patent issued....”).

overcome the potential rejection of said amended claims over Laird... *in view of McCloskey [III]*"). And the second '981 Notice of Allowance expressly concluded the art of record (including Linnarsson, McCloskey II, and Miner (both of which render McCloskey cumulative)) did not render the claims obvious: "A thorough search of the prior art, including the prior art submitted in the newly filed IDS..., shows no art that teaches *or reasonably suggests* the claimed invention." EX2001, 306. Thus, although Petitioner wholly ignores these aspects of '013's prosecution history, Petitioner's third pre-AB case, *Limelight*,⁷ and *Weber* (an institution decision that issued one day after AB), which Petitioner cites as support for this argument, are also inapposite, as both of Petitioner's references were considered in obviousness rejections in related applications for the same teachings and therefore are not "new" arguments. Pet.66 (citing *Limelight Networks, Inc. v. Akamai Techs., Inc.*, IPR2016-01631, 2016 WL 8115506, at *5 (P.T.A.B. Dec. 30, 2016); *Weber, Inc. v. Provisur Tech., Inc.*, IPR2019-01467, Pap.7, 9-10 (Feb. 14, 2020)).

⁷ Additionally, the secondary references in *Limelight* were neither before the examiner nor cumulative of references that were—whereas here, McCloskey is cumulative of references previously cited by the Office, including, *e.g.*, McCloskey II, Kanda, and Miner. *See supra*, §IV.A; *Limelight Networks, Inc. v. Akamai Techs., Inc.*, IPR2016-01631, 2016 WL 8115506, at *5 (P.T.A.B. Dec. 30, 2016).

Thus, *AB* part one clearly points to denial.

B. Advanced Bionics Part Two

AB part two considers whether a petitioner has demonstrated that the Office erred in a manner material to the challenged claims' patentability. *AB*, 8-9. *Becton* factors relevant to the part two inquiry include: (c) the record developed by the Office in previously reviewing the art or arguments; (e) whether petitioner sufficiently pointed out how examiner erred in evaluating the art; and (f) the extent to which petitioner's additional evidence and facts warrant reconsideration of the prior art or arguments. *AB*, 9-10. "If a condition in the first part of the framework is satisfied and the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute *inter partes* review." *Id.*, 8-9. "If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability. At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.*, 9.

Petitioner's argument for error is simply that "the Examiner materially erred by not considering the relevant teachings in Linnarsson, McCloskey, and McCloskey II." Pet.66. Petitioner is, to begin with, wrong on the facts: Linnarsson and McCloskey II *were* raised by the Office and substantively

considered during prosecution of applications leading to '013, and were distinguished by Applicant. (With consideration of the more detailed McCloskey II, the Examiner also clearly considered the teachings of McCloskey.) And Petitioner is also wrong on the law: Petitioner's conclusory assertion fails to show any actual Examiner "error."

Petitioner is factually incorrect, ignoring the prosecution history of '013's parent applications where the Office raised and expressly considered (and Applicant expressly distinguished) both Linnarsson and McCloskey II.

Petitioner completely fails to address the prosecution history of '013's parent applications, but this history is considered under the *AB* analysis. *Becton*, 22-23; *see Motorola*, 16 n.8 ("In determining whether the same or substantially the same prior art previously was presented to the Office, the Board considers *applications directly related to the challenged patent*, such as a parent application."). In applications related to '013, (1) the Applicant explicitly overcame a Linnarsson rejection, (2) the Applicant expressly distinguished McCloskey II from the claimed MID and overcame a potential rejection based on McCloskey II (EX2002, 335-336, 372-373, 383), (3) the Examiner made other rejections regarding the combination of tags (or MID) that were overcome (*supra*, §IV.A), (4) the Examiner expressly acknowledged the IDS that listed McCloskey II (EX2009, 76 (April 2, 2014 IDS), 130 ("The method steps... are non-obvious

improvements over the arts of the record and the ones cited in the IDS of April 2, 2014”)), and (5) the Examiner confirmed in the second Notice of Allowance of the related ’981 that the claims were patentable over the newly-filed IDS containing Miner (EX2001, 285, 306). Petitioner fails to explain how the teachings of Linnarsson or McCloskey II, summarized in McCloskey, were purportedly “overlook[ed]” in light of this prosecution history. *E.g.*, Pet.66-67. This is especially unlikely where the Applicant filed a terminal disclaimer against ’981, which issued over Linnarsson and other references of record, including, *e.g.*, McCloskey II and Miner. *See Ivantis*, IPR2022-01529, Pap.16, 15-18 (considering prosecution histories of continuations “determined by Examiner to not be patentably distinct” from parent application). Petitioner also fails to explain why *Becton* factor “(c)” weighs against exercising the Board’s discretion to deny institution where both Linnarsson and McCloskey II were the basis of actual or expressly-contemplated rejections by the Office. Pet.66-67; EX2002, 335-336, 372-373, 383.

Linnarsson. In the prosecution of ’981 and its parent application, the Examiner raised Linnarsson as a rejection. *Supra*, §§IV.A, V.A. Indeed, as detailed above, the Examiner made the same arguments Petitioner does here, and Applicant overcame them. *Supra*, §§IV.A, V.A. Petitioner is aware of this prosecution history, as it acknowledged *some* of it in its Petition seeking *inter*

partes review against '981. EX2008, 17-19. For example, Petitioner wholly ignores (both here and in its '981 Petition) the Examiner's statements in '981's second Notice of Allowance:

A thorough search of the prior art, including the prior art submitted in the newly filed IDS, filed after the Notice of Allowance mailed on 8/28/2018, shows no art that teaches or reasonably suggests the claimed invention. Likewise, amendments to the claims... further clarify ***the claimed invention***, which ***is free of the art***.

EX2001, 306. These statements affirmatively confirm that the Examiner performed and considered the results of a “thorough search of the prior art” and “the newly filed IDS,” *which also included Miner*, and concluded Linnarsson (which Applicant had just overcome) together with this other art did not “teach[] or reasonably suggest[] the claimed invention.” EX2001, 285, 306; EX1013. Petitioner's expert, Dr. Cooper, concedes Miner includes the same teachings as McCloskey, namely “removing amplification bias” by “add[ing] molecular tags... to target sequences prior to the amplification step” and quotes Miner's batch-stamp and barcode disclosure. EX1002, ¶¶72, 86-88; *see also* EX2008, 10-11 (citing EX1013, Miner). Indeed, Miner uses McCloskey's same oligonucleotide for the same purpose: a batch-stamp and barcode to identify contamination and redundant sequences in PCR. EX1013, 1; EX1004, 6. Petitioner neither acknowledges nor

confronts this explicit evidence that contradicts Petitioner's arguments of error regarding Linnarsson (and McCloskey and McCloskey II via Miner).

McCloskey. In the '450 application, the Examiner "requested that the Applicants provide a brief summary of how the claims are distinguished from [a set of] references." EX2002, 335. One of these references explicitly raised by the Office and distinguished by Applicant was McCloskey II. *Id.* Applicant explained that McCloskey II "does not provide *segments* of a region, where each of the segments has the same MID sequence; [and] also doesn't provide [a] composition in which all of the segments have a multiplex identifier that *uniquely identifies the individual molecule* of said contiguous region from which said segments originate." *Id.* (italics on first use of "segments" original). As Applicant's submissions reflect, the "Examiner indicated that the [discussed] amendment [*see supra*, 15] would likely distinguish the claims...." EX2002, 336. Further, the Office's Notice of Allowance in the '450 application acknowledged that "specific claim languages were discussed *to overcome the potential rejection* of said amended claims over Laird... *in view of McCloskey [III]* (cited in the previous interview)." EX2002, 372-373. The Notice continued:

It is also noted that *the bulk of the cited references in the said IDSs or in the field of molecular tagging prior to the filing date of the instant application discloses tagging of sample or a nucleic acid of interest with an identifier in the form of barcode, or multiplex*

identifier or zipcode or tagging sequences to track it in further analysis. However, it is [sic] in the Examiner's opinion it would not have been obvious to [POSITA] to modify the references of the record... to arrive at the claimed composition... wherein, in said composition, all of the segments of each of the nucleic acid molecules of the contiguous region comprises a unique MID sequence that uniquely identifies each of the nucleic acid molecules.

EX2002, 375. Thus, contrary to Petitioner's assertions, the Office certainly did not "overlook[]" McCloskey II during the prosecution leading to '013 (Pet.66-67)—to the contrary, McCloskey II was raised by the Office, explicitly discussed, and overcome by Applicant.

Nor did the Office overlook the numerous other references asserted to disclose a polynucleotide-distinguishing tag in the applications to which '013 claims priority, and over which McCloskey and McCloskey II are cumulative. *See supra*, §IV.A; Pet.66-67. And, as noted above, the Examiner expressly considered still more references and arguments in this same vein that Petitioner ignores. For example, in '343 application, the Examiner argued Kanda, cited on '013's face, taught the "limitation of broadly recited multiplex identifier because F2 can be used as the tag to differentiate a polynucleotide in the sample." EX2005, 728-729. The Examiner also argued that Laird disclosed the same. EX2005, 807-817. Applicant overcame both rejections, and the Examiner stated in its "Reasons for

Allowance” that “Laird alone or in combination with the art of record does not disclose or make it obvious the claimed method steps ‘a’ to ‘c’, wherein the polynucleotide strand comprises... *a multiplex identifier (MID) comprising a unique nucleotide sequence that distinguishes said polynucleotide strand from other polynucleotide strands in said sample...*” EX2005, 868. The Examiner continued, noting “[t]he instant method has several advantages... as compared to other extraction methods... that only use a single oligonucleotide sequence, allows to analyze homologous genomic locations in a multiplexed sample (i.e., a sample having polynucleotides from different genomic samples) in which the polynucleotides are tagged with the multiplex identifier domain.” EX2005, 868-869. And, finally, the Examiner confirmed the related ’981 was allowed—*after a Linnarsson rejection*—over the art in a newly filed IDS containing Miner, *which discloses McCloskey’s batch-stamp and barcode* approach. EX2001, 285, 306. Thus, these same arguments were explicitly considered in the prosecution of the parent applications and were overcome, and there was no “error” in the Examiner determining that McCloskey II and similar art did not disclose or render obvious the Challenged Claims’ polynucleotide-distinguishing tag.⁸

⁸ Similarly, in ’013’s related ’694 application, the Office once again expressly confirmed it had considered McCloskey II, stating in its Notice of Allowance that

As detailed above, Petitioner is clearly incorrect that the Examiner “erred by not considering the relevant teachings in Linnarsson, McCloskey, and McCloskey II.” Pet.66-67. Both Linnarsson and McCloskey II were raised by the Office, considered multiple times, and distinguished—including specifically in connection with Linnarsson’s purported disclosures of a first tag and McCloskey II’s purported disclosure of a second tag. *See, e.g.*, EX2001, 193-194 (discussing rejection in part because Linnarsson purportedly discloses a first tag); EX2002, 335-336 (McCloskey II “doesn’t provide [a] composition in which all of the segments have a *multiplex identifier that uniquely identifies the individual molecule* of said contiguous region from which said segments originate”), 372-373. Thus, Petitioner’s only allegation of “error” is, itself, wrong.

Petitioner’s allegation of “error” is legally insufficient under AB part two. Even setting aside Petitioner’s mistakes of fact, Petitioner’s bare conclusory assertion that “the Examiner materially erred by not considering the relevant

the “method steps of instant pending claims comprise the allowed limitation of ’767 patent, which are non-obvious improvements over the arts of the record *and the ones cited in the IDS of April 2, 2014.*” EX2009, 130. McCloskey II is the ninth reference listed in that IDS. EX2009, 75-76.

teachings in Linnarsson, McCloskey, and McCloskey II” is also legally insufficient to meet Petitioner’s burden of showing a material error. Pet.66-67.

First, Petitioner argues that “the Examiner did not discuss or cite any passage or disclosure of Linnarsson or McCloskey II” in the Notice of Allowance and that “the Examiner committed major error in Examination by erroneously stating that the prior art fails to teach a dual tagging approach when, in fact, this approach is plainly taught in both McCloskey and McCloskey II.” Pet.66-67. Both assertions are baseless.

Petitioner cites no case supporting its argument that an examiner errs if it fails to discuss each and every reference of record in a notice of allowance. Pet.66-68. Moreover, as explained above, this ignores the related ’981’s second Notice of Allowance where the Examiner discussed Linnarsson and stated she affirmatively considered “the prior art in the newly filed IDS,” which included Miner and its near-verbatim disclosure of McCloskey’s cited teachings. EX2001, 285, 306. (Again, ’013 is a continuation of ’981 and is terminally disclaimed against it—and those statements are equally applicable here. *Ivantis*, IPR2022-01529, Pap.16, 15-18.) It also ignores the substantive consideration of McCloskey’s teachings in the prosecution of the ’343 and ’450 applications leading to ’013. *Supra*, §§IV.A, V.A. These affirmative discussions of Linnarsson and McCloskey II and other references belie Petitioner’s attempt to limit the Office’s extensive prosecution

analysis over the chain of thirteen non-provisional applications leading to '013 to just '013's Notice of Allowance. Pet.66-67; *supra*, §IV.

And while Petitioner asserts it was “major error” to “stat[e] that the prior art fails to teach a dual tagging approach when, in fact, this approach is plainly taught in both McCloskey and McCloskey II,” that is not what the Examiner concluded. Pet.66-67. The Examiner stated that “the prior art does not teach or fairly suggest Applicants’ claimed method of... a first tag sequence which distinguishes the sample polynucleotide from the sample polynucleotide from other cells and a second tag sequence which distinguishes the sample polynucleotide from other sample nucleotides.” EX1005, 131. Petitioner apparently agrees with the Examiner, as *Petitioner included no anticipation ground* and uses McCloskey only for its purported “barcode.” Pet.27-59.

Second, Petitioner argues that “the fact that neither Linnarsson nor McCloskey II was ‘the basis of a rejection weighs strongly against exercising [the Board’s] discretion to deny institution.’” Pet.67. But this is nothing more than “equat[ing an] Examiner’s ***silence*** in discussing relevant prior art to a material error,” which (even if, *arguendo*, it were factually applicable here (it isn’t)) would ***not*** be a showing of error. *E.g.*, *Ivantis*, IPR2022-01533, Pap.14, 19; *Eyenovia*, IPR2022-00965, Pap.7, 23 (exercising §325(d) discretion and finding petitioner failed to show material error where there was no rejection issued over the IPR

references but each reference was before the examiner or cumulative of references before the examiner); *Microsoft Corp. v. AlmondNet, Inc.*, IPR2022-01319, Pap.9, 10-11 (Jan. 30, 2023) (rejecting petitioner’s argument that “the prior art references in the Petition ‘were not substantively considered during [prosecution]’” where identical art was before the Examiner and there was no evidence it was concealed); *Microsoft Corp. v. ThroughPuter, Inc.*, IPR2022-00757, Pap.10, 20-22 (Nov. 1, 2022) (no error even though art was not the basis of a rejection); *Motorola*, 22-23.

Petitioner cites an array of inapposite cases, for *AB* part two, based on its attempt to ignore the numerous related applications in ’013’s prosecution history. When the full prosecution history is considered, as it must be, Petitioner’s error in relying on these decisions is glaringly apparent. Petitioner’s reliance on *Cellco Partnership v. Huawei Device Co.*, IPR2020-01117, Pap.10, 13 (Feb. 3, 2021) is misplaced. Pet.67. There, petitioner’s reference was not the basis of a rejection during prosecution, which weighed against exercising discretion to deny institution. Here, in contrast, both Linnarsson and McCloskey II *were* expressly identified by the Office in the related applications as actual and contemplated bases for rejection, and both were overcome by Applicant. EX2002, 335-336, 372-372. Indeed, if anything, *Cellco* supports the Board exercising its discretion and denying institution. *See Cellco*, IPR2020-01117, Pap.10, 12-13. Similarly, unlike in *Amber.IO, Inc. v. 72LUX, Inc.*, IPR2020-00015, Pap.8, 20 (Apr. 1, 2020), the

alleged prior art teachings of Linnarsson and McCloskey II were substantively considered and distinguished in prosecution of the related applications for the same teachings Petitioner uses here—and Petitioner never identifies any specific teaching it alleges the Examiner overlooked. Pet.66-67; EX2002, 335-336, 372-373. Indeed, Petitioner does not even *discuss*, let alone contend there was any error in, Applicant’s or the Office’s stated understanding of Linnarsson or McCloskey II when they were distinguished during prosecution of related applications. Pet.66-67.

Thus, both parts one and two of *AB* point to denial, and—as a threshold reason to deny the Petition without the need for further discussion—the Board should exercise its discretion under § 325(d) to deny institution here.

VI. 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). PO agrees that at this time, solely for purposes of an institution decision on the Petition, no terms require explicit construction.

VII. Petitioner’s Obviousness Arguments Fail

Petitioner’s Ground 1 is based on the combination of Linnarsson and McCloskey. As discussed below, Petitioner concedes *neither* Linnarsson nor McCloskey teaches ligating a tag to a polynucleotide, and Petitioner fails to meet

its burden to establish obviousness more generally. Petitioner’s Ground 2 builds on its Ground 1 arguments, and accordingly fails for at least the same reasons.

**A. The Petition Must Be Denied Because Petitioner Fails to Allege—
Let Alone Establish—That Its References Are Analogous Art *To*
*’013***

Nowhere does Petitioner assert—let alone attempt to prove—that any of the three references named across its two grounds (primary reference Linnarsson and secondary references McCloskey and McCloskey II) are analogous art *to ’013*. See Pet.35. This omission is *fatal* to the Petition: A petitioner *cannot meet its burden* when it “argue[s] that [the prior art reference] is analogous to another prior art reference *and not the challenged patent*.” *Sanofi-Aventis*, 66 F.4th at 1374. “[A] patent challenger must compare the reference *to the challenged patent*.” *Id.* Petitioner here failed to perform the required analogous art analysis by not addressing whether its relied-upon art is analogous *to the challenged ’013 patent*; it only asserts that McCloskey, Petitioner’s secondary reference, is analogous to Linnarsson, its primary reference. Pet.35; EX1002, ¶170. (Petitioner does not even allege McCloskey II is analogous to Linnarsson.) Because Petitioner’s grounds rely entirely on obviousness and Petitioner was therefore required to establish that its obviousness art is analogous *to the challenged ’013 patent* as a threshold issue, both Grounds must be rejected because Petitioner cannot establish obviousness as a matter of law. *Sanofi-Aventis*, 66 F.4th at 1380.

B. Petitioner Fails to Clearly Identify The Art In Its Combinations

Ground 1 alleges obviousness based on “Linnarsson in view of McCloskey, and further in view of *the knowledge of a POSA*.” Pet.5, 27. Ground 2 builds on Ground 1, and relies on “Linnarsson in view of McCloskey, McCloskey II, and further in view of *the knowledge of a POSA*.” Pet.5, 60. However, Petitioner *also* cites, *e.g.*, Hug, Okayama, Shibata, and Hayazhizaki in arguing obviousness of the “ligation reaction” limitation despite not listing any of those references as part of Petitioner’s grounds. Pet.37-39; *see also* Pet.5. It is unclear what Petitioner’s various grounds actually *are*; whether Petitioner is relying on each of these additional references separately, together, or in sub-combinations; and whether Petitioner has any ground that does *not* rely on at least one (or two, or more) of those references. Petitioner’s approach lacks the required particularity, may tempt Petitioner to improperly attempt to shift its theories in Reply, deprives PO of due process and a meaningful opportunity to fully respond to such an amorphous set of grounds, and requires denial under at least §§314(a) and 312(a)(3). *Avant Tech., Inc. v. Anza Tech., Inc.*, IPR2018-00828, Pap.7, 13-14 (Oct. 16, 2018) (“This lack of clarity means that if [PO] were to defend against fewer than all of these theories, Petitioner could shift its position to one of the unchallenged combinations.”); *Jiangsu Sainty Sumex Tools Corp. v. Milwaukee Elec. Tool Corp.*, IPR2021-00373, Pap.19, 23-24 (July 6, 2021) (denying institution where petitioner’s asserted

combinations included “one or more of” five references “in combination with one or more of common knowledge [or] common sense,” explaining this “raises a formidable number of possible... combinations” and finding “no good reason to subject Patent Owner to the burden and expense of a trial”); *Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Pap.20, 22-23 (Mar. 6, 2019) (informative) (“The extent to which these additional documents may be relied upon to fill gaps... increases our concern that the Petition lacks the required particularity, and, instead, turns the Petition into an empty invitation for the Board and Patent Owner to search the record for evidence that might support the full breadth of Petitioner’s contentions.”); *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 296 (2016) (Alito J., concurring-in-part) (“[I]f a petition fails to state its challenge with particularity... the patent owner is forced to shoot into the dark. The potential for unfairness is obvious.”); *see also* §312(a)(3).

C. Petitioner Fails to Clearly Articulate How The Art Is Combined

Petitioner also fails to clearly articulate the modifications it proposes making to the art in its obviousness combination(s). Its unexplained grab-bag of obviousness theories cannot meet its burden. As discussed in more detail below, Petitioner’s approach improperly forces PO (and the Board) to guess at what Petitioner is arguing and prevents PO from fully rebutting Petitioner’s arguments. “Merely identifying where limitations may be found in several prior art references

is not sufficient... without articulating *how* and why *specific teachings of the references would have been combined.*” *John Crane, Inc. v. Finalrod IP, LLC*, IPR2016-01827, Pap.6, 13-14 (Jan. 31, 2017); *Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 994 (Fed. Cir. 2017) (reversing obviousness determination where there was no “clear, evidence-supported account of the contemplated workings of the combination” which “is a prerequisite to adequately explaining and supporting a conclusion” of obviousness); *ActiveVideo Networks, Inc. v. Verizon Commc’ns, Inc.*, 694 F.3d 1312, 1327-28 (Fed. Cir. 2012) (affirming reversal of obviousness verdict where expert “failed to explain how specific references could be combined” including “how any specific combination would operate or read on the asserted claims”); *Axon Enter., Inc. v. Digital Ally, Inc.*, IPR2017-00515, Pap.10, 18-19 (July 6, 2017) (denying institution, stating neither petitioner nor its expert “explains in sufficient detail the nature of Petitioner’s proposed modification... Petitioner does not explain in sufficient detail *how* the proposed modification is supposed to work”). Indeed, the inability to identify the obviousness combination Petitioner is arguing prevents “informed evaluation” by the Board and deprives PO “of an appropriate opportunity to respond.” *E.g., John Crane*, IPR2016-01827, Pap.6, 13-14.

**1. It Is Not Clear If The “Second Tag” Is Added To
Linnarsson Or Replaces Linnarsson’s “Tags”**

It is not clear whether Petitioner proposes *adding* a “tag” to Linnarsson or *replacing* a Linnarsson “tag” with a McCloskey “tag.”⁹ Petitioner begins by suggesting Linnarsson’s nucleotides include or “can” include two tags. Pet.33. Petitioner alleges that the polynucleotide sample in Linnarsson “comprises a *combination* of tags” after vaguely stating that “[b]oth the CDS and the TSO *can* include a tag” (whatever Petitioner might intend “can” to suggest). Pet.33-34. But Petitioner then asserts it would have been obvious to “*further introduce a second* tag to distinguish polynucleotides (as taught by McCloskey) using ligation....” Pet.35. It is unclear whether Petitioner is arguing that this results only in a “*second*” tag (essentially replacing one or some portion of one of Linnarsson’s alleged already-existing “*combination* of tags” with McCloskey’s “encoding

⁹ Petitioner’s make-weight suggestion that *Linnarsson* teaches ligating a second oligonucleotide (which Petitioner’s analysis seems to indicate would include a tag distinguishing each polynucleotide from the others) doesn’t pass the straight-face test. Pet.34 (“To the extent Linnarsson does not teach ligating a second oligonucleotide tag...”). Petitioner identifies no alleged Linnarsson tag that is *ligated* nor any tag that *distinguishes each polynucleotide* (and, indeed, Linnarsson teaches neither).

oligonucleotide” (or some unarticulated portion of it) to yield a total of *two* tags) or a “*further*” tag, which would make it a *third* tag.

Elsewhere, Petitioner refers to a “second sequence [ligated] to Linnarsson’s CDS or TSO” (Pet.38), seeming to suggest that an alleged second tag is *added to* a tag in Linnarsson. Again, Petitioner never squares its assertions about *adding* a tag versus *replacing* a tag in the primary reference.

2. It Is Not Clear Where Or When The Argued Second “Tag” Is Added, Or How It Is Ligated

In part because it is not clear whether Petitioner argues a second tag is added to or replaces an alleged tag in Linnarsson, the Petition is also unclear about *where* the second tag is added or *when* it is added in Linnarsson’s reverse transcription process. It is also unclear from Petitioner’s argument *how* the ligation (and subsequent steps, such as the required amplification) occurs. This lack of clarity is exacerbated by the fact that (as Petitioner recognizes) *neither Linnarsson nor McCloskey teaches ligating any claimed tag to any polynucleotide*. See Pet.35.

First, it is not clear where the alleged second tag is ligated under Petitioner’s theory. See Pet.38-39. For example, it is not clear whether Petitioner’s theory involves ligating the “second tag” to Linnarsson’s TSO/CDS or to some part of a(nother) polynucleotide. In portions of its obviousness argument, Petitioner seemingly asserts that the “second tag” would be ligated to Linnarsson’s CDS or TSOs. See, e.g., Pet.38 (asserting POSITA “would have had a reasonable

expectation of success in ligating a *second* sequence to *Linnarsson's CDS or TSOs.*"). Petitioner elsewhere asserts that *McCloskey* introduces tags through primer extension, and argues it would have been obvious to "instead introduce the molecule tag via ligation." Pet.37. But *McCloskey's* tags are annealed to a "genomic target binding site" (and not to an extension product) before any extension. EX1004, 3-4. Thus, unlike the first theory, this second theory (to the extent it can be understood) does not seem to involve ligating a sequence to *Linnarsson's CDS or TSO*.

It is also unclear when in *Linnarsson's* reverse transcription process the alleged ligation occurs. For example, Petitioner briefly references "**adding**" a "tag sequence" (whatever that "sequence" might include) "**after extension**" (Pet.39 (citing EX1002, ¶149)). But, there are multiple steps in *Linnarsson*, and Petitioner does not identify the "extension step" after which tagging allegedly occurs. *See* EX1003, Figs.2, 11; *see infra*, 54. Petitioner elsewhere seemingly argues the alleged molecule tag from *McCloskey* would **substitute** for an alleged tag in *Linnarsson's* CDS or TSO (Pet.37), but again, Petitioner fails to identify when in *Linnarsson's* process this substitution would occur. *See* Pet.37-39.

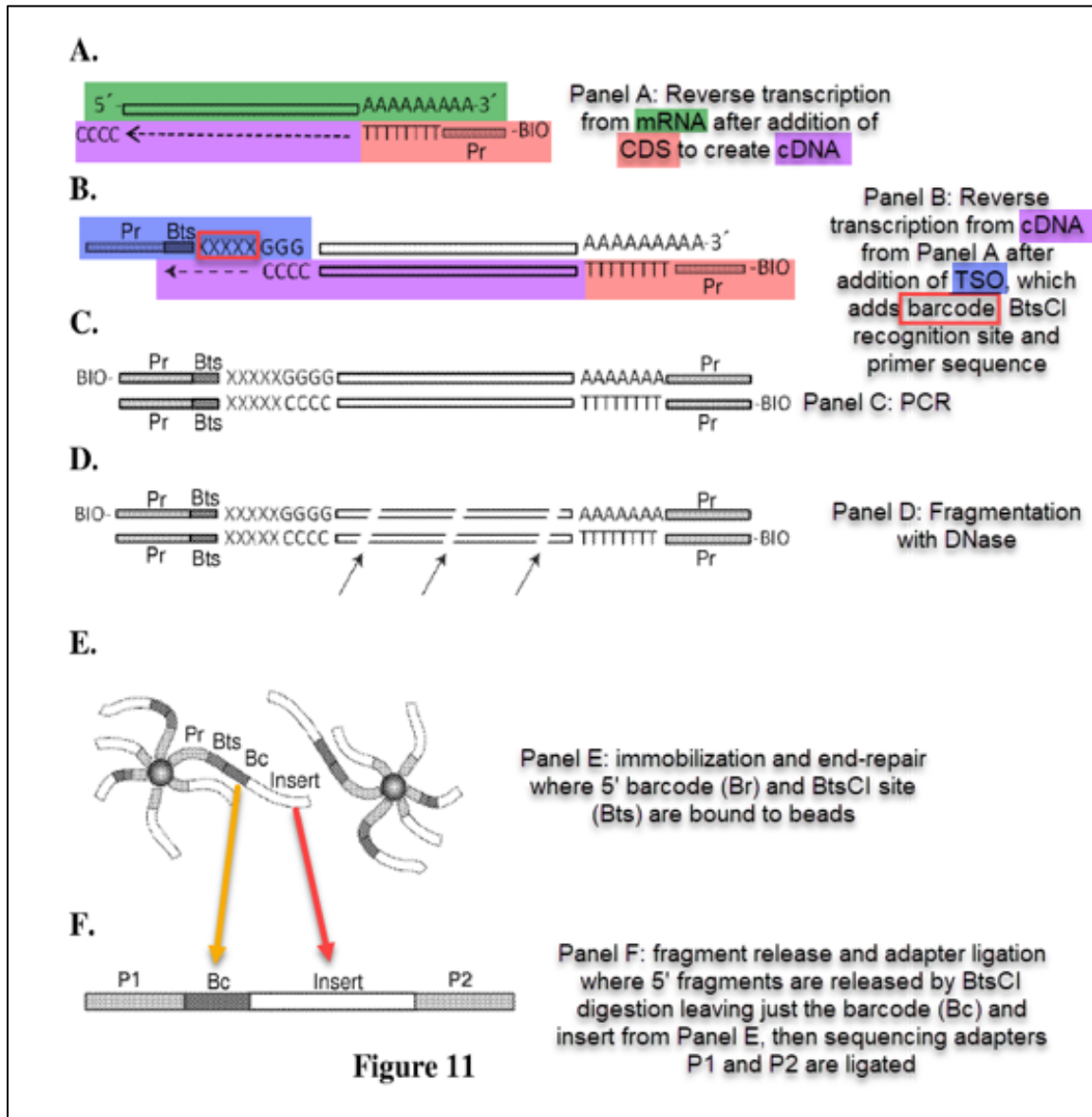
Finally, it is unclear from Petitioner's arguments exactly how Petitioner's argued ligation in the combined method would occur and how the claimed subsequent step of amplification (of a tagged polynucleotide) would then proceed.

For example, to the extent Petitioner is arguing that McCloskey’s alleged “molecule tag” is separately added to Linnarsson “via ligation” *instead* of through Linnarsson’s CDS or TSO (which themselves are argued to be somehow modified—in unspecified fashion—by McCloskey’s “molecule tag” (Pet.37)), Petitioner fails to explain how any such substitution would work. In contrast to how Linnarsson adds a CDS or TSO to a polynucleotide (*i.e.*, annealing part of it to a *complementary* strand to form a short section of double-stranded oligonucleotide), ligation essentially involves gluing the sequence *to the end of an existing polynucleotide*. EX1001, 6:23-40.¹⁰

Petitioner also fails to explain how its combination would result in the claimed “tagged polynucleotide,” which must then be amplified, if McCloskey’s alleged tag were added to the *end* of Linnarsson’s disclosed polynucleotide. *See* EX1001 30:43-67. Linnarsson relies on part of the CDS (and TSO) acting as a primer—“a point of initiation of nucleic acid synthesis [capable of] being extended from its 3’ end... so that an extended duplex is formed.” EX1003, 16:10-26; *see*

¹⁰ And Linnarsson adds a CDS *before any extension product exists* (EX1003, 24:13-20), whereas the Challenged Claims require that the second oligonucleotide tag be ligated “*to said extension product*.” Thus, under this theory, Petitioner fails to identify any extension product to which a tag could even be ligated.

also Pet.18-19; EX1001, 9:60-64. To the extent Linnarsson has “tags,” those tags (which Petitioner equates to Linnarsson’s barcodes) are located *inside* the primer sequence (identified in Figure 11 below as “Pr”) not on the *end* of a tagged polynucleotide (as in Petitioner’s McCloskey argument). EX1003, Fig.11.



Linnarsson’s alleged tag is instead capped with a primer sequence and a biotin molecule. EX1003, Fig.11. And, as discussed below, Linnarsson has a Bts

sequence between the cell tag and the end of the cDNA. EX1003, Fig.11.

According to Linnarsson, any sequence towards the 5' end of the Bts sequence will be **removed**—*i.e.*, “released by BtsCI digestion, **leaving just the barcode (Bc) and insert.**” EX1003, 5:28-6:12, Fig.11 (Panel F). Thus, even if Petitioner is arguing one would simply ligate the second tag to the end of the Linnarsson’s TSO, Petitioner fails to address why the alleged tag would not be **cleaved off**. Once cleaved, there would be no “second tag sequence” on the tagged polynucleotide when sequenced, and thus no ability to distinguish among sample polynucleotides as required by the claims. EX1001, cl.1. Further, Petitioner does not address the significance of a **primer** not being on the 5' end of the tag. Petitioner does not explain how replication of the tag sequence would work (or even if it could work) if a “tag” (rather than, *e.g.*, a primer) is at the end of the polynucleotide. *See, e.g.*, EX1003, 15:1-11, 15:32-16:26, Fig.11.

Even assuming a second strand of DNA complementary to the “tag sequence” were somehow created, issues with Petitioner’s vague ligation theory remain. For example, Petitioner asserts that Hug’s method “could” be used to “ligate the oligonucleotide comprising the tag sequences to Linnarsson’s CDS or TSO.” Pet.39. But Hug is not part of Petitioner’s articulated combination, and Petitioner never even asserts Hug is analogous to ’013.

Moreover, Petitioner fails to explain how Hug would be combined with

Linnarsson and McCloskey. *See* Pet.38-39; *Health Care Logistics, Inc. v. Kit Check, Inc.*, IPR2019-00385, Pap.7, 14-15 (June 3, 2019) (denying institution because petitioner failed to explain how to modify a reference to meet a limitation and why a POSA would be motivated to do so). Hug describes cutting double-stranded DNA with a particular restriction enzyme, resulting in double-stranded DNA with a 5' sticky end with a particular overhanging sequence, and then adding short linkers. EX1007, 7-8, Fig.3. But unlike tags that distinguish polynucleotides (EX1001, cl.1), ***Hug's linkers are not unique.*** Instead, the linkers consist of the recognition site of a restriction enzyme (a sequence that hybridizes to the sticky end resulting from cutting the DNA in the sample with a particular restriction enzyme, such as BamH1) and an end with a short polynucleotide sequence that hybridizes to the other linker. EX1007, 7-8, Fig.3. Petitioner never acknowledges these conflicting details of Hug's ligation method, let alone explains how to use Hug's technique to ligate a "second tag" to the combination of Linnarsson and McCloskey, or what further modifications would be necessary to achieve ligation. Petitioner also fails to acknowledge and address the differences between McCloskey's "encoding oligonucleotide," which contains multiple different sites and is in a hairpin formation (EX1004, Fig.1; *see also* Pet.34), with the very short non-unique sequences of Hug's linkers.

Further, Petitioner asserts that Hug's "linker" would have been

“hybridize[d] to Linnarsson’s CDS and/or TSO as well as the oligonucleotide, which would then be ligated to the CDS and/or TSO.” Pet.39. In addition to ignoring the fact that Hug’s linkers are not customized in this way, this argument makes no sense and seems to suggest ligation of a CDS or TSO to McCloskey’s oligonucleotide, but says nothing about ligating a *“second tag”* to the CDS or TSO. Further, Petitioner ignores the biotin group at the 5’ end of the CDS (Pet.32; EX1003, Fig.11), and fails to address how this would impact ligation, or how adding a tag *without* having a biotin group on the end would impact Linnarsson’s method. Pet.37-39, 32-33; EX1003, 32:18-25.

3. It Is Not Clear Which Part of McCloskey’s “Encoding Polynucleotide” Is Incorporated In The Combination

As an even more basic matter, Petitioner never sufficiently explains exactly *what* would comprise the “molecule tag” in its asserted combination. Even setting aside Petitioner’s unsupported suggestion that *Linnarsson* teaches a “molecule tag” (which Petitioner seems to equate to the “second tag”) (*see* n.9), Petitioner never clearly identifies what teaching of *McCloskey* corresponds to what it calls the “molecule tag.” *See, e.g.*, Pet.22-26, 35 (referring generally to “McCloskey’s encoding oligonucleotide”), 37. For example, Petitioner does not articulate whether what it calls “McCloskey’s molecule tag” (Pet.34-35) is all or part of McCloskey’s “encoding oligonucleotide.”

D. Petitioner Ignores The Differences And Incompatibilities Between Linnarsson And McCloskey

As part of the cascade of insufficiently-articulated modifications Petitioner vaguely proposes making to its base reference, Petitioner asserts that McCloskey's barcode would simply be added to or substituted for Linnarsson's tagged CDS or TSO. Pet.34-37. But, even setting aside issues discussed above (*see supra*, §VII.C), Petitioner fails to acknowledge the *differences* between the two references, let alone address how those differences would be resolved in combining them. Indeed, Linnarsson is focused on gene *expression* (based on mRNA transcribed from the genes to be expressed). *See* EX1003, 1 (Abstract). Linnarsson's tags track the cell of origin of the transcribed mRNA when reverse-transcribing the mRNA to cDNA as part of the creation of a comprehensive cDNA *library*. EX1003, 9:24-25, 10:32-33; Pet.17-18. McCloskey, in contrast, is not about gene expression. Rather, McCloskey is about tagging copies of the DNA of a *particular gene*. EX1004, 6; Pet.22-23. McCloskey's oligonucleotides anneal only to a specific binding site on a gene, and are used when amplifying a gene of interest via PCR in a bulk analysis to identify whether the gene (including any allele or mutation) is present in the tested sample, but provides no information about whether that gene is expressed (EX1004, 4; Pet.22-26). *See also supra*, §§III.A-III.B.

Petitioner vaguely refers to the use of Linnarsson's "CDS and/or TSO" in

the combination, but fails to address, for example, that Linnarsson's *CDS* tags are designed to analyze gene expression and anneal to **every** mRNA molecule in the sample in connection with reverse-transcribing it into cDNA. Indeed, Petitioner admits that the tags in Linnarsson's CDSs anneal to **every** mRNA molecule—for example, to mRNA's poly-A tail. Pet.18; EX1003, 24:13-20, Fig.2. Similarly, Linnarsson's *TSO* tags are designed to universally anneal “to the series of cytosine nucleotides at the end of the newly-synthesized [cDNA] strand.” Pet.19-20; EX1003, 18:19-26. In other words, Linnarsson's tags are designed to anneal to **each and every** mRNA and/or cDNA to analyze gene expression, and are **not** designed to anneal solely to a **particular** gene or allele; nor does Petitioner claim they are. McCloskey's tag, in contrast, has a “3' genomic target binding site” that anneals **only** to a DNA sequence specific to the genomic target binding site and is particular **only** to the specific gene (and targeted DNA sequence) to which it is designed to bind. EX1004, 3-4; Pet.22-24. And, even according to Petitioner, its barcode distinguishes among allele copies. Pet.23. But nowhere does Petitioner address the distinction between the tags in McCloskey, which anneal to a specifically-targeted sequence, and Linnarsson's tags, which generically anneal to each and every mRNA and reverse-transcribed cDNA strand. EX1003, 18:19-30. Indeed, McCloskey's tag is not designed to anneal to Linnarsson's mRNA sample polynucleotides or a reverse-transcribed cDNA, which Petitioner does not establish

are present in McCloskey. Petitioner ignores these distinctions in summarily asserting that there would be a motivation to combine and REOS. Pet.34-37.

E. Petitioner Fails to Show Any Motivation to Ligate A “Second Tag”

Taken at face value, Petitioner’s assertion that ligation “would be *entirely equivalent* to the method already disclosed by Linnarsson” negates any motivation to modify Linnarsson given that any resulting method would be “equivalent.” Pet.39; *In re Schweickert*, 676 F. App’x 988, 995 (Fed. Cir. 2017) (reversing Board’s obviousness determination where modification was “unnecessary” to prior art system that “already” performs function of proposed modification and “would do little more than add unwanted cost and complexity to the system”); *Current Lighting Sols., LLC v. ALSI Holdings, LLC*, IPR2023-00125, Pap.12, 18-20 (May 3, 2023) (denying institution where petitioner asserted it “would have been an obvious design choice” to retrofit prior art with a LED lighting system without any “objective evidence sufficient to show that the proposed modification would provide any particular benefit”); *Thor Indus., Inc. v. Grand Design RV, LLC*, IPR2022-00411, Pap.9, 41-44 (July 14, 2022) (similar).

To the extent Petitioner’s threadbare argument and combination can be understood, the Petition appears to suggest that ligating a tag may *add* steps to Linnarsson’s additions of a CDS and TSO. Pet.39. Petitioner never explains why POSITA would have been motivated to add a step (of ligating a tag) only to yield

an “equivalent” process. Petitioner tries to justify modifying Linnarsson by asserting “POSA would have been motivated to utilize this design choice because it would allow for added flexibility in selecting tag sequences during an experiment” (a statement its expert repeats verbatim, without additional analysis or support). Pet.39 (citing EX1002, ¶149). But this is contradicted by Petitioner’s assertion about the method being “entirely equivalent.” Pet.39. And, neither Petitioner nor its expert explains how or what this “added flexibility” is, or why such “flexibility” would not be achieved *without* this further modification. Pet.39 (citing EX1002, ¶149). Indeed, Petitioner asserts that Linnarsson and McCloskey each provide “tags,” and Petitioner does not explain why *ligating* a tag (rather than, *e.g.*, adding it via primer extension, which Petitioner says would have been obvious *before* further modifying its combination with ligation) would “allow for added flexibility in *selecting* tag sequences.” Pet.39. Petitioner’s assertion is conclusory, and the Petition fails for that reason alone. *Salpeter v. ARP Wave, LLC*, IPR2019-01384, Pap.12, 16-17 (Jan. 27, 2020) (denying institution and stating that “[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements”) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)); *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”); *Motorola*, 34-35 (same).

F. Petitioner’s Motivation To Combine Fails Because Petitioner Fails To Establish Its Amplification Bias Premise

Petitioner erroneously argues McCloskey includes a second tag sequence on the MID to “distinguish individual molecules,” asserting this supplies a motivation to combine because McCloskey “provides the exact solution” to Linnarsson’s “amplification bias” problem. *See* Pet.35-36. Petitioner argues that “[b]y incorporating a ‘second’ tag in an oligonucleotide that uniquely identifies *the sample polynucleotides* prior to amplification, McCloskey ‘*solve[s]*’ this source-uncertainty problem for DNA sequences generated by standard PCR.” Pet.36; *see also* EX1002, ¶190.

First, Petitioner does not establish that McCloskey *tags the sample polynucleotides*. Indeed, as discussed above, McCloskey tags *only* copies of a *particular* gene of a cell’s DNA. Petitioner fails to explain how McCloskey could solve any alleged amplification bias problem (in the context of Linnarsson’s creation of a cDNA library based on mRNA of genes expressed in a cell) *when McCloskey teaches tagging only a particular gene to solve the problem of false-positives due to contamination, and does not teach how to tag, let alone distinguish, each and every gene, let alone each expressed mRNA molecule within a sample*. EX1004, 1-2. Indeed, Petitioner identifies no teaching in McCloskey of a second tag “that uniquely identifies *each* sample polynucleotide,”

as Petitioner’s expert argues is necessary to motivate the combination—

McCloskey only tags specific polynucleotides. EX1002, ¶173; Pet.35-37 (citing EX1002, ¶¶171-174). And because McCloskey’s tags are specific to copies of a particular gene, McCloskey does not teach giving each mRNA molecule (or even each DNA molecule) in a cell its own barcode.

Second, Petitioner attempts to sidestep the fact that Linnarsson itself already addresses amplification bias issues that could interfere with its process and describes how to do so. Pet.35-37. Petitioner does not explain how any remaining amplification bias in Linnarsson creates any issues with its own process, how any amplification bias “solution” from McCloskey would improve Linnarsson, or why POSITA would have been motivated to address in Linnarsson an issue that Linnarsson already addresses. Pet.35-37; *Life Spine, Inc. v. Globus Med., Inc.*, IPR2022-01603, Pap.8, 40 (June 12, 2023) (denying institution where petitioner “has not articulated sufficient reasoning to explain why a POSITA would modify [its base reference] to address a concern [it] already addresses via a different mechanism.”); *Google LLC v. Jawbone Innovations, LLC*, IPR2022-00889, Pap.12, 20 (Nov. 14, 2022) (similar).

G. Petitioner Fails To Establish REOS

Petitioner’s REOS argument fails because Petitioner did not describe its combination in sufficient detail to be able to fully assess REOS. *John Crane*,

IPR2016-01827, Pap.6, 13-14; *Autostore Sys. Inc. v. Ocado Innovation Ltd.*,
IPR2022-00443, Pap.7, 24 (July 20, 2022) (“[w]ithout any explanation as to how
the final design implements Petitioner’s proposed structural changes... we have
little guidance, and inadequate support, for Petitioner’s argument that its proposed
modifications would have a high degree of success”). In addition to the issues
raised above in terms of how the combination would work (*see, supra, e.g.*,
§VII.C), Petitioner’s REOS argument also fails because it expressly depends on
Petitioner’s expert’s unexplained and unsupported assumption that McCloskey has
a tag that “that uniquely identifies each sample polynucleotide.” EX1002, ¶173;
Pet.35-37 (citing EX1002, ¶¶171-174). Petitioner does not explain how *each*
sample nucleotide in Linnarsson would be tagged based on McCloskey’s teachings
(to create Linnarsson’s library) especially where Linnarsson’s CDS tags anneal to
all mRNA molecules and Linnarsson’s TSO tags anneal to *all recently synthesized*
cDNA created from cellular mRNA, but McCloskey’s tags anneal *only* to copies of
a particular gene. *See supra* §VII.F. Thus, because Petitioner has made no
showing that McCloskey even tags—let alone “distinguishes”—*each*
polynucleotide in the sample (as opposed to, say, specific alleles (different versions
of the same gene)), Petitioner cannot satisfy its own specified condition for
showing REOS, which is expressly conditioned on McCloskey disclosing tags that

uniquely identify each sample polynucleotide. *See* Pet.36.¹¹

VIII. Conclusion

As detailed above, Petitioner has failed to meet its burden to show there is a reasonable likelihood it will prevail in proving the Challenged Claims unpatentable, and the Petition should be denied in its entirety. In addition, or alternatively, the Board should exercise its discretion to deny the Petition under §§325(d) and/or 314.

Respectfully submitted by:

Dated: September 15, 2023

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¹¹ And even if only tagging copies of a particular gene, Petitioner does not explain how that would be done if, *e.g.*, the tag were ligated to the end of a preexisting sequence. *See supra*, §VII.C.1-2.

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 complies with the type-volume limitation in 37 C.F.R. §42.24(c)(1). According to the word-processing system's word count, the brief contains 13,696 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

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