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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.

Petitioner,

v.

10X GENOMICS, INC.

Patent Owner

Case No. IPR2023-_____
U.S. Patent No. 10,240,197

**PETITION FOR *INTER PARTES* REVIEW
OF
U.S. PATENT NO. 10,240,197**

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PETITIONER'S EXHIBIT LIST

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EX1001	U.S. Patent No. 10,240,197 (“the ’197 patent”)
EX1002	Declaration of Gregory Cooper, Ph.D.
EX1003	PCT Patent Publication No. WO 2010/117620 to Linnarsson et al. (“Linnarsson”)
EX1004	Megan L McCloskey et al., <i>Encoding PCR Products with Batch-Stamps and Barcodes</i> , 45 Biochemical Genetics, 761-767 (2007) (“McCloskey”)
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EX1007	Hubert Hug et al., <i>Measurement of Number of Molecules of a Single mRNA Species in a Complex mRNA Preparation</i> , 221 J. Theor. Bio., 615-624 (2003) (“Hug”)
EX1008	Intentionally left blank.
EX1009	Gerald Schochetman et al., <i>Polymerase Chain Reaction</i> , 158 J. of Infectious Diseases 1154-1157 (1988) (“Schochetman”)
EX1010	Intentionally left blank.
EX1011	H.C. Yang et al., <i>A genome-wide study of preferential amplification/hybridization in microarray-based pooled DNA experiments</i> , 34 Nucleic Acids Research 1-11 (2006) (“Yang”)
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EX1013	Brooks E. Miner et al., <i>Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR</i> , 32 Nucleic Acids Research 1-4 (2004) (“Miner”)

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EX1020	Curriculum Vitae of Gregory Cooper
EX1021	Jonas Binladen et al., <i>The Use of Coded PCR Primers Enables High Throughput Sequencing of Multiple Homolog Amplification Products by 454 Parallel Sequencing</i> , 2(2): e197 PLoS ONE 1-9 (2007) (Binladen)
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EX1023	Motion Success for Stay Pending IPR In Delaware District
EX1024	Hiroto Okayama and Paul Berg, <i>High-Efficiency Cloning of Full-Length cDNA</i> , 2 Molecular and Cellular Biology 161-170 (1982) (“Okayama”)
EX1025	Bruce Alberts, et al., “Chapter 6 How Cells read the Genome: From DNA To Protein,” <i>Molecular Biology of the Cell</i> , Garland Science 299-335 (4th ed. 2002)

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EX1026	Assignment Record for U.S. Patent 8,298,767
EX1027	10x Genomics Legal Notice
EX1028	Declaration of Sylvia D. Hall-Ellis, Ph.D.
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EX1030	S. Clancy et al., <i>Translation: DNA to mRNA to Protein</i> , Nature Education (2008), at https://www.nature.com/scitable/topicpage/translation-dna-to-mrna-to-protein-393/
EX1031	Cole Trapnell, <i>Defining cell types and states with single-cell genomics</i> , 25(10) Genome Research 1491-1498 (2015) (“Trapnell”)
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EX1034	Maria de Fatima Bonaldo et al., <i>Normalization and Subtraction: Two Approaches to Facilitate Gene Discovery</i> , 6(9) Genome Research 791-806 (1996) (“Bonaldo”)
EX1035	Sydney Brenner et al., <i>In vitro cloning of complex mixtures of DNA on microbeads: Physical separation of differentially expressed cDNAs</i> , 97.4 Proceedings of the Nat’l Academy of Sci. 1665-1670 (2000) (“Brenner”)
EX1036	David H. Persing, <i>Polymerase Chain Reaction: Trenches to Benches</i> , J. of Clinical Microbiology 1281-1285 (1991) (“Persing”)
EX1037	Kazuki Kurimoto et al., <i>An improved single-cell cDNA amplification method for efficient high-density oligonucleotide microarray analysis</i> , 34(5) Nucleic Acids Research 1-17 (2006) (“Kurimoto”)
EX1038	Shigeyuki Esumi et al., <i>Method for single-cell microarray analysis and application to gene-expression profiling of GABAergic neuron progenitors</i> , 60 Neuroscience Research 439-451 (2008) (“Esumi”)

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EX1039	Y. Shibata et al., <i>Cloning Full-length, Cap-Trapper-Selected cDNAs by Using the Single-Strand Linker Ligation Method</i> , 30(6) Biotechniques 1250-1254 (2001) (“Shibata”)
EX1040	U.S. Patent Application 2004/0166499
EX1041	Athina Gkazi, <i>An Overview of Next-Generation Sequencing</i> , Technology Networks Genomics Research at Figure 2 (March 17, 2021) at https://www.technologynetworks.com/genomics/articles/an-overview-of-next-generation-sequencing-346532
EX1042	Rami Sukarieh, <i>Relocalization of eIF4E by its binding partners upon stress</i> , Figure 2 (August 2009) at https://www.researchgate.net/publication/41663010_Relocalization_of_eIF4E_by_its_binding_partners_upon_stress
EX1043	Clyde A. Hutchinson, <i>DNA sequencing: bench to bedside and beyond</i> , 35(18) Nucleic Acids Research 6227-6237 (2007) (“Hutchinson”)
EX1044	Beáta G Vértessy and Judit Tóth, <i>Keeping Uracil Out of DNA: Physiological Role, Structure and Catalytic Mechanism of dUTPases</i> , Acc Chem Res. 1-20 (2009) (“Vértessy”)
EX1045	Elaine R. Mardis, <i>Next-Generation DNA Sequencing Methods</i> , 9 Annual Review Genomics and Human Genetics 387-402 (2008) (“Mardis”)
EX1046	Jay Shendure and Hanlee Ji, <i>Next-Generation DNA Sequencing</i> , 26(10) Nature Biotechnology 1135-1145 (2008) (“Shendure”)
EX1047	Elaine R. Mardis, <i>The impact of next-generation sequencing technology on genetics</i> , 24(3) Trends in Genetics 133-141 (2008) (“Mardis 2”)
EX1048	Robert A. Holt and Steven J.M. Jones, <i>The new paradigm of flow cell sequencing</i> , 18(6) Genome Research 839-846 (2008) (“Holt”)
EX1049	National Human Genome Research Institute, <i>Nucleotide</i> (March 21, 2023) at https://www.genome.gov/genetics-glossary/Nucleotide

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EX1050	National Human Genome Research Institute, <i>Polymerase Chain Reaction</i> (March 21, 2023) at https://www.genome.gov/genetics-glossary/Polymerase-Chain-Reaction
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EX1052	Exhibits 26 and 27 attached with Plaintiffs’ First Amended Complaint, <i>Becton, Dickinson and Company and Cellular Research, Inc. v. 10X Genomics, Inc.</i> , C.A. No. 18-1800-RGA (Feb 08, 2019 D. Del.) (No. 15-3)
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EX1054	Georgi K. Marinov et. al, <i>From single-cell to cell-pool transcriptomes: Stochasticity in gene expression and RNA splicing</i> , 24.3 Genome Research 496-510 (2014) (“Marinov”)
EX1055	United States Patent Application Publication to McCloskey et al. (“McCloskey II”)
EX1056	Boris Hollas and Rainer Schuler, <i>A Stochastic Approach to Count RNA Molecules Using DNA Sequencing Methods</i> , 2812 Algorithms in Bioinformatics 55-62 (2003) (“Hollas”)
EX1057	Thomas J Albert et al., <i>Direct Selection of Human Genomic Loci by Microarray Hybridization</i> , 4 Nature Methods 903-905 (2007) (“Albert”)
EX1058	US 7,537,897 B2
EX1059	Intentionally left blank.
EX1060	Reinhard Stöger, <i>Epigenetics and Obesity</i> , 9(12) Pharmacogenomics 1851-1860 (2008) at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2652025/ (“Stöger”)

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EX1062	Pierre Nicolas et. al., <i>The Stem Cell Population of the Human Colon Crypt: Analysis via Methylation Patterns</i> , 3 Plos Computational Biology 0364-0374 (2007) (“Nicolas”)

I. INTRODUCTION

Parse Biosciences, Inc. (“Petitioner”) requests *inter partes* review and cancellation of all claims of U.S. Patent No. 10,240,197 (“the ’197 Patent”), entitled “Methods for Analyzing Nucleic Acids from Single Cells.”

The ’197 Patent claims pertain to methods of counting nucleic acid sequences (*i.e.*, polynucleotides) from different single cells by appending two “tags” to the polynucleotides. The first tag allows one to identify the single cell origin of the polynucleotide, and the second tag allows one to distinguish polynucleotides originating from the same single cell. One then sequences or analyzes the tagged DNA.

While Patent Owner seeks to extract damages and injunctive relief based on the tagging techniques claimed in the ’197 Patent, it previously confirmed in a prior litigation that such methods are not remotely patentable. In particular, in a previous case against Becton-Dickinson, Patent Owner alleged that “labeling different objects with different labels” is “as old as the scientific method and is familiar to every student in any introductory science class.” EX1016.009. According to Patent Owner, “[m]erely apply[ing] this ‘old solution’ of different labels in the particular technological environment of DNA” is nothing new. *Id.* at .016.

In fact, the patents at issue in 10x’s previous case against Becton-Dickinson included claims directed to the specific dual tagging approach claimed in the ’197

Patent, wherein a first tag distinguishes among different cells and a second tag distinguishes among different polynucleotides. *See* EX1016.006; EX1051.117. Patent Owner previously included this very approach among those that it attacked as being “as old the scientific method itself” and based on nothing but routine and conventional methods. As documented herein, Patent Owner previously confirmed that ***every aspect*** of the claims of the ’197 Patent was routine and conventional well before the priority date.

While Patent Owner has since attempted to backtrack from its prior admissions by drafting claims in the ’197 Patent little different from the methods it previously criticized as being “as old as the scientific method itself,” Patent Owner’s previous statements were undeniably correct.

Specifically, the Linnarsson prior art reference discloses virtually every element of the claims of the ’197 Patent, including the use of a tag to track which cell a particular nucleic acid molecule comes from. To the extent Linnarsson does not teach a second tag to distinguish among different molecules, this concept is undeniably taught in McCloskey, which proposes a dual-tagging system of precisely the type claimed in the ’197 Patent in the context of a system that operates according to the same principles as the Linnarsson system. As documented herein and in the accompanying declaration of Dr. Gregory Cooper, it would have been

straightforward and obvious to combine McCloskey's dual-tagging approach with Linnarsson so as to achieve the claims of the '197 Patent. The claims of the '197 Patent are thus obvious in view of the prior art and the Board should now cancel them.

II. MANDATORY NOTICES

A. Real Party-In-Interest

The real party-in-interest is Parse Biosciences, Inc.

B. Related Matters

As of the filing date of this Petition, the '197 Patent is involved in litigation in *10x Genomics v. Parse Biosciences, Inc.*, 22-cv-01117 (D. Del. filed Aug. 8, 2022). Additionally, in parallel with the instant Petition, Petitioner is seeking review of U.S. Patent Nos. 10,155,981 and 10,697,013 in co-pending *inter partes* reviews.

C. Grounds For Standing

Petitioner certifies that the '197 Patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting *inter partes* review challenging the patent claims on the grounds identified in this Petition.

D. Lead And Back-Up Counsel And Service Information

Petitioner provides the following designation of Lead and Back-Up Counsel.

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III. IDENTIFICATION OF CHALLENGES

Petitioner presents the following challenges:

- **Ground 1:** Claims 1-4, 6-11, 20, and 23-25 of the '197 Patent are unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Linnarsson (EX1003) in view of McCloskey (EX1004).
- **Ground 2:** Claims 5, 12, 21, 22 and 26 of the '197 Patent are unpatentable under 35 U.S.C. § 103 as being obvious over the

combination of Linnarsson in view of McCloskey and further in view of the knowledge of a POSA.

- **Ground 3:** Claims 13-19 of the '197 Patent are unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Linnarsson in view of McCloskey and further in view of McCloskey II (EX1055).

IV. RELATIONSHIP BETWEEN THIS IPR AND RELATED PROCEEDINGS

In addition to seeking review of the '197 Patent in the instant petition, Petitioner is also seeking review of U.S. Patent Nos. 10,155,981 (“the '981 Patent”) and 10,697,013 (“the '013 Patent”) in co-pending *inter partes* reviews. Petitioner requested review of the '981 Patent on April 20, 2023. *See* Paper No. 1, IPR2023-00876.

Petitioner notes that the claims of the '197 Patent at issue here are highly similar to those of the '981 and '013 Patents. Accordingly, the technical background material appearing in the Petition and supporting expert declaration in IPR2023-00876 is directly applicable to not only the instant Petition but also the co-pending petition directed to the '013 Patent. For the convenience of the Board, Petitioner notes that it should be sufficient for the Board to review only the technical background sections in IPR2023-00876 to gain an understanding of the necessary technical subject matter relevant to all three petitions.

V. BACKGROUND RELATED TO THE '197 PATENT

A. Priority Date Of The '197 Patent

The '197 Patent, filed on November 16, 2018, identifies two provisional applications, the earlier of which was filed on August 20, 2009. EX1001 at (60). Thus, the earliest priority date of the '197 Patent is August 20, 2009.

B. The Brenner Family And The Reflex Method

The subject matter of the '197 Patent was not developed by Patent Owner, but rather by a now-defunct company called PGT in the 2009 time frame. Patent Owner purchased the patent rights from PGT in 2016, and then filed the application that resulted in the '197 Patent in 2019. EX1026; EX1005.083.

The '197 Patent shares an identical specification with other patents (collectively, “the Brenner Patents”), four of which were filed by PGT and later purchased by Patent Owner in 2016¹. The Brenner Patents purport to solve a problem with prior art DNA sequencing methods, which were often only able to sequence a short stretch of DNA sequence within much larger fragments of genomic DNA. EX1001 at 1:32-37. As the Brenner Patents state, the “present invention removes the limitations imposed by current sequencing technologies as well as being

¹ The PGT Patents include U.S. 8,298,767, 8,563,274, 8,679,756, and 9,102,980. EX1026.005. There is no indication that Patent Owner practices the PGT Patents. See EX1027.024-027.

useful in a number of other nucleic acid analyses.” *Id.* at 1:45-47. To this end, the Brenner Patents purport to teach the so-called “reflex method,” a technique for breaking up a long sequencing project into a series of smaller individual sequencing projects, the result of which can be pieced together to generate a long stretch of DNA sequence. *See id.* at 16:62-19:6.

The Brenner Patents are clear that this technique of introducing sequences via the “reflex” method is “the invention” itself. *See, e.g., id.* at 12:52-56. The “reflex” method is the very first thing mentioned in the “Summary Of The Invention” section, and it is referred to no less than 225 additional times throughout the common specification of the Brenner Patents. *See generally id.* Every example and embodiment pertains to this “reflex” method.

Rather than pertaining to the “reflex” method, however, Patent Owner’s newly-drafted claims in the ’197 Patent pertain to the concept of putting tags on a DNA sequences so that one can track where the DNA sample originated from. But as explained below, the Brenner Patents characterize this “tagging” process not as an invention, but rather as a prior art technique that the inventors and others had previously accomplished. *See, e.g., EX1001* at 1:26-29.

C. Overview Of The Claimed Methods And Disclosure Related To “Tagging”

The Challenged Claims of the '197 Patent are directed to methods of counting genetic sequences (*i.e.*, polynucleotides) from different cells by appending “tags” to the polynucleotides. EX1001 at Claim 1; *see also id.* at Abstract. A full listing of the challenged “tagging” claims appears in the Appendix to this Petition.

Briefly, tagging involves adding synthetic DNA to a sequence of interest by various methods, including ligation or annealing techniques. EX1002 ¶ 72. As acknowledged in the '197 Patent itself, tagging is not the invention, but was rather a prior art concept. For example, the specification recites: “We have previously described methods that enable tagging each of a population of fragmented genomes.” EX1001 at 1:26-29; *see also id.* at 15:20-29 (incorporating by reference prior art references “for their description of nucleic acid tags and their use in identifying polynucleotides”); EX1002 ¶ 72. The '197 Patent acknowledges that “[a]ny convenient method for tagging and/or counting individual nucleic acid molecules with unique tags may be employed.” EX1001 at 22:38-40

And indeed, it was common practice to use tags as unique “barcode” identifiers or primers to facilitate amplification, for counting, tracking, or tracing molecules to their sources, and/or for removing amplification bias. *See* EX1002 ¶ ¶ 72-74; EX1034.003; EX1035.001; EX1007.001; EX1004.003; EX1013.001;

EX1003 at 19:4-5. For example, Linnarsson discloses a method for preparing a cDNA library by tagging cDNA samples originating from different cells with unique tags that identify which single cell each cDNA sample originated from. EX1003 at 19:4-5.

Tagging methods known in the art also involved the use of multiple tags or a combination of tags. For instance, McCloskey discloses a method of analyzing single cell samples by using an encoding oligonucleotide with five information regions, two of which are tag sequences: (1) a “barcode” that uniquely identifies and distinguishes polynucleotides “arising from different cell or allele copies”; and (2) a “batch-stamp” that is “unique to each experiment” and “specifies the DNA source such as the patient or sample identification.” EX1004.002, .004. Linnarsson also discloses tagging a cDNA sample with a combination of tags. EX1003 at 19:6-7. It was also routine and conventional to use a large number of tags to ensure efficient tagging of all polynucleotides in a cell. EX1002 ¶ 76; EX.1056.001.

The Challenged Claims recite the prior art approach of using two tags to count and track through amplification and sequencing two types of information available in the originating sample. The tags allow a researcher to distinguish (1) from which single cell the polynucleotide originates, and (2) one polynucleotide from another within that single cell.

D. Prosecution History Overview

The Examiner did not issue any rejections during prosecution of the '197 Patent, and allowed all claims after the Applicant filed a terminal disclaimer disclaiming the term of the '197 Patent beyond the expiration date of U.S. 10,155,981 (the "'981 Patent"). The only stated Reasons for Allowance is the terminal disclaimer. EX1005.136. During prosecution of the '197 Patent, the Applicant submitted an Information Disclosure Statement (IDS) identifying Linnarsson (EX1003) and McCloskey II (EX1055). EX1005.106, 108, 147, 149. Linnarsson and McCloskey II, however, were not cited or discussed during prosecution. The '197 Patent then issued on March 26, 2019.

E. Patent Owner's Admissions Regarding The Prior Art and the Novelty of the Claimed Inventions

Patent Owner has acknowledged the well-known nature of not just the above-mentioned background technology, but the claimed inventions themselves. Specifically, in an unrelated case between Patent Owner and Becton, Dickinson and Company ("Becton-Dickinson"),² Patent Owner challenged the eligibility of seven asserted patents (the "Fodor Patents") that are directed to tagging DNA molecules

² *Becton, Dickinson and Company et al. v. 10X Genomics, Inc.*, C.A. No. 18-1800-RGA (D. Del.).

for the purpose of counting and tracking individual molecules. EX1016.007-008. This is the exact thing to which the claims of the '197 Patent are directed. Petitioner's expert, Dr. Gregory Cooper, explains in detail the similarity between the claims at issue in the prior Becton-Dickinson case and the claims at issue now. See EX1002 ¶¶ 39-44.

According to Patent Owner, the Fodor Patents are “nakedly directed at the abstract idea of labeling different objects (two or more ‘nucleic acid molecules’, e.g., portions of DNA) with different labels (‘a plurality of nucleic acid label-tags with different sequences.’).” EX1016.010. Patent Owner argued that the concept of “labeling different objects with different labels” is “as old as the scientific method and is familiar to every student in any introductory science class.” *Id.* at .009. And the Fodor Patents “[m]erely apply[] this ‘old solution’ of different labels in the particular technological environment of DNA.” *Id.* at .016. This idea of labeling information, in the Patent Owner's own words, is not “any less abstract when applied, as here, to the context of counting DNA molecules.” EX1017.006.

Patent Owner further argued that the other elements of the Fodor Patents—which also are claimed by the '197 Patent—are “*well-known and conventional.*” *Id.* at .011. In Patent Owner's words, for instance, the method for attaching a tag

to a DNA sample was “well-known and conventional before 2009.” *Id.*; *compare with* EX1001 at Claim 1 (“(b) generating a plurality of tagged polynucleotides”).

Indeed, one of the concepts that Patent Owner characterized as being “as old as the scientific method” is the idea of dual-tagging, as claimed by claims 13 and 19 of one of the Fodor Patents (U.S. Pat. 9,708,659). *See* EX1053 at claims 13, 19; EX1051.117 (Becton-Dickinson’s complaint asserting claims 13 and 19 of the ’659 Patent); EX1052.013-019, .031-039 (Becton-Dickinson’s infringement charts for these claims accusing 10X’s dual-tag single-cell analysis system). As explained by Dr. Cooper, these two Fodor claims are directed to tagging all molecules in a cell with the same cell tag, and further tagging individual molecules within the cell with an additional molecular identifier. EX1002 ¶ 44 (explaining that these claims are directed to the idea of dual tagging). Patent Owner challenged these claims, among others, as being well-known.

Patent Owner further confirmed that detecting and sequencing the tagged DNA were nothing but “generic, routine, well-known laboratory techniques.” EX1016.018; *compare with* EX1001 at Claim 1 (“(c) sequencing the tagged polynucleotide”). Patent Owner also confirmed that “PCR” and “hybridization-based techniques” are known and conventional. EX1016.013. As shown in the chart that ***Patent Owner*** submitted in its prior litigation against Becton Dickinson,

Patent Owner admitted that elements common to both the Fodor Patents (*e.g.*, claim 6 of U.S. Patent No. 8,835,358) and the '197 Patent are “generic, conventional” techniques:

358 patent Claim 6	Summary
6. A method comprising:	Preamble
(a) combining a mixture comprising at least two distinct target nucleic acid molecules with a pool of nucleic acid label-tags, wherein the pool of nucleic acid label-tags comprises a plurality of nucleic acid label-tags with different sequences;	Different molecules (“two distinct target nucleic acid molecules”) and Different labels (“a pool of nucleic acid label-tags”)
(b) attaching at least two nucleic acid label-tags from the pool of nucleic acid label-tags to the at least two distinct target nucleic acid molecules to obtain at least two label-tag-target nucleic acid molecules, wherein the distinct target nucleic acid molecules have different sequences from one another;	Generic, conventional attaching techniques
(c) amplifying at least a portion of the label-tag-target nucleic acid molecules, wherein an amplified portion of the label-tag-target nucleic acid molecules comprises at least a portion of said target nucleic acid molecule; and	Generic, conventional amplifying techniques
(d) detecting an amplified product of step (c).	Generic, conventional detecting techniques

EX1016 at .010-.012. Notably, as shown above, Patent Owner even said that the idea of “attaching at least two nucleic acid label tags” to a DNA molecule reflect nothing but “[g]eneric, conventional attaching techniques.” This is the very thing that Patent Owner now relies upon as the point of novelty in the '197 Patent.

VI. LEVEL OF ORDINARY SKILL IN THE ART OF THE '197 PATENT

A person of ordinary skill in the art (“POSA”) relating to the '197 Patent would have had (1) a Masters degree and/or Ph.D. in molecular biology, genetics, chemistry, engineering, or a related discipline and at least two years of post-Masters, postdoctoral, or industry experience or (2) a Bachelor of Science in such disciplines

and at least five years of academic or industry experience (including any experimental work toward a graduate degree), relating to DNA sequencing technologies, amplification methods, and gene expression analysis. EX1002 ¶ 52. Further, a POSA would have been familiar with associated tools, methods, and techniques including: (1) polynucleotide tagging, (2) amplification, (3) use of tags to overcome amplification bias, (4) single cell analysis, (5) ligation and primer extension, and (6) sequencing. *See generally* EX1002 ¶¶ 53, 72-99.

VII. THE CITED PRIOR ART

A. Linnarsson

Linnarsson, entitled “Gene Expression Analysis In Single Cells,” was published on October 14, 2010 as international PCT patent application publication WO 2010/117620 A2. EX1003.001. Linnarsson claims priority to U.S. Provisional Patent Application No. 61/164,759 (“Linnarsson Provisional”), filed on March 30, 2009. EX1015 at 1:3-5.

1. Linnarsson Is § 102(e) Prior Art

Linnarsson is § 102(e) prior art as of at least March 30, 2009, the date of the filing of Linnarsson Provisional, because the Linnarsson Provisional provides written description support for Linnarsson’s claimed invention of preparing a cDNA library by tagging cDNAs with unique identifiers. *See* MPEP § 2136; *Dynamic*

Drinkware, LLC. v. Nat'l Graphics, Inc., 800 F.3d 1375, 1382 (Fed. Cir. 2015); *In re Giacomini*, 612 F.3d 1380, 1383 (Fed. Cir. 2010).

Linnarsson was cited as prior art during prosecution of the '197 Patent, and the Applicants did not contest its prior art status. Instead, the Applicants identified Linnarsson as prior art in an IDS. EX1005.108, 149. Therefore, Linnarsson is prior art to the challenged claims even if the Challenged Claims of the '197 Patent are entitled to their earliest priority date of August 20, 2009.

The following chart shows that each and every limitation of claim 1 of Linnarsson is disclosed by the Linnarsson Provisional Application:

Linnarsson	Linnarsson Provisional Application
1. A method of preparing a cDNA library from a plurality of single cells, the method comprising the steps of:	“In particular, the invention relates to a method for preparing a cDNA library from a plurality of single cells, and to a cDNA library produced by this method.” EX1015 at 1:4-6; <i>see also</i> 2:23-25, 8:33-35.
(i) releasing mRNA from each single cell to provide a plurality of individual mRNA samples, wherein the mRNA in each individual mRNA sample is from a single cell;	“the method comprising: (i) releasing mRNA from each single cell to provide a plurality of individual samples, wherein the mRNA in each individual mRNA sample is from a single cell;” EX1015 at 2:28-32; <i>see also id.</i> at 3:5-6, 4:12-15.
(ii) synthesizing a first strand of cDNA from the mRNA in each individual mRNA sample and incorporating a tag	“(ii) synthesising a first strand of cDNA from the mRNA in each individual mRNA sample and incorporating a tag

Linnarsson	Linnarsson Provisional Application
into the cDNA to provide a plurality of tagged cDNA samples, wherein the cDNA in each tagged cDNA sample is complementary to mRNA from a single cell;	into the cDNA to provide a plurality of tagged cDNA samples, wherein the cDNA in each tagged cDNA sample is complementary to mRNA from a single cell;” EX1015 at 2:33-37; <i>see also id.</i> at 5:4-7, 5:24-32.
(iii) pooling the tagged cDNA samples; and	“pooling the tagged cDNA samples; and” EX1015 at 3:1; <i>see also id.</i> at 3:9-20.
(iv) amplifying the pooled cDNA samples to generate a cDNA library comprising double-stranded cDNA,	“amplifying the pooled cDNA samples to generate a cDNA library comprising double-stranded cDNA.” EX1015 at 3:2-3; <i>see also id.</i> at 11:14-17, 14:5-7.

Thus, Linnarsson is § 102(e) prior art, because at least one of its published claims is supported by the disclosure of the Linnarsson Provisional Application, which was filed before the earliest possible priority date of the '197 Patent. Moreover, the disclosures of Linnarsson that Petitioner relies upon for the ground are supported by the disclosure of the Linnarsson Provisional Application, as shown below by parallel citations.

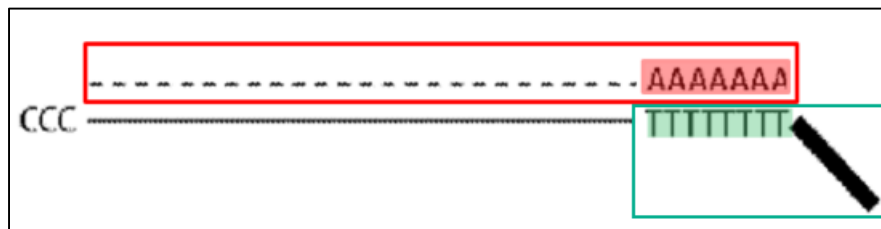
2. Linnarsson Overview

Linnarsson discloses a method of preparing a cDNA library for sequencing by appending unique oligonucleotide sequences, or “tags,” to cDNA samples originating from a plurality of cells. EX1003 at 10:15-22. Linnarsson teaches

that its method is useful for distinguishing polynucleotides arising from different single cells in a multi-cell experiment, thus reducing cell-to-cell amplification bias. *Id.* at 37:28-29, 19:9-10.

According to Linnarsson's method, tagged cDNA is synthesized from mRNA by reverse transcription using a tagged cDNA synthesis primer ("CDS") and/or a tagged template switching oligonucleotide ("TSO") to incorporate a tag into the resulting cDNA. EX1003 at 18:31-32. Linnarsson further discloses performing PCR on the tagged cDNA and subsequently analyzing and sequencing the tagged cDNA. EX1003 at 3:29-4:2, 19:16-17, 21:13-20.

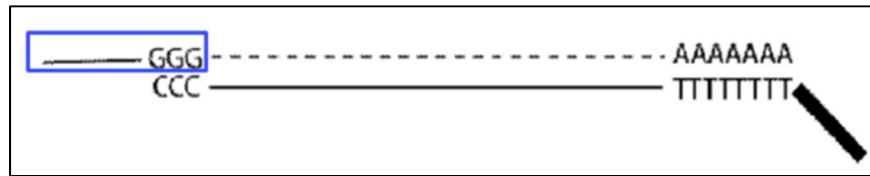
Specifically, Linnarsson discloses a cDNA synthesis primer ("CDS") (boxed in green) that includes a sequence of thymines (highlighted in green) and that "directs synthesis of a cDNA strand" by hybridizing with a sequence of adenine nucleotides making up the poly-A tail (highlighted in red) of an mRNA strand (boxed in red). This is shown in both Figures 1 and 11 of Linnarsson:



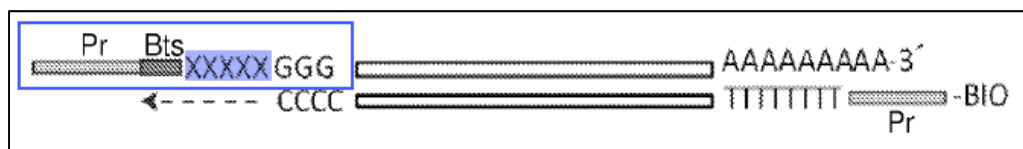
EX1003 at Fig. 2.

synthesized strand “and cDNA synthesis proceeds using the oligo as template.”

This too is shown in both Figures 2 and 11 of Linnarsson:

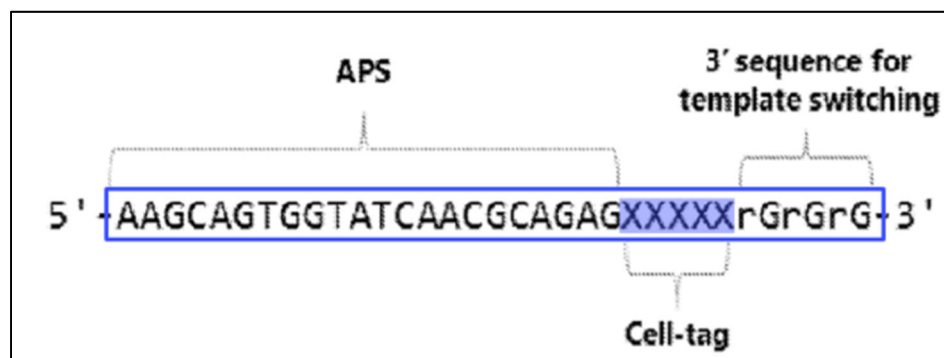


EX1003 at Fig. 2.



Id. at Fig. 11; *id.* at 5:31-33, 24:15-20 (explaining Figure 11); EX1002 ¶ 108.

Figure 3 similarly depicts an example of a TSO (boxed in blue) with a cell-tag (highlighted in blue):

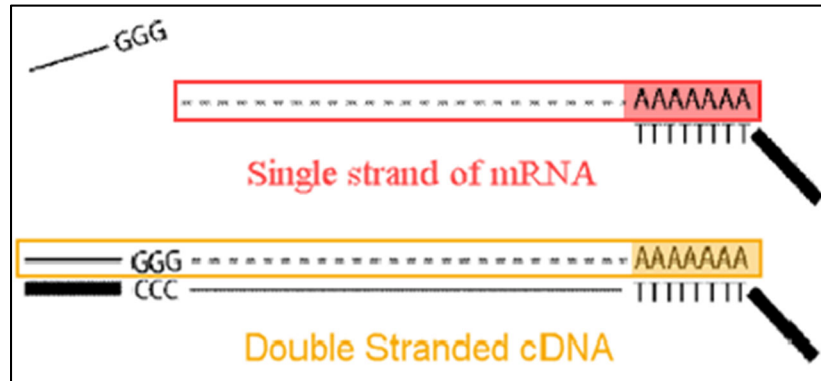


EX1003 at Fig. 3. Linnarsson discloses that the TSO cell-tag “can be incorporated into the cDNA” and can “be used to identify which single cell from each cDNA sample originated.” *Id.* at 18:31, 19:9-10. Linnarsson disclose that the tagged CDS and tagged TSO can be used alone or in combination to identify the single-cell

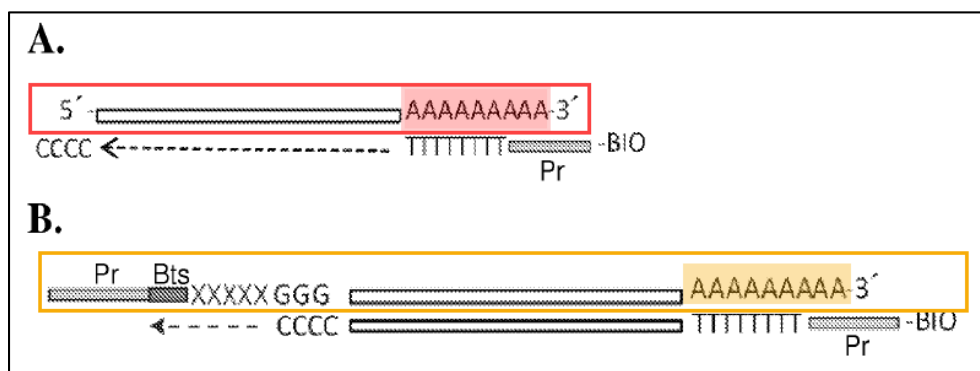
origin of the tagged cDNA. EX1003 at 18:32 (“[T]he CDS and/or the TSO can include a tag.”); *id.* at 19:4-5 (“As the tag is present in the CDS and/or the TSO it will be incorporated into the cDNA during its synthesis and can therefore act as a ‘barcode’ to identify the cDNA.”).

Linnarsson further teaches that the tagged cDNA can be amplified by PCR. EX1003 at 19:16-17. Linnarsson explains that “PCR [and] ligation amplification (or ligase chain reaction, LCR)...are known and widely practiced in the art.” EX1003 at 12:18-20. Linnarsson also teaches that after generating the tagged cDNA, “sequencing is performed” thereon. *See* EX1003 at 4:8-13, 19:28-32, 21:13-25.

Notably, during reverse transcription, the sample mRNA is denatured from the first synthesized cDNA and a new complementary strand of cDNA is formed along the synthesized cDNA strand, which generates a double-stranded cDNA. As a result, one strand of the double-stranded cDNA molecule (boxed in orange) has the same sequence as the original mRNA strand (boxed in red), including the same sequence of adenines (highlighted in orange) that made up the poly-A tail (highlighted in red) of the mRNA:



EX1003 at Fig. 2. Figure 11 of Linnarsson discloses the same:



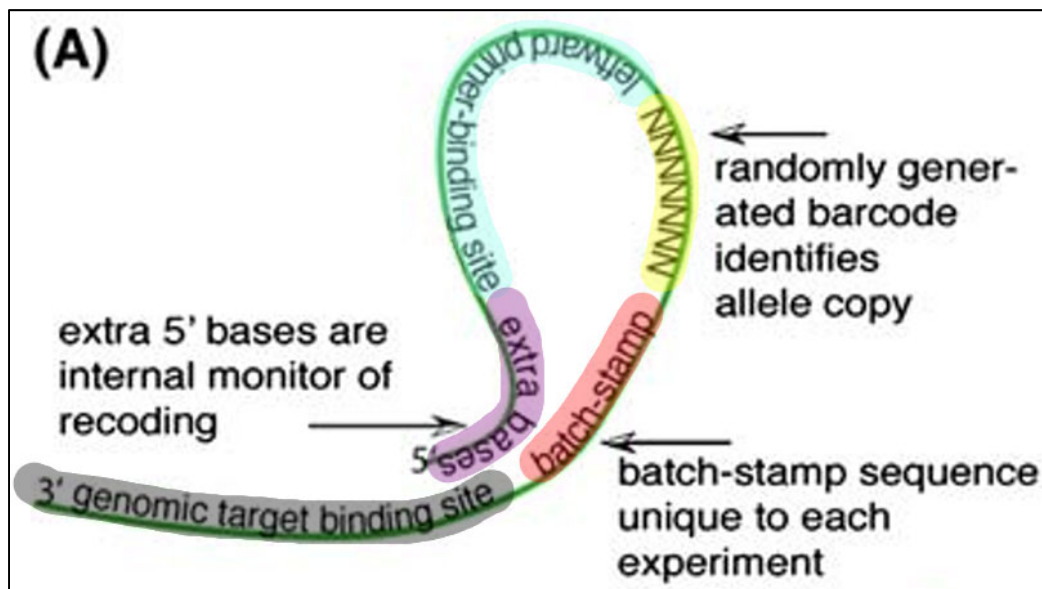
Id. at Fig. 11; *id.* at 6:1-3 (explaining Figure 11); *see also* EX1002 ¶ 112.

B. McCloskey

The McCloskey reference, titled “Encoding PCR Products with Batch-Stamps and Barcodes,” published in the December 2007 print issue of the Biochemical Genetics journal. The journal published the McCloskey reference online on October 23, 2007. EX1028; EX1004.001. McCloskey is prior art under pre-AIA 35 U.S.C. § 102(a) and (b). The Examiner did not consider McCloskey during prosecution.

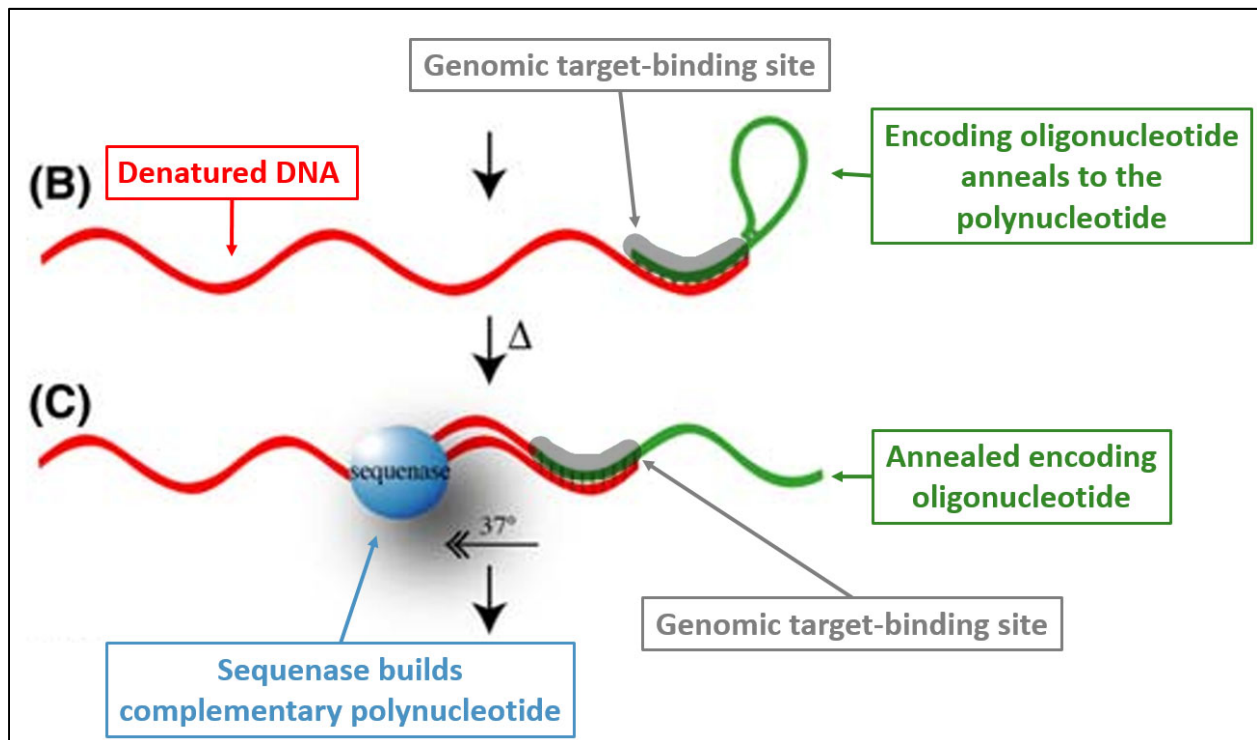
McCloskey discloses a method of DNA analysis for single-cell samples that utilizes an “encoding oligonucleotide” having “five distinct information regions,” two of which are tag sequences that distinguish, respectively, polynucleotides and samples.

As depicted below, McCloskey teaches a first tag sequence, the “barcode” (highlighted in yellow), which “distinguishes among sequences arising from different cell or allele copies.” EX1004.002-004. McCloskey further teaches a second tag sequence, the “batch-stamp” (highlighted in red), that is unique to each experiment and is intended to associate a polynucleotide with “a specific sample run on a specific date.” *Id.* at .004.



Id. at Fig. 1.

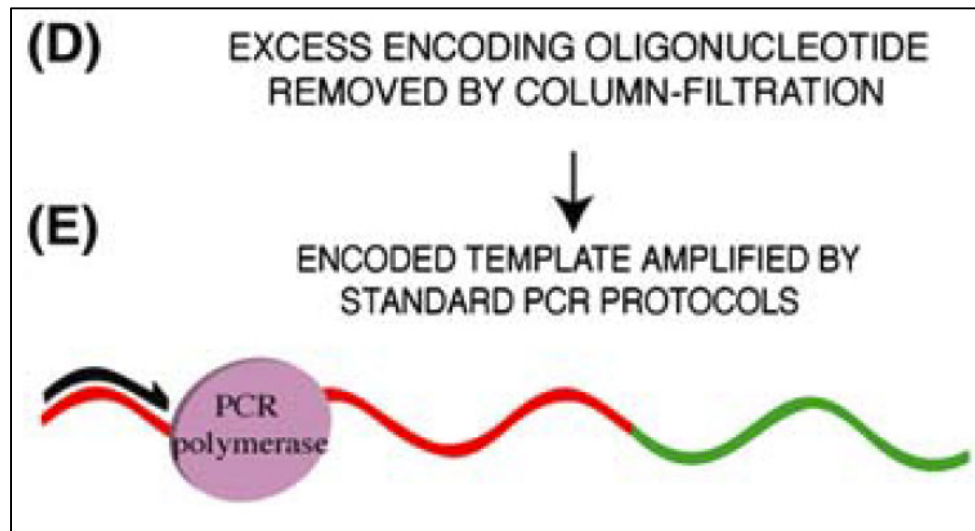
According to McCloskey's method, the encoding oligonucleotide's genomic target binding site (shown in grey, above) anneals to a denatured polynucleotide strand and is then extended by Sequenase, a type of DNA polymerase. *Id.* at .002-005. The annealing and extension steps are shown at the top and bottom, respectively, of the figure below:



Id. at Fig. 1.

After the annealing and extension steps, McCloskey teaches purifying the sample to remove encoding oligonucleotides that were not annealed, followed by PCR amplification and sequencing. *Id.* at .005-007 ("Sequenase extension products were purified to remove any unincorporated encoding oligonucleotides

using the Qiagen QIAquick PCR purification kit.”). These steps are illustrated below:



Id. at Fig. 1.

McCloskey teaches that an advantage of its method is that it allows an experimenter to distinguish redundant sequences resulting from PCR amplification from redundant sequences that existed in the sample before amplification. Two identical sequences that have the *same* barcode almost certainly arose from duplication of an original parent molecule by PCR amplification, whereas two identical sequences with *different* barcodes almost certainly arose from two different parent molecules of the exact same species being present in the sample prior to amplification. *See id.* at .006 (“Redundant sequences recovered from the same PCR reaction are readily identified because they are identical in both barcode and

batch-stamp.”). Therefore, the number of *unique* barcodes identified at the sequencing stage represents the diversity of different molecules present in the original sample. *Id.* (“An additional benefit of our method for mosaic samples is that counting sequences with nonredundant barcodes provides a quantitative measure of template diversity.”).

McCloskey teaches that this method increases reliability: “Our approach thus enables classification of each PCR-derived sequence as valid, contaminant, or redundant, and provides a measure of sequence diversity.” EX1004.001; *see also id.* at Figs. 1(F) – 1(I) (showing various barcode and batch-stamp sequences from one experiment); *id.* at .003. McCloskey also recommends “that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs for forensic, clinical, *single cell*, and ancient DNA analyses.” *Id.* at .005.

C. McCloskey II

U.S. Patent Publication 2007/0020640 (“McCloskey II”), entitled “Molecular Encoding Of Nucliec Acid Templates For PCR And Other Forms Of Sequence Analysis,” was published on January 25, 2007. EX1055.001. McCloskey II is prior art under pre-AIA 35 U.S.C. § 102(a) and (b). During prosecution of the ’197 Patent, the Applicant identified McCloskey II as prior art in an IDS. EX1005.106, 147. The Examiner raised no prior art rejection based on McCloskey II.

McCloskey II is a sister patent application that goes along with the McCloskey publication discussed in the immediately preceding section. Thus, similar to McCloskey, McCloskey II also discloses a method for tagging polynucleotides with “a molecular barcode and batch-stamp.” EX1055 at Abstract. In addition, McCloskey II discloses that its barcode sequence may comprise up to 30 nucleotides. EX1055 at [0021].

VIII. CLAIM CONSTRUCTION

For purposes of this Petition, Petitioner does not believe that any terms require explicit construction in view of the prior art being presented. To the extent Patent Owner identifies terms for construction, Petitioner reserves the right to respond. Claim terms are given their ordinary and customary meaning as interpreted by a POSA at the time of the invention. That being said, Petitioner notes that Claim 1 of the '197 Patent recites “providing a sample.” The specification defines a “sample” to mean “a quantity of material from a biological, environmental medical, or patient source in which detection, measurement, or labeling of target nucleic acids is sought.” *Id.* at 12:7-10.

IX. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Ground 1

Claims 1-4, 6-11, 20, and 23-25 of the '197 Patent would have been obvious to a POSA over the combination of Linnarsson and McCloskey.

1. Claim 1

a. [1A] A method of counting nucleic acids in a sample, the method comprising:

To the extent the preamble is limiting, Linnarsson discloses this limitation. Specifically, Linnarsson discloses a method of counting nucleic acids in a sample: “Sequence reads are mapped to the genome to reveal sites of transcription, and quantitation is based simply on hit counts, with great sensitivity and nearly unlimited dynamic range.” EX1003 at 2:21-22; *see also id.* at 36:31-33. A POSA would have understood that “reads” refers results of sequencing nucleic acid sequences, which comprises the recited “nucleic acids.” EX1002 ¶ 121. McCloskey also discloses “counting nucleic acids using nonredundant barcodes.” EX1004.006. As documented further below, the combination of McCloskey’s “nonredundant barcodes” with the approach of Linnarsson directly yields a method for counting nucleic acids in a sample. *See infra* Section IX.A.1.h.

b. [1B] (a) providing a sample comprising a plurality of cells, wherein a cell of the plurality of cells comprises a plurality of sample polynucleotides;

Linnarsson discloses this claim element.

First, Linnarsson teaches providing a sample comprising a plurality of single cells. According to Linnarsson, this sample of “[c]ells [can be] obtained from a tissue of interest...” EX1003 at 22:22-23; EX1015 at 11:9; *see also* EX1003 at 4:8-10; EX1015 at 9:35-37; EX1002 at ¶ 126. Linnarsson explains that the sample of single cells can take various forms:

Single cells useful in the methods described herein can be obtained from a tissue of interest, or from a biopsy, blood sample, or cell culture.

EX1003 at 13:11-12; EX1015 at 3:31-34. Linnarsson further teaches that these single cells are placed in a 96-well plate for subsequent processing and analysis. *See* EX1003 at 4:10-11, 22:23-24; EX1015 at 9:37-10:1, 11:10-11.

Second, Linnarsson teaches that each single cell comprises a plurality of sample polynucleotides. For example, Linnarsson discloses that the single cells comprise mRNA, which is a polynucleotide. *See* EX1003 at 4:10-11, 13:28; EX1015 at 4:12, 9:37-10:3; *see also* EX1003 at 22:24-26; EX1015 at 11:11-14. Linnarsson further teaches that these cells contain a plurality of mRNA molecules. *See, e.g.*, EX1003 at 3:26-30; EX1015 at 2:27-3:3.

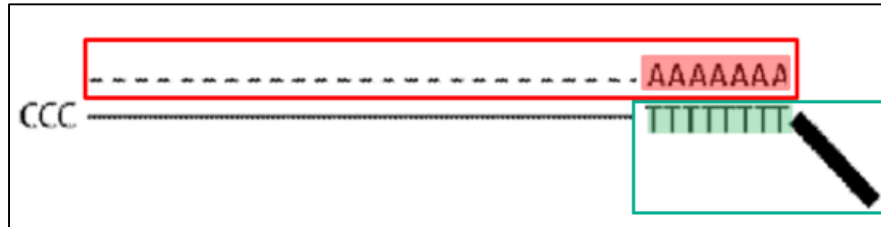
c. [1C] (b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides of said cell and a plurality of oligonucleotide tags,

Linnarsson teaches a plurality of single cells comprising a plurality of sample polynucleotides (*i.e.*, mRNA). According to Linnarsson, these sample mRNAs are released from the single cells via lysis. *See* EX1003 at 4:10-11, 13:28; EX1015 at 4:12, 9:37-10:1.

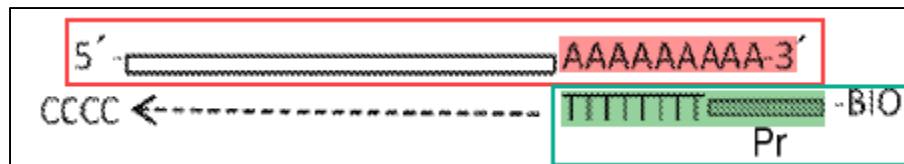
Linnarsson then teaches performing reverse transcription on the plurality of sample mRNA molecules to synthesize, or generate, a plurality of cDNA molecules. *See* EX1003 at 3:25-30, 22:24-26 (“The cells are lysed and reverse transcription reaction mix is added directly to the lysates....This results in the synthesis of cDNA from cellular mRNA....”); EX1015 at 2:27-3:3, 11:11-14; *see also* EX1003 at 14:9-32; EX1015 at 4:29-5:22. Furthermore, Linnarsson teaches that during cDNA synthesis, oligonucleotide tags (*i.e.*, CDS and/or TSO) can be used to tag the cDNA. *See* EX1003 at 19:4-7; EX1015 at 7:23-26. The resulting tagged double-stranded cDNA are the claimed “plurality of tagged polynucleotides.”

Specifically, ***first***, Linnarsson teaches using a tagged CDS during cDNA synthesis to generate tagged cDNA. As shown in Figures 2 and 11, a CDS (boxed in green, below) is used to “direct[] synthesis of a cDNA strand.” The CDS includes a sequence of thymines (highlighted in green, below) that hybridize with a

sequence of adenines making up a poly-A tail (highlighted in red, below) of an mRNA molecule (boxed in red, below):

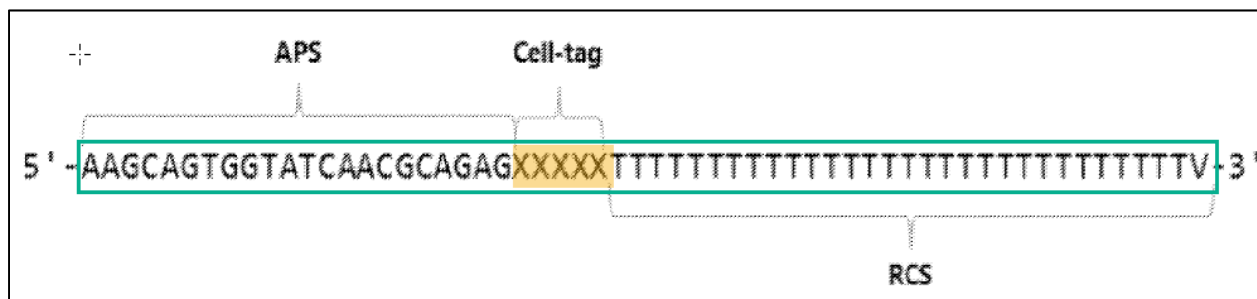


EX1003 at Fig. 2; *see also* EX1015 at Fig. 2. Figure 11 of Linnarsson discloses the same:



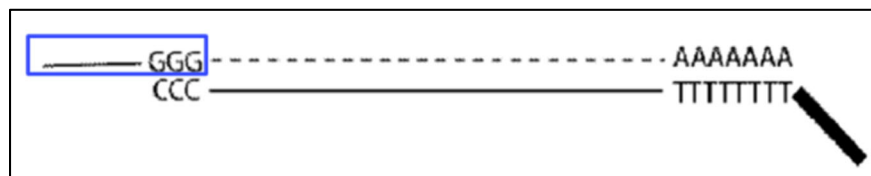
Id. at Fig. 11; *see also* EX1015 at Fig. 2; EX 1003 at 5:29-31 (explaining the disclosure of Figure 11); EX1015 at 5:24-32, 13:8-14 (same); EX1002 ¶ 137.

As shown in Figure 4, Linnarsson discloses that the CDS (boxed in green), comprises a cell-tag sequence (highlighted in yellow):

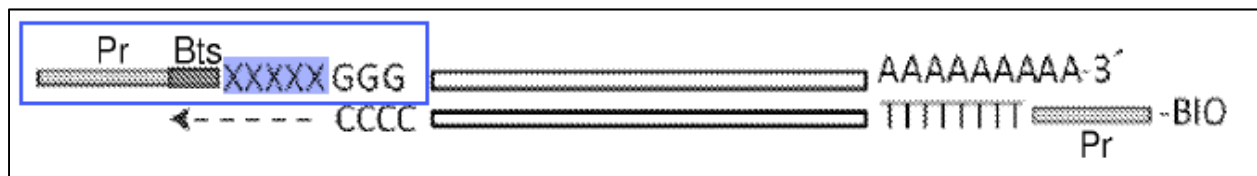


EX1003 at Fig. 4; *see also* EX1015 at Fig. 4.

Second, Linnarsson teaches using a tagged TSO during reverse transcription to generate tagged cDNA. As shown in Figure 2 below, a TSO (boxed in blue) that comprises the tag “XXXXX” (highlighted in blue) “anneals transiently, and cDNA synthesis proceeds using the oligo as template.” EX1003 at 5:31-33; *see also* EX1015 at 13:14-25; EX1003 at 16:10-17 (discussing another method of forming the second strand of cDNA); EX1015 at 6:1-11; EX1002 ¶ 141.

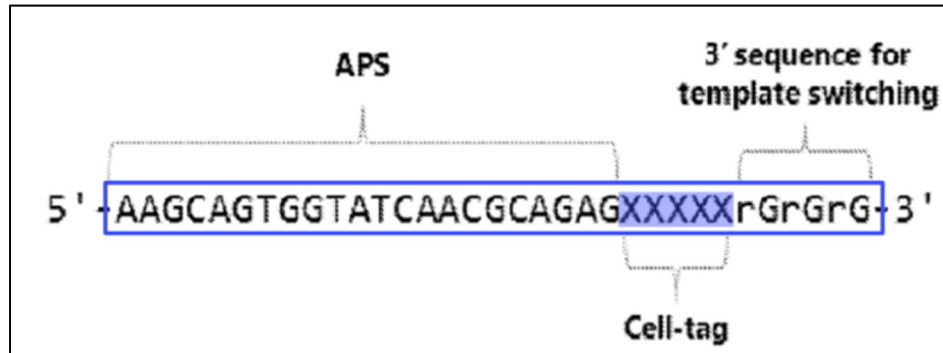


EX1003 at Fig. 2; *see also* EX1015 at Fig. 2. Linnarsson Figure 11 discloses the same:



EX1003 at Fig. 11; EX1015 at Figs. 2, 3.

Figure 3 of Linnarsson similarly discloses that the TSO (boxed in blue, below) comprises a cell-tag sequence (highlighted in blue):



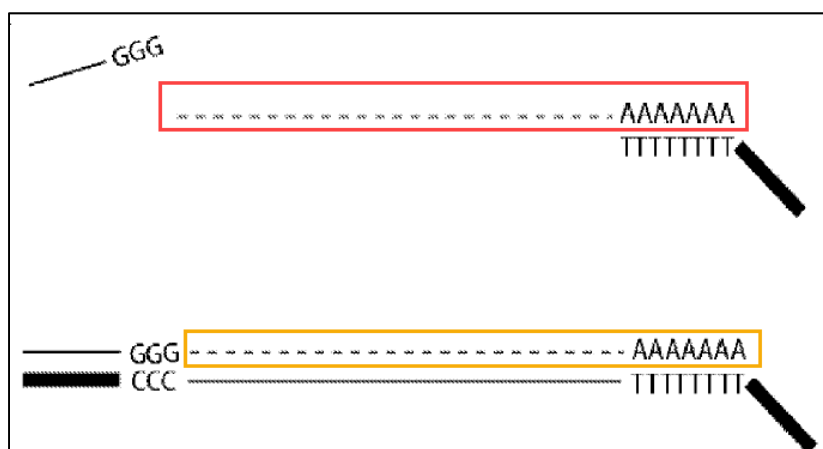
EX1003 at Fig. 3; EX1015 at Fig. 3. Linnarsson further teaches that “[b]oth the CDS and the TSO can include a tag. The CDS and the TSO can each include a different tag, such that the tagged cDNA sample comprises a combination of tags.” EX1003 at 19:5-7; EX1015 at 7:23-28.

After cDNA synthesis, the plurality of tagged cDNA are then amplified to generate copies of each tagged double-stranded cDNA, and such copies also constitute the claimed “plurality of tagged polynucleotides.” EX1003 at 10:20-22; EX1015 at 3:2-3.

Thus, Linnarsson teaches generating a plurality of tagged polynucleotides (*i.e.*, tagged double-stranded cDNA and/or amplified copies) from the plurality of sample polynucleotides (*i.e.*, mRNA) of said cell and a plurality of oligonucleotide tags (CDS and/or TSO), as required by this claim limitation.

- d. [1D] wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises:...(i) a sample sequence from a sample polynucleotide of the plurality of sample polynucleotides;

As explained above in Section IX.A.1.c, Linnarsson teaches generating a plurality of tagged polynucleotides (*i.e.*, tagged double-stranded cDNA and/or amplified copies) from the plurality of sample polynucleotides (*i.e.*, sample mRNA). As shown in Figure 2, Linnarsson further discloses that the resulting double-stranded cDNA comprises one strand (boxed in orange) that is identical to the original sample mRNA (boxed in red):

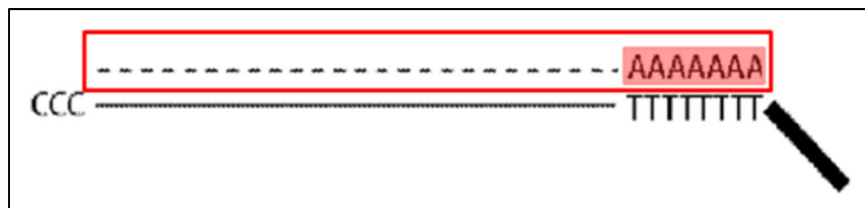


EX 1003 at Fig. 2. Indeed, because the cDNA is synthesized from the sample mRNA using reverse transcription, one strand of each cDNA is necessarily identical to the sample mRNA. See EX1002 ¶ 148.

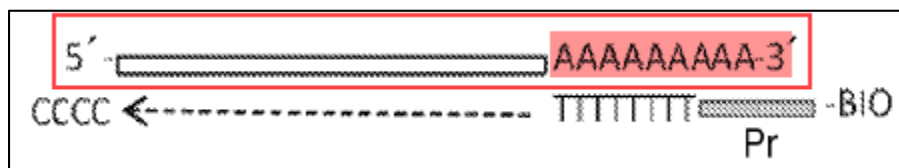
A POSA would have further concluded that a cDNA synthesized from a sample mRNA comprises the same sample sequence. EX1002 ¶ 149. While

mRNA comprises uracil and DNA comprises thymine, any POSA in the field of gene analysis would have understood that uracil and thymine are functionally equivalent because they code for the same protein. *See id.* ¶ 59.

Alternatively, Linnarsson discloses that the tagged cDNA comprises a sequence from the sample mRNA—a poly-A tail. Linnarsson discloses that the sample mRNA comprises a poly-A tail. EX1003 at Fig. 2; EX1015 at Fig. 2; EX 1002 ¶ 150 (explaining that mRNA have a poly(A) tail). A “poly(A) tail” is a sequence of adenosine nucleotides found at the 3’ end of mRNA molecules, such as the sample polynucleotides. *See* EX1002 ¶ 62. Figure 2 of Linnarsson, reproduced and annotated below, shows an mRNA molecule (boxed in red) with its poly-A tail (highlighted in red):

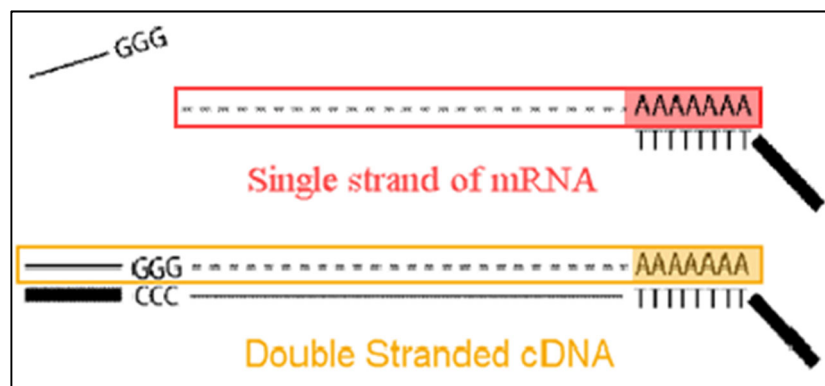


EX1003 at Fig. 2; EX1015 at Fig. 2; EX1003 at 4:14 (describing Fig. 2); *id.* at 24:13-20 (same); EX1015 at 10:8, 13:8-18. Linnarsson’s Figure 11 shows the same:

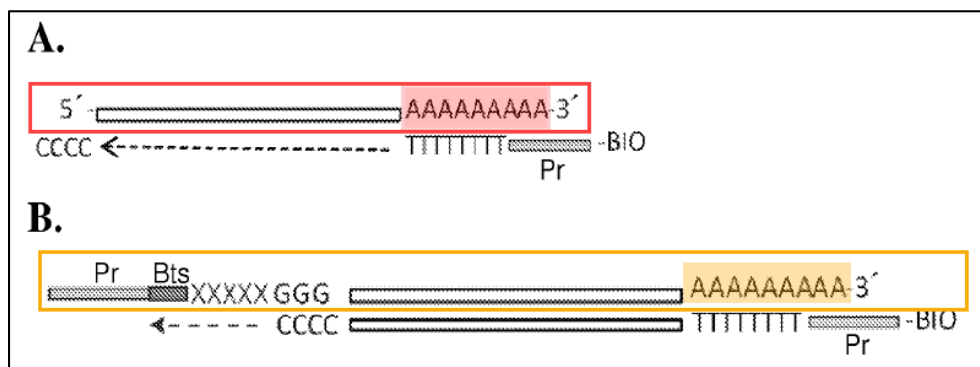


EX1003 at Fig. 11(A); EX1015 at Fig. 2; *see also* EX1002 ¶ 150.

Linnarsson discloses that after reverse transcription, the resulting double-stranded cDNA has a poly-A tail identical to the poly-A tail of the sample mRNA. Specifically, Linnarsson at Figure 2 discloses the resulting double-stranded cDNA, whereby one strand of the double-stranded cDNA (boxed in orange) shares the same sequence as the original mRNA strand (boxed in red), including the same poly-A tail (highlighted in orange) that is the same as the poly-A tail (highlighted in red) of the original sample mRNA strand:



EX1003 at Fig. 2; EX1015 at Fig. 2. Figure 11 of Linnarsson discloses the same:



EX1003 at Fig. 11(A) and (B); EX1015 at Figs. 2, 3.

Therefore, Linnarsson discloses that each tagged polynucleotide (*i.e.*, tagged double-stranded cDNA and/or amplified copies) comprises a sample sequence (*i.e.*, the sample mRNA sequence and/or the poly-A tail) from a sample polynucleotide (*i.e.*, sample mRNA) of the plurality of sample polynucleotides.

- e. **[1E] wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises:...(ii) a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells; and**

Linnarsson discloses that the tag polynucleotide comprises a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein that first tag sequence distinguishes the sample polynucleotide from sample polynucleotides from other cells. EX1002 at ¶ 154. Linnarsson discloses “tagged reverse transcriptase is performed on each sample to produce cDNA,” which allows for “identification of expressed genes and identification of *cells from which they originated*.” EX1003 at 4:8-13; EX1015 at 9:35-10:6. Linnarsson also explains that each CDS and/or the TSO comprises a cell-tag sequences, which is incorporated into the cDNA to provide “a distinct tag, or a distinct combination of tags, such that...the tag can be used to identify *which single cell from each cDNA sample originated*” and so that “each cDNA sample can be linked to a single cell....” EX1003 at 19:5-11; EX1015 at 7:26-34.

Thus, Linnarsson discloses that each tagged polynucleotide comprises a first tag sequence (i.e. cell-tag sequence) distinguishing said sample polynucleotide from sample polynucleotides from other cells. EX1003 at 19:9-10 (“the tag can be used to identify which single cell from each cDNA sample originated”).

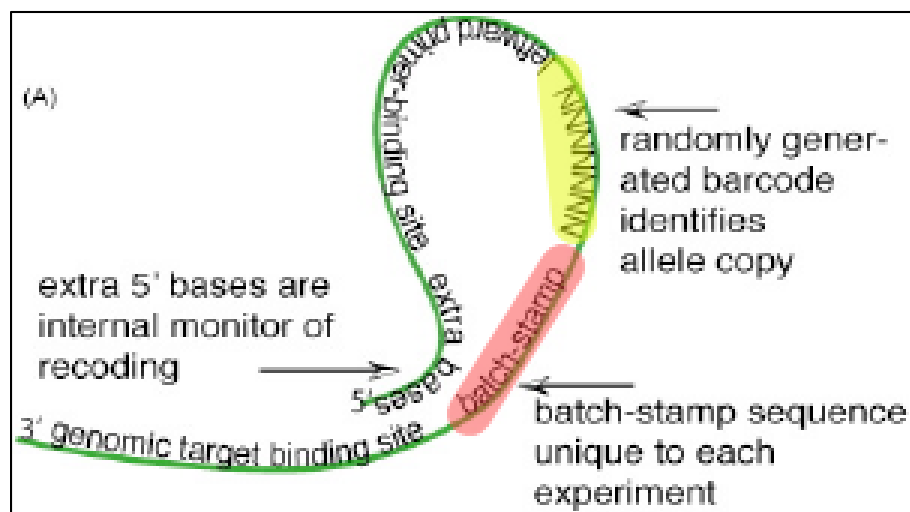
f. **[1F] wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises:...(iii) a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell;**

i. **The Combination of Linnarsson and McCloskey Teaches This Limitation**

The combination of Linnarsson and McCloskey teaches this claim element.

McCloskey teaches an “encoding oligonucleotide” as depicted below in

Figure 1:



EX1004 at Fig. 1. As shown above, McCloskey’s encoding oligonucleotide comprises two tag sequences: (1) a “batch-stamp” sequence (highlighted in red,

above) to identify the experimental batch or genomic source (*e.g.*, a single cell) and (2) a “barcode” (highlighted in yellow, above) to distinguish polynucleotide sequences “arising from different cell or allele copies.” *See* EX1004.001-002 (“the batch-stamp, unique to each experiment, specifies the DNA source such as the patient or sample identification, and the date of reaction;...the random barcode distinguishes among sequences arising from different cell or allele copies...”); *id.* at .003 (describing the batch-stamp and barcode tags).

A POSA would have understood that McCloskey’s reference to “different cell or allele copies” encompasses cDNA (*i.e.*, sample polynucleotides) from single cell experiments. *See* EX1002 ¶ 160. Indeed, McCloskey teaches that the “batch-stamps and barcodes [should] be used when amplifying irreplaceable DNAs *and cDNAs* for...*single cell*...analyses,” and that its method of tagging applies “to single-stranded cDNA templates.” EX1004.001, .005. Thus, McCloskey teaches a second tag sequence (*i.e.*, the barcode) distinguishing a sample polynucleotide (*e.g.*, cDNA) from other sample polynucleotides derived from the same single cell.

ii. It Would Have Been Obvious to a POSA to Combine Linnarsson’s and McCloskey’s Teachings

It would have been obvious to combine Linnarsson’s methods of cDNA library preparation and analyzing tagged nucleic acids with McCloskey’s teachings

to use an encoding oligonucleotide comprising a second tag sequence that distinguishes sample polynucleotides derived from the same single cell.

First, a POSA would have had a reason to consider McCloskey because Linnarsson and McCloskey are analogous art that focus on significantly the same subject matter. Both references describe methods of genetic analysis of single cells whereby polynucleotides are annealed to oligonucleotides comprising tag sequences (Linnarsson's CDS and TSO; McCloskey's encoding oligonucleotide) and primer extension takes place to generate tagged polynucleotides. PCR amplification is then performed and the results are sequenced. EX1003 at 3:25-4:2; EX1015 at 2:27-3:3; EX1004 at Fig. 1. They are thus in the same field of endeavor and reflect virtually identical approaches.

Linnarsson teaches synthesizing cDNA samples with two tags. EX1003 at 19:6-7 ("The CDS and the TSO can each include a different tag, such that the tagged cDNA sample comprises a combination of tags"); EX1015 at 7:27-28. A POSA would have understood that using an oligonucleotide comprising a second tag to distinguish sample polynucleotides derived from the same single cell would have been an obvious design choice. EX1002 ¶ 168. As Patent Owner itself acknowledged in its case against Becton-Dickinson, "using different labels to differentiate and distinguish between different instances of similar objects is

commonplace.” EX1016.005. Just like the Fodor Patents that Patent Owner was addressing in the Becton-Dickinson case, the ’197 Patent simply takes the idea of assigning multiple labels “and attempt[s] to limit the use of the idea to the particular technological environment of DNA (and other nucleic acids) by adding ‘attaching’, ‘amplifying’, and ‘detecting’ steps and other similarly generic techniques that were well-known and conventional before 2009....” *Id.*, .001; *see also id.*, .018-019.

Second, a POSA would have been motivated to combine Linnarsson and McCloskey because Linnarsson discloses a well-understood problem that McCloskey’s teachings resolve, also according to well-known methods which, as Dr. Cooper explains, had been available since at least 2004. EX1002 ¶¶ 91-93, 164-167. Specifically, Linnarsson discloses that analyzing gene expression in single cells results in “potential amplification bias,” while McCloskey also recognizes the problems of amplification bias. EX1003 at 2:3-15, 11:6-10; EX1015 at 2:6-21, 3:14-20; EX1004 at Abstract (“The risks of...biased amplification...are especially high when limited amounts of template DNA are used.”). Gene expression analysis and single cell genomics typically rely on limited amounts of template DNA, thus amplification bias is particularly important to correct. *Id.* McCloskey’s method of including a second tag sequence on the oligonucleotide to distinguish sample polynucleotides derived from the same single

cell solves this problem. See EX1004 at Abstract (“We have developed and applied molecular encoding principles to solve this source-uncertainty problem for DNA sequences generated by standard PCR.”).

Linnarsson discloses that prior to sequencing, the “cDNA library can be further amplified, e.g. by PCR, to obtain a sufficient quantity of cDNA for sequencing.” EX1003 at 21:21-22; EX1015 at 9:4-6; *see also* EX1002 ¶¶ 84-88 (explaining how PCR uses DNA polymerase and other reagents to synthesize new strands of DNA from template strands of DNA or RNA). But Linnarsson notes a problem with amplifying: “as the cDNA of each cell must be amplified to an amount that can be reasonably handled for the subsequent analysis, there is potential amplification bias.” EX1003 at 2:3-13; EX1015 at 2:6-18. Linnarsson attempts to address the problem of amplification bias as follows: “as cDNA samples are pooled before amplification, less amplification is required to generate sufficient amounts of cDNA for subsequent analysis compared to amplifying and treating cDNA samples from each single cell separately. This reduces amplification bias.” EX1003 at 11:6-9; EX1015 at 3:14-18. This approach only *reduces amplification bias*, and it does not actually solve the problem. EX1002 ¶¶ 164, 166.

McCloskey, however, provides the exact solution. By incorporating a second tag in an oligonucleotide that uniquely identifies each sample polynucleotide

prior to amplification, McCloskey “*solve[s]*” this source-uncertainty problem for DNA sequences generated by standard PCR.” EX1004.001; *see also id.* at .005 (“An additional benefit of our method...is that counting sequences with nonredundant barcodes provides a quantitative measure of template diversity.”). As mentioned, the risks of amplification bias are “especially high when limited amounts of template DNA are used,” such as for single cell genomics or gene expression analysis in single cells. EX1003 at 2:3-15, 11:6-10; EX1015 at 2:6-21, 3:14-20; EX1004 at Abstract. A POSA therefore would have been motivated to incorporate McCloskey’s teachings into Linnarsson’s methods to detect true sample complexity/template diversity. EX1002 ¶ 167. Indeed, as Dr. Cooper explains, this technique for avoiding amplification bias was not new in McCloskey, but was rather a tried-and-true technique that had been available since 2004. *See id.* ¶¶ 89-93.

Third, a POSA would have had a reasonable expectation of successfully incorporating McCloskey’s teachings into Linnarsson. Linnarsson discloses annealing oligonucleotide tags (*e.g.*, CDSs and TSOs) that comprise “a distinct tag, or a distinct combination of tags.” EX1003 at 19:5-10; EX1015 at 7:26-32. McCloskey also discloses annealing an “encoding oligonucleotide,” but it expressly teaches that its oligonucleotide comprises two tag sequences, one of which identifies

the sample polynucleotide. *See, e.g.*, EX1004.002 (“Our method utilizes an encoding oligonucleotide with five distinct informational regions[:] the random barcode distinguishes among sequences arising from different cell or allele copies....”). A POSA would have understood that Linnarsson’s oligonucleotide tags—CDS or TSO—could be modified through routine methods to incorporate a second tag sequence to uniquely identify each sample polynucleotide according to McCloskey’s teachings. EX1002 ¶ 168. Indeed, as Dr. Cooper explains, the method would be identical to the approach already set forth in Linnarsson, except that the cell-tag sequence in Linnarsson would be conceptually divided into two portions: one that codes for the unique cell and one that codes for the unique molecule. EX1002 ¶ 169.

Alternatively, both tag sequences in Linnarsson’s TSO and CDS can be used in combination, wherein one is used to identify the single-cell origin of the tagged polynucleotide, and the other is used to distinguish tagged polynucleotides originating from the same cell. EX1003 at 19:6-7. (“The CDS and the TSO can each include a different tag, such that the tagged cDNA sample comprises a combination of tags.”). As Dr. Cooper explains, such a method would be identical to Linnarsson’s method, except that one of the CDS tag or the TSO tag is modified to be different for each tagged cDNA. EX1002 ¶ 170.

Thus, a POSA would have found it obvious to combine the teachings of Linnarsson and McCloskey.

* * *

Therefore, Linnarsson and McCloskey teach and render obvious that each tagged polynucleotide comprises a second tag sequence (i.e., Linnarsson's cell-tag sequence or McCloskey's barcode) distinguishing the sample polynucleotide (i.e., mRNA/cDNA template) from other sample polynucleotides derived from the same single cell.

- g. [1G] (c) sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence; and**

Linnarsson teaches that after generating the tagged polynucleotides, "sequencing is performed" thereon. *See* EX1003 at 4:8-13, 19:28-32, 21:13-25; EX1015 at 8:22-28, 8:33-9:10, 9:35-10:6. A POSA would have understood that such sequencing is performed on the entire tagged polynucleotide, which includes the sample sequence and both tag sequences. EX1002 ¶ 176.

- h. [1H] (d) using the first tag sequence and the second tag sequence to count a number of sample polynucleotides in said plurality of sample polynucleotides of said cell.**

The combination of Linnarsson and McCloskey discloses this claim element. As discussed above in Sections IX.A.1.e-f, the combination of Linnarsson and

McCloskey discloses and renders obvious using a first tag to identify the single-cell origin of sample polynucleotides, and using a second tag to uniquely identify each sample polynucleotide.

Further, McCloskey discloses that these tags allow the precise count of sample polynucleotides in each sample single-cell to be determined. McCloskey teaches that by evaluating the determined sequences that “counting sequences with nonredundant barcodes provides a quantitative measure of template diversity.” EX1004.006. Thus, as was routine, McCloskey’s method provides that counting unique molecular tags would provide a count of sample polynucleotides. *See supra* Section VII.B. Consistent with this, an exemplary description of how the combination of Linnarsson and McCloskey teaches counting sample polynucleotides is described in Dr. Cooper’s accompanying declaration. *See* EX1002 ¶¶ 213-218.

Moreover, the use of molecular tags for counting sample polynucleotides was well-known and routine as of the earliest priority date of the ’197 Patent. The specification of the ’197 Patent provides that any “convenient method for tagging and/or counting individual nucleic acid molecules with unique tags may be employed.” EX1001 at 22:38-45; *see also* EX1002 (describing prior art counting

technique cited by the '197 Patent). As Dr. Cooper explains, the use of molecular tags for this purpose had been tried-and-true since at least 2004. *See* EX1002 ¶ 79.

Thus, the combination of Linnarsson and McCloskey discloses and renders obvious using the first and second tag to count a number of sample polynucleotides in said plurality of sample polynucleotides of said cell.

2. Claim 2: The method of claim 1, wherein the method further comprises amplifying the plurality of tagged polynucleotides prior to the sequencing step (c).

According to Linnarsson, after reverse transcription is performed on the mRNA molecules (*i.e.*, sample polynucleotides) to generate cDNA molecules (*i.e.*, tagged polynucleotides), the plurality of tagged cDNA are amplified to generate copies of each tagged double-stranded cDNA. EX1003 at 10:20-22 (“amplifying the pooled cDNA samples to generate a cDNA library comprising double-stranded cDNA.”); EX1015 at 3:2-3; *see also* EX1003 at 4:11-12; EX1015 at 10:2-3; EX1002 at ¶ 185. Next, “sequencing is performed to obtain 100 million reads....” EX1003 at 4:12; EX1015 at 10:3; *see also* EX1003 at 6:9-12, 10:22-24, 11:12-15, 13:1-2, 22:5-21; EX1015 at 3:24-29, 8:33-9:26.

3. Claim 3: The method of claim 1, wherein the plurality of sample polynucleotides is selected from DNA and RNA.

As described above in Section IX.A.1.b, Linnarsson teaches sample polynucleotides that are mRNA. *See* EX1003 at 3:26-27; EX1015 at 2:27-31;

EX1002 ¶ 188. Thus, Linnarsson teaches and renders obvious plurality of sample polynucleotides is selected from DNA and RNA. *See Fresenius USA, Inc. v. Baxter Intern., Inc.*, 582 F.3d 1288, 1298 (Fed. Cir. 2009) (“Element (a) is written in Markush form, such that the entire element is disclosed by the prior art if one alternative in the Markush group is in the prior art.”).

4. Claim 4: The method of claim 1, wherein the plurality of sample polynucleotides comprises mRNA.

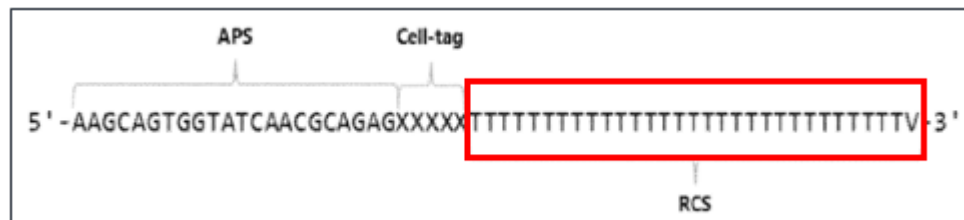
Disclosed. *See supra* Section IX.A.3.

5. Claim 6: The method of claim 1, wherein an oligonucleotide tag of said plurality of oligonucleotide tags comprises said first tag sequence and said second tag sequence.

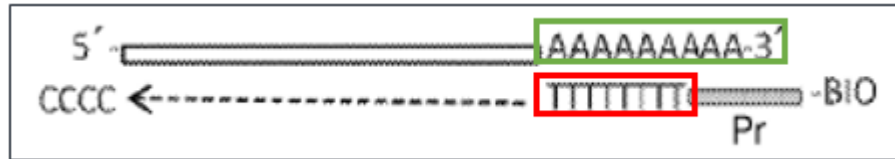
As explained above, it would have been obvious to combine McCloskey’s teaching of an encoding oligonucleotide comprising two tags sequences and Linnarsson’s method of preparing a tagged cDNA library. *See supra* Section IX.A.1.f. Specifically, it would have been obvious to use the approach of McCloskey and conceptually divide Linnarsson’s tag sequence in either the TSO or CDS into two portions, such that the first portion (*i.e.*, “said first tag sequence”) is used to distinguish single-cell origins of sample polynucleotides, and the second portion (*i.e.*, “said second tag sequence”) is used to distinguish among sample polynucleotides originating from the same single-cell. *See id.*

- 6. Claim 7: The method of claim 1, wherein an oligonucleotide tag of said plurality of oligonucleotide tags comprises a sequence that is configured to hybridize to said sample polynucleotide.**

The combination of Linnarsson and McCloskey discloses and renders obvious claim 7. Specifically, Linnarsson discloses that its CDS includes an RNA complementary sequence (RCS). EX1003 at 15:2-3; EX1015 at 25-26; EX1002 ¶ 195. Figure 4 of Linnarsson depicts an example of a CDS with an RCS (boxed in red):



EX1003 at Fig. 4. Linnarsson further discloses that the RCS “is at least partially complementary to one or more RNA in an individual mRNA sample,” which allows the CDS “to hybridize to at least some mRNA in an individual mRNA sample to direct cDNA synthesis using the mRNA as a template.” EX1003 at 15:3-6; EX1015 at 5:26-30. As seen in the figure below, the RCS has a sequence of thymines (boxed in red) that hybridizes with the poly-A tail sequence at the 3’ of the mRNA (boxed in green):



EX1003 at Fig. 11; EX1002 ¶ 196.

7. **Claim 8: The method of claim 1, wherein the plurality of tagged polynucleotides is generated by (i) hybridizing an oligonucleotide tag of said plurality of oligonucleotide tags to said sample polynucleotide and (ii) extending said oligonucleotide tag or said sample polynucleotide or both.**

As discussed in Section IX.A.1.c, Linnarsson teaches that a CDS (*i.e.* “an oligonucleotide tag”) which includes a sequence of thymines that hybridizes with a sequence of adenines making up the poly-A tail of the template mRNA strand (*i.e.* “said sample polynucleotide”). EX1003 at Fig. 2 and 11; EX1015 at Fig 2 and 11; *see also* EX1003 5:29-31; EX1015 5:24-32. Linnarsson further teaches extending the CDS using a reverse transcriptase enzyme. EX1003 at 5:29-30 (“A tailed oligo-dT primer directs synthesis of a cDNA strand.”); *id.* at 15:1-6, 16:10-15, 16:22-26, 18:19-24, Figs. 2, 11; EX1015 at 6:19-24; EX1002 ¶ 200.

8. **Claim 9: The method of claim 1, wherein the plurality of tagged polynucleotides is generated through at least one linear amplification reaction.**

Linnarsson teaches generating tagged polynucleotides through linear amplification of the plurality of sample polynucleotides. Specifically, Linnarsson teaches performing reverse transcription on the plurality of sample mRNA

molecules to generate a plurality of cDNA molecules. *See* EX1003 at 3:25-30 (describing the steps of cDNA synthesis through reverse transcription); *see also id.* at 22:24-26; EX1015 at 2:27-3:3, 11:11-14; EX1003 at 14:9-32; EX1015 at 4:29-5:22. A POSA would have understood that reverse transcription is a type of linear amplification method because it generates a single copy of an original parent nucleic acid strand. EX1002 ¶ 202.

9. Claim 10: The method of claim 1, wherein the plurality of tagged polynucleotides is generated through at least one reverse transcription reaction.

Disclosed. *See supra* Section IX.A.8.

10. Claim 11: The method of claim 1, wherein the plurality of tagged polynucleotides is generated through at least one polymerase chain reaction (PCR).

Linnarsson teaches generating the tagged polynucleotides through PCR. According to Linnarsson, after “synthesizing a first strand of cDNA from the mRNA in each individual mRNA sample” and “incorporating a tag,” PCR amplification is performed to generate “a cDNA library comprising double-stranded cDNA”—*i.e.*, tagged polynucleotides. *See* EX1003 at 10:18-22; EX1015 at 2:33-3:3; *see also* EX1003, 20:3-6 (“PCR is a reaction in which replicate copies are made of a target polynucleotide....”); EX1015 at 8:7-9; EX1002 ¶ 207. As explained above, each

cDNA copy generated through PCR is a recited “tagged polynucleotide.” *See supra* Section IX.A.1.c.

11. Claim 20: The method of claim 1, wherein said plurality of sample polynucleotides are randomly associated with said plurality of oligonucleotide tags to generate said plurality of tagged polynucleotides.

Linnarsson discloses adding a plurality of oligonucleotide tags to a mixture containing sample polynucleotides to generate tagged polynucleotides. EX1003 at 18:27-29 (“the CDS and/or the TSO can be added to each individual mRNA sample during cell lysis, as this will aid hybridization of the oligonucleotides.”).

A POSA would understand that by adding the oligonucleotide tags to a mixture containing sample polynucleotides under the conditions disclosed in Linnarsson, the tags would randomly associate with the sample polynucleotides to generate the plurality of tagged polynucleotides. EX1007.002 (“hybridization of DNA molecules with identical sequences is competitive and therefore, the tags are selected randomly”); EX1002 ¶ 210. Indeed, Linnarsson teaches that tags attach to mRNA nonspecifically; for example, every CDS attaches to mRNA by hybridizing with the poly-A tail, regardless of its unique tag sequence. *See supra* Section IX.A.1.c.

- 12. Claim 23: The method of claim 1, wherein step (d) comprises using said first tag sequence to distinguish (i) the number of sample polynucleotides having said sample sequence from said cell from (ii) the number of sample polynucleotides having said sample sequence from other cells.**

The combination of Linnarsson and McCloskey teaches and renders obvious the method of claim 23.

First, the combination of Linnarsson and McCloskey teaches counting the number of sample polynucleotides having the same sample sequence. As explained above in Sections IX.A.1.c. and IX.A.1.f.-h., the combination of Linnarsson and McCloskey teaches attaching unique molecule-tag sequences (*i.e.*, “second tag sequences”) to each sample polynucleotide during the process of generating tagged polynucleotides, and counting the number of different molecule-tags in the sequenced cDNA to count the number of sample polynucleotides.

Because a unique molecule-tag is attached to each sample polynucleotide (*see* Section IX.A.1.h. and IX.B.2.), the number of sample polynucleotides can be determined even if some of the sample polynucleotides have the same sample sequence (*i.e.*, mRNA sequence). Similarly, one can count the number of different molecule-tags having the same sample sequence to determine the number of sample polynucleotides having said sample sequence. This technique of determining the number of sample polynucleotide having the same sequence was routine and well-

known in the art. EX1002 ¶ 213; EX1007.001 (providing two exemplary methods “to calculate the number of molecules of a single mRNA species in a complex mRNA preparation.”).

Second, as explained above in Section IX.A.1.e, the combination of McCloskey and Linnarsson teaches a method of using a cell-tag (i.e., the “first tag sequence”) to identify the single-cell origin of the sample polynucleotides. As a result, tagged cDNA comprising an mRNA sequence from any one single-cell would carry the same unique cell-tag (i.e., Linnarsson’s TSO and/or CDS tag; McCloskey’s batch-stamp), which is different from other unique cell-tags used for cDNA comprising the same mRNA sequence from other single-cells. EX1002 ¶ 215. When counting the number of sample polynucleotides having the same sample sequence, the cell-tag distinguishes which cell each sample polynucleotide originates. Thus, by using the unique cell-tags (“said first tag sequence”), the number of sample polynucleotides comprising a sample sequence from any one cell may be distinguished from the number of sample polynucleotides comprising the same sample sequence from other cells.

- 13. Claim 24: The method of claim 1, wherein step (d) comprises determining the number of different second tag sequences associated with said sample sequence, thereby estimating the number of sample polynucleotides having said sample sequence from said cell.**

As discussed above in Section IX.A.12, the combination of Linnarsson and McCloskey teaches that by counting the number of different molecule-tags (*i.e.*, “second tag sequences”) in the sequenced cDNA comprising the same mRNA sequence, the number of sample polynucleotides having the same sample sequence from the cell is determined.

- 14. Claim 25: The method of claim 1, wherein said plurality of sample polynucleotides comprises substantially all mRNA molecules of said cell.**

As explained above in Sections IX.A.1.b. and IX.A.3., Linnarsson describes that the plurality of sample polynucleotides can comprise mRNA molecules of a cell. Further, Linnarsson teaches that said plurality of sample polynucleotides can comprise substantially all mRNA molecules of said cell.

Specifically, Linnarsson’s method includes the step of “releasing mRNA from each single cell to provide a plurality of individual mRNA samples.” EX1003 at 3:26-28; EX1015 at 2:30-32. Because the mRNA is indiscriminately released from each single cell without any elimination or filtration, the released mRNA sample that is tagged, amplified, and sequenced comprises substantially all mRNA molecules of

said cell. Also, as explained in Section IX.B.2, it would have been obvious to tag substantially every sample polynucleotides from a cell. Thus, the tagged, amplified, and sequenced samples necessarily comprise substantially all mRNA molecules from the cell.

Further, the purpose of Linnarsson's method is gene expression analysis, which a POSA would have understood contemplates the analysis of substantially all mRNA molecules of a cell. EX1002 ¶ 222; EX1003 at 1:11-12, 1:25-26 ("direct sequencing of the *all*, or parts, *of the mRNA content* of a tissue is being increasingly used."); EX1015 at 1:10-11, 1:31-33. Thus, a POSA would have understood that such a method was designed to be applied to substantially all mRNA molecules of a given cell.

Therefore, even to the extent not expressly disclosed by Linnarsson, a POSA would have found it obvious in view of Linnarsson that the plurality of sample polynucleotides would comprise substantially all mRNA molecules of said cell. EX1002 ¶ 222.

B. Ground 2

As explained below, Claims 5, 12, 21-22, and 26 of the '197 Patent would have been obvious over the combination of Linnarsson and McCloskey, and further in view of the knowledge of a POSA.

1. Claim 5: The method of claim 1, wherein the plurality of tagged polynucleotides is generated through at least one ligation reaction.

As explained above in Section IX.1.f.ii., a POSA would have been motivated to adopt McCloskey's teachings to modify Linnarsson's method so that the tags include both a first sequence identifying the cell of origin and a second sequence distinguishing sample polynucleotides from the same single-cell. It would have also been a simple and obvious design choice with a reasonable expectation of success to introduce these tags by ligating an oligonucleotide comprising the tag sequences to Linnarsson's CDS or TSO.

As of the earliest priority date of the '197 Patent, it was well-known and routine in the art to attach tag sequences to other sequences by ligation. *See* EX1002 ¶ 225. The '197 Patent itself acknowledges this, explaining that a "variety of template-driven ligation reactions" are available and citing nine different prior art references to this effect. *See* EX1001 at 6:23-32. Likewise, in the Detailed Description of the Invention, the '013 Patent affirms that the "practice of the present invention may employ, unless otherwise indicated, conventional techniques" and that such "conventional techniques" include "polymer array synthesis, hybridization, **ligation**, and detection of hybridization using a label." *Id.* at 13:33-38.

While this alone establishes that the use of ligation would have been nothing but a routine and obvious design choice, Patent Owner further confirmed in its prior litigation against Becton-Dickinson that one would not require “*any* new, non-conventional attachment techniques” “to attach ‘diverse’ (*i.e.* different) labels” by ligation. EX1017.011-012 (emphasis in original). Patent Owner stated with respect to the Fodor Patents, for instance, that “the specification admits that ‘in one embodiment’ of the invention ‘the label-tag is attached by ligation’ and that ‘methods of ligation will be known to those of skill in the art.’” *Id*; *see also* EX1016.020 (admitting that “primer binding [was] known and conventional,” citing references “describing known ligation techniques”). Patent Owner attacked the Fodor Patents, which specifically claim attaching tags to polynucleotides by ligation, as claiming nothing but “well-known and conventional” elements. EX1029 at Claim 17.

Given the undisputedly well-known and routine nature of ligation to attach label tags to polynucleotides, a POSA would have had a reasonable expectation of success in ligating a second sequence to Linnarsson’s CDS or TSO. For example, it would have been obvious to do this by using a linker molecule. A 2003 article (“Hug”) discloses ligating tag sequences to a polynucleotide by hybridizing a linker to the target polynucleotide, which is designed to hybridize to another

polynucleotide used as a tag such that the tag is then ligated to the target polynucleotide. EX1007.008; *see also* EX1002 ¶¶ 228-229 (explaining Hug's methods in detail).

A POSA could have used Hug's method as one exemplary method to ligate the oligonucleotide comprising the tag sequences to Linnarsson's CDS or TSO. Specifically, a POSA could have designed a linker to hybridize to Linnarsson's CDS and/or TSO as well as the oligonucleotide, which could then be ligated to the CDS and/or TSO. *See* EX1002 ¶¶ 228-229 (describing the process in more detail). This approach was commonplace in the art at the time. *See id.* ¶¶ 229-231; *see also see also* EX1007.007; EX1024.005; EX1039.001-002; EX1040 at Fig. 2, ¶¶ 71-75, ¶¶ 235-239. As Dr. Cooper explains, this approach would be entirely equivalent to the method already disclosed by the combination of Linnarsson and McCloskey, except that instead of having the tag sequence be part of the CDS or TSO prior to extension, the tag sequences are added to the CDS or TSO after extension. A POSA would have been motivated to utilize this design choice because it would allow for added flexibility in selecting tag sequences during an experiment. *See* EX1002 ¶ 230.

Thus, because it would have been a simple and obvious design choice to use ligation to generate the recited tagged polynucleotide, claim 5 is obvious over Linnarsson, McCloskey, and the knowledge of a POSA.

2. Claim 12: The method of claim 1, wherein substantially every sample polynucleotide of said plurality of sample polynucleotides is associated with the same first tag sequence.

The combination of Linnarsson, McCloskey, and the knowledge of a POSA discloses and renders obvious claim 12.

As discussed above, Linnarsson discloses a cell-tag (*i.e.*, the “first tag sequence”) that identifies the single-cell origin of sample polynucleotides. *See supra* Section IX.A.1.e; EX1003 at 19:5-11. It would have been obvious to tag ***substantially every*** sample polynucleotide with the same cell-tag.

First, a POSA would have been motivated to tag substantially every sample polynucleotide with the same cell-tag.³ Linnarsson discloses using a cell-tag to identify the single-cell origin of sample polynucleotides. *See supra* Section IX.A.1.h. A POSA would have understood that tagging every sample polynucleotide (as opposed to only some of the sample polynucleotides) would

³ Claim 12 depends from claim 1, which recites “***a cell*** of the plurality of cells comprising ***a plurality of sample polynucleotides.***” Therefore, the recited “every sample polynucleotide of ***said plurality of sample polynucleotides***” in claim 12 originates from “a cell” (*i.e.*, the same single-cell) as recited in claim 1.

allow one to maximize the amount of information gleaned from each cell. EX1002 ¶ 234.

Second, a POSA would have had a reasonable expectation of successfully tagging substantially every sample polynucleotide with the same cell-tag. The '197 Patent does not disclose any special methods or techniques for ensuring that substantially every sample polynucleotide becomes associated with the same first tag sequence. Just the opposite, the '197 Patent acknowledges it was known in the art to have “*each* polynucleotide in the sample...tagged with a MID” by using a number of “MID tags...many times greater than the actual number of molecules to be analyzed.” EX1001 at 22:51-57 (citing EX1035). The Brenner 2000 prior art article (EX1035), cited in the '197 patent specification, teaches, for instance, using over 100 times more tags than sample polynucleotides to accomplish this. See EX1001 at 22:54-60; EX1035.003-004. Consistent with this, as set forth in the accompanying declaration of Dr. Gregory Cooper, a POSA would have readily understood that increasing the amount of oligonucleotide tags relative to the number of sample molecules would drive the tagging reaction to completion so that every sample polynucleotide is associated with the same first tag sequence. See EX1002 ¶ 235. Achieving the appropriate concentrations of oligonucleotide tags for this

purpose, Dr. Cooper explains, would have been nothing more than a straightforward optimization. *Id.*

Thus, the combination of Linnarsson, McCloskey, and the knowledge of a POSA teaches and renders obvious this claim.

3. Claim 21: The method of claim 1, wherein step (c) comprises hybridizing said tagged polynucleotide to a solid support.

Linnarsson discloses sequencing via “any high-throughput screening methods,” such as the routine and commercially available method of SOLiD sequencing. EX1003 at 21:16-18; EX1015 at 9:19-22. As Dr. Cooper explains, as of the 2009 timeframe, SOLiD sequencing was a standard DNA sequencing platform. EX1002 ¶ 241; EX1045.007. The SOLiD platform, along with other standard sequencing platforms that were commercially available in the 2009 timeframe, such as Roche 454, utilize as a standard step in the sequencing protocol the immobilization of sample nucleotides to a solid support. EX1002 ¶¶ 240-241. In the SOLiD platform, this is achieved via a biotin-streptavidin interaction whereas in the Roche 454 platform this is achieved via hybridization. *See* EX1045.003; EX1002 ¶ 241.

Linnarsson further teaches that the APS, which is incorporated in the CDS or TSO tag, “can be identical to the SOLiD P1 primer, and/or a SOLiD P2 sequence inserted in the CDS, so that the P1 and P2 sequences required for SOLiD sequencing

are integral to the amplified library.” EX1003 at 19:31-20:2; EX1015 at 8:28-31; *supra* Section VII.A.14. Thus, Linnarsson contemplates that the tagged DNA should include sequences to facilitate DNA sequencing.

While Linnarsson used the SOLiD platform for sequencing, it further teaches that “any high-throughput screening method” can be used. EX1003 at 21:16-18. As Dr. Cooper explains, this would have encompassed the prior art Roche 454 platform, which was widely used in the 2009 time frame. EX1002 ¶ 243. Because Linnarsson teaches that “any high-throughput screening method” can be used and because the Roche 454 platform was so well-known at the time, a POSA would have been motivated to use Roche 454 as a routine alternative to the SOLiD platform used in Linnarsson. Importantly, in the Roche 454 system, this entails hybridizing the DNA to a solid support that is a bead. As one article that summarize the Roche 454 technology explains, “the library fragments are mixed with a population of agarose beads whose surfaces carry oligonucleotides complementary to the 454-specific adapter sequences on the fragment library, so each bead is associated with a single fragment.” EX1045.003; *see also id.* at 1045.004 at Fig. 1b (“Anneal sstDNA to an excess of DNA capture beads.”).

4. Claim 22: The method of claim 20, wherein said solid support is a bead.

For the same reason as explained above with respect to claim 21, this claim is rendered obvious by the combination of Linnarsson, McCloskey, and the knowledge of a POSA, as exemplified by SOLiD and Roche 454 sequencing. *See supra* Section IX.B.3; EX1002 ¶ 246.

5. Claim 26: The method of claim 1, wherein said plurality of sample polynucleotides comprises a subset of polynucleotides of said cell having the same sequence.

The combination of Linnarsson and McCloskey, further in view of the knowledge of a POSA, renders claim 26 obvious.

It would have been a simple and obvious design choice to modify the combination of Linnarsson and McCloskey to target a specific sequence or set of sequences such that the plurality of sample polynucleotides comprise a subset of polynucleotides having the same sequence. The '197 Patent itself acknowledges that there had long since existed a “wide variety” of techniques for performing this very task and that “any convenient method” can be used. *See* EX1001 at 14:25-43. And Dr. Cooper confirms this, explaining that numerous routine and conventional methods were available for targeted selection of genomic loci (specific sequences). EX1002 ¶ 249; EX1057.001 (“The targeted enrichment of specific regions in complex genomes is a fundamental practice of modern molecular biology.”).

For example, it would have been obvious to use targeted capture, such as with a microarray—which allows selection of a specific target sequence from a diverse polynucleotide sample and excludes all other polynucleotides. A 2007 article (“Albert”) teaches a method where custom microarrays are used to “capture” by “hybridiz[ing] single-stranded products to the capture arrays.” EX1057.001. Following capture of the target polynucleotides by hybridization, Albert’s method “removed non-hybridized materials by washing,” thus isolated the target polynucleotide sequence. EX1057.001; *see also* EX1002 ¶ 249 (detailed description of Albert’s method). A POSA would use Albert’s method with a reasonable expectation of success as one exemplary method for designing a capture system such that it would target a specific sample mRNA sequence of interest. EX1002 ¶ 249. Using this method, the microarray would selectively hybridize exclusively with a subset of polynucleotides having the same sequence—limiting the plurality of sample polynucleotides to a subset having the same target sequence.

Further, a POSA would be motivated to target a specific sample sequence of interest for a variety of routine reasons. For example, genes may be targeted for their relevance to a disease, a common mutation, or to explore variation in a population for research purposes. EX1057.002 (explaining that genes may be

selected to “determine our ability to discover variation in the human genome.”); EX1002 ¶ 250.

Thus, because it would have been a simple and obvious design choice to have the plurality of sample polynucleotides comprise a subset of polynucleotides having the same sequence, claim 26 is obvious over Linnarsson, McCloskey, and the knowledge of a POSA.

C. Ground 3

As explained below, Claims 13-19 of the '197 Patent would have been obvious to a POSA over the combination of Linnarsson, McCloskey, and further in view of McCloskey II.

1. Claim 13: The method of claim 1, wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence.

The combination of Linnarsson, McCloskey, and McCloskey II renders this claim obvious.

First, a POSA would have been motivated to tag each sample polynucleotide with a unique second tag sequence. As explained above, the combination of Linnarsson and McCloskey discloses a second tag sequence used for counting and distinguishing sample polynucleotides originating from the same single-cell. *See supra* Sections IX.A.1.f, h. A POSA would have understood that increasing the

number of polynucleotides tagged with a unique second tag sequence increases the accuracy of counting, and would have thus been motivated to ensure that each polynucleotide is tagged with a unique second tag sequence. EX1002 ¶ 252.

Second, a POSA would have had a reasonable expectation of successfully tagging each polynucleotide with a unique second tag sequence. As explained above in Section IX.B.2, it would have been obvious to ensure that each sample polynucleotide of said plurality of sample polynucleotide is tagged by using a large number of tags (*e.g.*, at least 100 times more) relative to the number of sample polynucleotides. *See also* EX1001 at 22:51-57 (admitting that it was known to ensure that “each polynucleotide in the sample...tagged with a MID...different from every other MID on every other polynucleotide in the sample” by using a “number of distinct MID tags...many times greater than the actual number of molecules to be analyzed.”) (citing EX1035).

Furthermore, it would have been obvious to design molecular tags to have a sufficient number of randomly selected nucleotides to ensure that each sample polynucleotide is tagged with a *unique* second tag sequence. McCloskey teaches that using second tag sequences each containing n number of random base pairs “enables one to distinguish among 4^n allele copies per reaction.” EX1004.004. It would have been a simple design choice to design the second tag sequences with

appropriate number of nucleotides to ensure sufficient number of distinct second tag sequences in the reaction mixture (e.g., at least 100 times for than the number of sample polynucleotides) such that each sample polynucleotide is uniquely tagged. EX1002 ¶ 254.

For example, McCloskey II teaches using molecular-tags each comprising 30 random base pairs, which would allow the creation of 4^{30} (1.15×10^{18}) unique second tag sequences. EX1055 at [0021] (“the length of the second sequence is between 3 and 30 nucleotides”). Linnarsson also teaches that its tag sequence can comprise at least 20 nucleotides, which would allow the creation of 4^{20} (1.10×10^{12}) unique barcodes. Ex. 1003, 18:32-19:3. Using molecular tags comprising 30 or 20 nucleotides would more than ensure that each sample polynucleotide from a single cell is tagged with a unique tag sequence. A typical mammalian cell comprises approximately between 50,000 to 360,000 mRNA molecules. *See* EX1002 at ¶ 255.

Thus, the combination of Linnarsson, McCloskey, and McCloskey II renders obvious claim 13.

2. **Claim 14: The method of claim 1, wherein at least 95 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence.**

For the same reason as explained above with respect to claim 13, the combination of Linnarsson, McCloskey, and McCloskey II renders obvious this claim. *See supra* Section IX.C.1.

3. **Claim 15: The method of claim 1, wherein at least 99 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence.**

For the same reason as explained above with respect to claim 13, the combination of Linnarsson, McCloskey, and McCloskey II renders obvious this claim. *See supra* Section IX.C.1.

4. **Claim 16: The method of claim 1, wherein substantially every sample polynucleotide of said plurality of sample polynucleotides is associated with a unique second tag sequence.**

For the same reason as explained above with respect to claim 13, the combination of Linnarsson, McCloskey, and McCloskey II renders obvious this claim. *See supra* Section IX.C.1.

5. **Claim 17: The method of claim 1, wherein the number of different second tag sequences is larger than the number of sample polynucleotides.**

The combination of Linnarsson and McCloskey II renders obvious the method of claim 17. As discussed above in Section IX.C.1., a POSA would have found it

obvious to use more unique second tag sequences than sample polynucleotides so that each sample polynucleotide tagged with a unique second tag sequence.

6. **Claim 18: The method of claim 17, wherein the number of different second tag sequences is at least ten times the number of sample polynucleotides.**

The combination of Linnarsson and McCloskey II renders obvious the method of claim 18. As discussed above in Section IX.C.1., a POSA would have found it obvious to use at least ten times more unique second tag sequences than sample polynucleotides so that each sample polynucleotide tagged with a unique second tag sequence.

7. **Claim 19: The method of claim 18, wherein the number of different second tag sequences is at least one hundred times the number of sample polynucleotides.**

The combination of Linnarsson and McCloskey II renders obvious the method of claim 18. As discussed above in Section IX.C.1., a POSA would have found it obvious to use at least 100 times more unique second tag sequences than sample polynucleotides so that each sample polynucleotide tagged with a unique second tag sequence.

X. THE BOARD SHOULD REACH THE MERITS OF THIS PETITION

A. Section 325(d) Does Not Apply Here, and Even if it Does, the Examiner's Material Errors Warrant Reaching the Merits of This Petition

In deciding whether to exercise its discretion to deny institution under 35 U.S.C. § 325(d), the Board applies a two-part framework that considers six non-exclusive factors. *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (precedential). As documented below, the same art and arguments presented herein were not previously presented to the Office in any meaningful or relevant way. In addition, the Examiner erred by not considering the relevant teachings in McCloskey alone or in combination with Linnarsson. As such, application of *Becton* overwhelmingly confirms that the Board should not exercise its discretion to deny institution under § 325(d).

1. Factors (a), (b) and (d): The Office Has Not Considered the Same or Substantially the Same Art or Arguments

McCloskey was not in front of the Examiner during prosecution of the '197 patent. Although the Applicant identified McCloskey II and Linnarsson in an IDS during the prosecution, the Examiner did not cite or discuss McCloskey II or Linnarsson in any rejection or in any remarks in response to a rejection. EX1005.106, 108, 147, 149.

Accordingly, with respect to McCloskey, McCloskey II, and Linnarsson, “the overlap between the arguments made during examination” and the arguments made in this petition is minimal, as *no arguments* were made during examination with respect to any of these references. *See 3Shape A/S v. Align Tech., Inc.*, IPR2019-00160, Paper 9 at 39-42 (P.T.A.B. June 11, 2019) (declining to apply § 325(d) where there was no evidence that the examiner substantively considered references that were of record during prosecution); *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00486, Paper 10 at 15 (P.T.A.B. July 15, 2015) (declining to exercise § 325(d) discretion because prior art reference at issue was only listed on IDS and “there is no evidence that the Examiner considered the particular disclosures cited by [Petitioner] in the Petition”).

Linnarsson and McCloskey II are cited on the face of the '197 Patent. However, mention of references in the specification does not justify denial under §

325(d), particularly where, as here, neither were cited nor discussed by the Examiner during prosecution. *See Limelight Networks, Inc. v. Akamai Tech., Inc.*, 2016 WL 8115506, at *5 (P.T.A.B. Dec. 30, 2016) (declining to exercise § 325(d) discretion because the Board was “not persuaded that merely referencing [references] in the ’102 patent’s specification necessarily is the same as presenting arguments with respect to those references”); *Weber, Inc. v. Provisur Tech., Inc.*, 2019-01467, Paper 7 at 9-10 (P.T.A.B. Feb. 14, 2020); *3Shape A/S and supra Microsoft*.

2. Factors (c), (e), and (f): The Examiner Erred by Not Considering the Art and Relevant Teachings Herein

Even if the Board determines that the same or substantially the same art or arguments were before the Office, the Examiner materially erred by not considering the relevant teachings in the Linnarsson and McCloskey II.

In the Notice of Allowance, the Examiner did not discuss or cite any passage or disclosure of Linnarsson or McCloskey II. EX1005.136. In such a case, where “the record of the Office’s previous consideration of the art is not well developed...a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f).” *Advanced Bionics*, at 10; *see Kayak Software Corp. v. Int’l Bus. Machs. Corp.*, CBM2016-00075, Paper 16 at 11 (P.T.A.B. Dec. 15, 2016) (informative) (“where the prior art at issue was only cursorily considered that can weigh against exercising the discretion”). Moreover, the fact that neither

Linnarsson nor the '640 Publication was “the basis of a rejection weighs strongly against exercising [the Board’s] discretion to deny institution.” *Cellco P’ship v. Huawei Device Co., Ltd.*, IPR2020-01117, Paper 10 at 13 (P.T.A.B. Feb. 3, 2021).

Here, the Examiner erred by failing to acknowledge any teachings in Linnarsson or McCloskey II. *Amber.IO, Inc. v. 72LUX, Inc.*, IPR2020-00015, Paper 8 at 20 (P.T.A.B. Apr. 1, 2020) (finding that the Examiner materially erred by failing to consider prior art references listed on IDS, when the Petitioner demonstrated that the references teach significant elements of the challenged claims). The Board should reach the merits of this petition and consider these relevant teachings in the first instance.

B. The Fintiv Factors Favor Institution

The factors set forth in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (P.T.A.B. Mar. 20, 2020) (“*Fintiv*”), for weighing discretionary denial when there is parallel, co-pending district court litigation, also favor institution.

The **first *Fintiv* factor**—whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted—is neutral. If instituted, Petitioner will seek stay in the district court litigation. As the court’s decision will come after institution, and is “based on a variety of circumstances and facts beyond [the Board’s] control and to which the Board is not privy.” *Sand Revolution II*,

LLC v. Continental Intermodal Grp. – Trucking, LLC, IPR2019-01393, Paper 24 at 7 (P.T.A.B. June 16, 2020) (informative); *see Western Digital Corp. v. Kuster*, IPR2020-01410, Paper 13 at 9-10 (P.T.A.B. Feb. 17, 2021). Moreover, the District of Delaware grants the majority of motions to stay pending IPR. EX1023; *see also, e.g., International Business Machines Corp. v. Rakuten Inc.*, No. 21-461-GBW, 2022 WL 17848779 (D. Del. Dec. 22, 2022) (granting defendant’s motion to stay after the Board instituted IPRs for the asserted patents). Thus, this factor is at least neutral.

The **second *Fintiv* factor**—proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision—favors institution. Currently, the trial in the district court litigation is scheduled to start on December 2, 2024, which will be after the anticipated final written decision in this IPR. EX1018.

But more realistically, it is far from certain that the district court trial will proceed as planned. There is a reasonable chance that the litigation may be stayed upon institution and/or ordinary delays in district court litigation may occur over the next 18 months. EX1023. Indeed, the median time to trial for civil cases in the District of Delaware is 33.7 months, which would place trial in July 2025. EX1019.014. Thus, this factor favors institution.

The **third *Fintiv* factor**—investment in the parallel proceeding by the court and the parties—favors institution. The Board has found that the third factor favors institution where in the parallel litigation, “the District Court has not issued any substantive orders,” “no claim construction orders have issued,” and “discovery is not complete, because ... neither party had taken any depositions.” *Snap, Inc. v. SRK Tech. LLC*, IPR2020-00820, Paper 15 at 10–11 (P.T.A.B. Oct. 21, 2020). This is all true for the district court litigation.

Fact discovery is ongoing. Further, expert discovery or dispositive motion briefing will not be completed until well after the institution deadline. EX1018. No claim construction brief has been filed by either party, and the claim construction hearing will not occur until February 21, 2024. EX1018. Furthermore, “the most burdensome parts of the case—filing and responding to pretrial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice—all lie in the future.” *CyWee Grp. Ltd. v. Samsung Elecs. Co. Ltd.*, No. 2:17-cv-00140-WCB-RSP, 2019 WL 11023976, at *6 (E.D. Tex. Feb. 14, 2019). Thus, this third factor favors institution.

The **fourth *Fintiv* factor**—overlap between issues raised in the petition and in the parallel proceeding—favors institution. If instituted, Petitioner will stipulate

to not pursuing, in the district court litigation, invalidity arguments based on any instituted IPR ground.

The **fifth *Fintiv* factor**—whether the Petitioner and the defendant in the parallel proceeding are the same party—is neutral. Petitioner is the defendant in the district court litigation, but that is often the case for a patent asserted in district court and challenged at the Board.

Finally, the **sixth *Fintiv* factor**—other circumstances that impact the Board’s exercise of discretion, including the merits—also favors institution. This Petition presents a compelling merits case that all claims of the ’197 Patent are unpatentable, and therefore this factor weighs in favor of institution. *Supra* Section IX; *Fintiv*, IPR2020-00019, Paper 11 at 14–15.

Thus, in view of the facts presented in this Petition, the *Fintiv* factors do not support discretionary denial.

XI. CONCLUSION

Petitioner respectfully requests cancellation of the Challenged Claims.

Dated: May 25, 2023

Respectfully submitted,

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APPENDIX : CHALLENGED CLAIM LISTING

No.	Limitation
1	A method of counting nucleic acids in a sample, the method comprising: (a) providing a sample comprising a plurality of cells, wherein a cell of the plurality of cells comprises a plurality of sample polynucleotides; (b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides of said cell and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises: (i) a sample sequence from a sample polynucleotide of the plurality of sample polynucleotides; (ii) a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells; and (iii) a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell; (c) sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence; and (d) using the first tag sequence and the second tag sequence to count a number of sample polynucleotides in said plurality of sample polynucleotides of said cell.
2	The method of claim 1, wherein the method further comprises amplifying the plurality of tagged polynucleotides prior to the sequencing step (c).
3	The method of claim 1, wherein the plurality of sample polynucleotides is selected from DNA and RNA.
4	The method of claim 1, wherein the plurality of sample polynucleotides comprises mRNA.

5	The method of claim 1, wherein the plurality of tagged polynucleotides is generated through at least one ligation reaction.
6	The method of claim 1, wherein an oligonucleotide tag of said plurality of oligonucleotide tags comprises said first tag sequence and said second tag sequence.
7	The method of claim 1, wherein an oligonucleotide tag of said plurality of oligonucleotide tags comprises a sequence that is configured to hybridize to said sample polynucleotide.
8	The method of claim 1, wherein the plurality of tagged polynucleotides is generated by (i) hybridizing an oligonucleotide tag of said plurality of oligonucleotide tags to said sample polynucleotide and (ii) extending said oligonucleotide tag or said sample polynucleotide or both.
9	The method of claim 1, wherein the plurality of tagged polynucleotides is generated through at least one linear amplification reaction.
10	The method of claim 1, wherein the plurality of tagged polynucleotides is generated through at least one reverse transcription reaction.
11	The method of claim 1, wherein the plurality of tagged polynucleotides is generated through at least one polymerase chain reaction (PCR).
12	The method of claim 1, wherein substantially every sample polynucleotide of said plurality of sample polynucleotides is associated with the same first tag sequence.
13	The method of claim 1, wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence.
14	The method of claim 1, wherein at least 95 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence.
15	The method of claim 1, wherein at least 99 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence.
16	The method of claim 1, wherein substantially every sample polynucleotide of said plurality of sample polynucleotides is associated with a unique second tag sequence.

17	The method of claim 1, wherein the number of different second tag sequences is larger than the number of sample polynucleotides.
18	The method of claim 17, wherein the number of different second tag sequences is at least ten times the number of sample polynucleotides.
19	The method of claim 18, wherein the number of different second tag sequences is at least one hundred times the number of sample polynucleotides.
20	The method of claim 1, wherein said plurality of sample polynucleotides are randomly associated with said plurality of oligonucleotide tags to generate said plurality of tagged polynucleotides.
21	The method of claim 1, wherein step (c) comprises hybridizing said tagged polynucleotide to a solid support.
22	The method of claim 20, wherein said solid support is a bead.
23	The method of claim 1, wherein step (d) comprises using said first tag sequence to distinguish (i) the number of sample polynucleotides having said sample sequence from said cell from (ii) the number of sample polynucleotides having said sample sequence from other cells.
24	The method of claim 1, wherein step (d) comprises determining the number of different second tag sequences associated with said sample sequence, thereby estimating the number of sample polynucleotides having said sample sequence from said cell.
25	The method of claim 1, wherein said plurality of sample polynucleotides comprises substantially all mRNA molecules of said cell.
26	The method of claim 1, wherein said plurality of sample polynucleotides comprises a subset of polynucleotides of said cell having the same sequence.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 13,962 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: May 25, 2023

By: /Derek C. Walter/
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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,240,197 WITH PARSE BIOSCIENCES, INC'S EXHIBIT LIST, POWER OF ATTORNEY AND EXHIBITS 1001-1062** are being served on May 25, 2023, via Priority Express Mail (Fed Ex) pursuant to 37 C.F.R. § 42.105 and § 42.6(e) to the Patent Owner at the address below:

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