UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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PARSE BIOSCIENCES, INC.
Petitioner,

v.

10X GENOMICS, INC.
Patent Owner

_____

Case No. IPR2023-____
U.S. Patent No. 10,155,981

_____

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,155,981

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a. [1A] A method of analyzing nucleic acids from a plurality of single cells, the method comprising: 37

b. [1B] providing a sample comprising a plurality of single cells, wherein each single cell of the plurality of single cells comprises a plurality of sample polynucleotides; 38

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d. [1D] wherein each tagged polynucleotide comprises: a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and 44

e. [1E] wherein each tagged polynucleotide comprises: … a multiplex identifier (MID) sequence comprising: I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and 47

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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., *Encoding PCR Products with Batch-Stamps and Barcodes*, 45 Biochemical Genetics, 761-767 (2007) ("McCloskey")
EX1005	Prosecution File History of U.S. Patent No. 10,155,981
EX1006	Leslie H. Brail et al., *Gene expression in individual cells: analysis using global single cell reverse transcription polymerase chain reaction (GSC RT-PCR)*, 406 Mutation Research Genomics, 45-54 (1999) ("Brail")
EX1007	Hubert Hug et al., *Measurement of Number of Molecules of a Single mRNA Species in a Complex mRNA Preparation*, 221 J. Theor. Bio., 615-624 (2003) ("Hug")
EX1008	Heather D. VanGuilder et al., *Twenty-five years of quantitative PCR for gene expression analysis*, 44 BioTechniques, 619-626 (2008) ("VanGuilder")
EX1009	Gerald Schochetman et al., *Polymerase Chain Reaction*, 158 J. of Infectious Diseases 1154-1157 (1988) ("Schochetman")
EX1010	Silvia G. Acinas et al., *PCR-Induced Sequence Artifacts and Bias: Insights from Comparison of Two 16S rRNA Clone Libraries Constructed from the Same Sample,* 17 Applied and Environmental Microbiology 8966-8969 (2005) ("Acinas")
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EX1012	Severine A Degrelle et al., *Amplification biases: possible difference among deviating gene expressions*, 9 BMC Genomics 1-15 (2008) ("Degrelle")

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EX1022	S. Kwok et al., *Effects of primer-template mismatches on the polymerase chain reaction: Human immunodeficiency virus type 1 model studies*, 18 Nucleic Acids Research 999-1005 (1990) ("Kwok")
EX1023	Motion Success for Stay Pending IPR In Delaware District
EX1024	Hiroto Okayama and Paul Berg, *High-Efficiency Cloning of Full-Length cDNA*, 2 Molecular and Cellular Biology 161-170 (1982) ("Okayama")

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EX1025	Bruce Alberts, et al., "Chapter 6 How Cells read the Genome: From DNA To Protein," *Molecular Biology of the Cell*, Garland Science 299-335 (4th ed. 2002)
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EX1027	10x Genomics Legal Notice
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EX1030	S. Clancy et al., *Translation: DNA to mRNA to Protein*, Nature Education (2008), at https://www.nature.com/scitable/topicpage/translation-dna-to-mrna-to-protein-393/
EX1031	Cole Trapnell, *Defining cell types and states with single-cell genomics*, 25(10) Genome Research 1491-1498 (2015) ("Trapnell")
EX1032	Gerard Brady et al., *Representative in Vitro cDNA Amplification From Individual Hemopoietic Cells and Colonies*, 2 Methods in Molecular and Cellular Biology 17-25 (1990) ("Brady")
EX1033	James Eberwine et al., *Analysis of gene expression in single live neurons*, 89 Proc. Natl. Acad. Sci. 3010-3014 (1992) ("Eberwine")
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EX1036	David H. Persing, *Polymerase Chain Reaction: Trenches to Benches*, J. of Clinical Microbiology 1281-1285 (1991) ("Persing")
EX1037	Kazuki Kurimoto et al., *An improved single-cell cDNA amplification method for efficient high-density oligonucleotide microarray analysis*, 34(5) Nucleic Acids Research 1-17 (2006) ("Kurimoto")

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EX1038	Shigeyuki Esumi et al., *Method for single-cell microarray analysis and application to gene-expression profiling of GABAergic neuron progenitors*, 60 Neuroscience Research 439-451 (2008) ("Esumi")
EX1039	Y. Shibata et al., *Cloning Full-length, Cap-Trapper-Selected cDNAs by Using the Single-Strand Linker Ligation Method*, 30(6) Biotechniques 1250-1254 (2001) ("Shibata")
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EX1041	Athina Gkazi, *An Overview of Next-Generation Sequencing*, 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, *Relocalization of elF4E by its binding partners upon stress*, Figure 2 (August 2009) at https://www.researchgate.net/publication/41663010_Relocalization_of_eIF4E_by_its_binding_partners_upon_stress
EX1043	Clyde A. Hutchinson, *DNA sequencing: bench to bedside and beyond*, 35(18) Nucleic Acids Research 6227-6237 (2007) ("Hutchinson")
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EX1050	National Human Genome Research Institute, *Polymerase Chain Reaction* (March 21, 2023) at https://www.genome.gov/genetics-glossary/Polymerase-Chain-Reaction
EX1051	Plaintiffs, Becton, Dickinson and Company and Cellular Research, Inc.'s First Amended Complaint, *Becton, Dickinson and Company and Cellular Research, Inc. v. 10X Genomics, Inc.*, C.A. No. 18-1800-RGA (Feb 08, 2019 D. Del.) (No. 15)
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I. INTRODUCTION

Parse Biosciences, Inc. ("Petitioner") requests *inter partes* review and cancellation of all claims (1-6) (collectively, the "Challenged Claims") of U.S. Patent No. 10,155,981 ("the '981 Patent"), entitled "Methods for Analyzing Nucleic Acids from Single Cells." The '981 Patent is assigned to 10x Genomics, Inc. ("Patent Owner").

The Challenged Claims pertain to methods of analyzing nucleic acid sequences (*i.e.*, polynucleotides) from different single cells by appending two "tags" to the polynucleotides, wherein the first tag allows one to identify the single cell origin of the polynucleotide, and the second tag allows one to distinguish different polynucleotides originating from the same single cell. One then sequences or analyzes the tagged DNA.

But such tagging and sequencing methods are not remotely what the '981 Patent specification characterizes as the alleged invention. Rather, the specification makes clear that the alleged invention is a technique called the "reflex method" (or "reflex process, reflex sequence process, reflex reaction, and the like") for rearranging DNA fragments to facilitate analyzing longer DNA sequences. *See* EX1001 at Summary Of The Invention. The specification mentions this reflex method dozens upon dozens of times as the key novel idea in the patent. The simplistic labeling methods that appear in the claims, by contrast, are described in

the specification as nothing but mere prior art techniques. *See, e.g.*, *id*. at 1:26-29 ("We have ***previously described*** methods that enable tagging each of a population of fragmented genomes….").[1]

While such disclosure in the specification of the '981 Patent itself raises a red flag as to the patentability of the claims of the '981 Patent, any doubt is put to rest by Patent Owner's numerous admissions in a prior litigation against Becton-Dickinson. In that case, Patent Owner admitted that methods for tagging, detecting, and sequencing DNA samples were nothing but "generic, routine, well-known laboratory techniques." EX1016.017.

In Patent Owner's own words, "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 .019. 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 the Becton-Dickinson case even includes claims directed to the very dual tagging approach claimed in the '981 Patent wherein a first tag distinguishes among different cells and a second tag distinguishes among different polynucleotides. *See* EX1016.006; EX1051.117. While Patent Owner

[1] All emphasis added unless otherwise indicated.

will now undoubtedly attempt to argue that this dual tagging approach was new and novel, it previously lumped it in among the ideas 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 '981 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 '981 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. As explained herein, the Challenged Claims of the '981 Patent would have been obvious by the combination of two prior art references: (1) International PCT Patent Application Publication WO 2010/117620 ("Linnarsson") and (2) a peer-reviewed scientific article entitled "Encoding PCR Products with Batch-Stamps and Barcodes" ("McCloskey").

During prosecution, the Examiner rejected all pending claims—which are substantially similar to the issued claims—as being ***anticipated*** by Linnarsson. EX1005.190-203. Although the Examiner ultimately allowed the claims, the Patent Owner did not dispute that Linnarsson discloses each and every limitation, except for limitations requiring a second tag to distinguish polynucleotides originating from the same single cell. Inexplicably, on this record, the Examiner

failed to give any consideration as to whether the claims would be invalid as ***obvious*** in view of Linnarsson and other prior art that does disclose the use of a second tag.

In fact, such prior art exists. McCloskey—which was not expressly considered by the Examiner—discloses such a second tag for single cell experiments like those described in Linnarsson. As documented herein and in the accompanying expert report of Dr. Gregory Cooper, the combination of Linnarsson with McCloskey renders obvious each and every claim of the ’981 Patent.

Accordingly, the Board should institute review of the ’981 Patent and find all Challenged Claims unpatentable.

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 ’981 Patent is involved in litigation in *10x Genomics v. Parse Biosciences, Inc.*, 22-cv-01117 (D. Del. filed Aug. 8, 2022).

C. Grounds for Standing

Petitioner certifies that the ’981 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.

Lead Counsel	**Back-Up Counsel**
Derek C. Walter Registration No. 74,656 (derek.walter@weil.com) Postal & Hand-Delivery Address: Weil, Gotshal & Manges LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 T: 650-802-3934 F: 650-802-3100	Adrian C. Percer Registration No. 46,986 (adrian.percer@weil.com) Postal & Hand-Delivery Address: Weil, Gotshal & Manges LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 T: 650-802-3124; F: 650-802-3100 William Sutton Ansley Registration No. 67,828 (sutton.ansley@weil.com) Postal & Hand-Delivery Address: Weil, Gotshal & Manges LLP 2001 M Street NW, Suite 600 Washington, DC 20036 T: 202-682-7018 F: 202-857-0940

III. IDENTIFICATION OF CHALLENGE

Claims 1-4 and 6 of the ’981 Patent are unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Linnarsson (EX1003) in view of McCloskey (EX1004). Claim 5 of the ’981 Patent is 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.

IV. TECHNOLOGICAL BACKGROUND

A. DNA and RNA

Deoxyribonucleic acid ("DNA") is a double-stranded molecule having a chain nucleotides. EX1002 ¶ 60. Each nucleotide comprises four types of bases: adenine ("A"), cytosine ("C"), guanine ("G"), and thymine ("T"). *Id.* ¶ 61. The order of these bases constitute genetic information, which can be copied to a ribonucleic acid ("RNA") strand by a process called transcription. *Id.* ¶ 67.

RNA is a molecule similar to DNA, where the nucleotides in RNA are adenine, cytosine, guanine, and uracil. Uracil and thymine are functionally equivalent including for both information storage and transmission. *Id.* ¶ 64. EX1044.001. A specific type of RNA—messenger RNA ("mRNA")—is read by ribosomes to make proteins. *Id.* ¶ 68. mRNA is critical to the study of epigenetics, or gene expression, because it shows the portions of DNA being transcribed for the production of proteins—*i.e.*, it shows which genes are expressed. *Id.* ¶ 70. In a clinical context, by sequencing the mRNA available in a cell it is possible to establish which genes are expressed and responsible for producing proteins in that cell. This is useful to understand aberrant gene activity (*e.g.*, in cancer cells) and to identify potential drug targets that alter gene expression. *Id.* ¶ 70.

B. Reverse Transcription

Reverse transcription is the process of synthesizing DNA, often referred to as complementary DNA ("cDNA"), from an RNA template. EX1002 ¶ 71. During reverse transcription, oligo(dT) primers pair with the template mRNA's poly(A) tail and a reverse transcriptase enzyme synthesizes cDNA from the mRNA. *Id.* ¶ 71.

C. Single Cell Genomics

Single cell genomics is the study of polynucleotides and proteins at a cell-by-cell resolution and was well known by 2009. *See, e.g.*, EX1006.001 (1999 study stating that "Global Single Cell Reverse Transcription-Polymerase Chain Reaction enables the study of single cell gene expression patterns"). Gene expression analysis, which is the process of determining the mRNA content of a cell or tissue, is useful when carried out through single cell genomics. EX1002 ¶¶ 74-75.

Gene expression is variable – genes may be expressed at high or low rates, corresponding to high or low quantities of mRNA. EX1025.005. Traditional techniques that rely on bulk analysis of mRNA content of a tissue result in loss of functional information present in single cells and only provide average expression profiles of individual cells. EX1002 ¶ 73; EX1003 at 1:26-30.

Single cell genomics, however, preserves each cell's unique information in a sample and with amplification techniques, mRNA can be detected even with very low levels of gene expression. Samples are analyzed on a single-cell basis to

preserve information unique to each cell in a sample, providing useful information about the heterogeneity of gene expression in tissues, particularly diseased tissues (*e.g.*, cancer). EX1002 ¶ 74; *see also* EX1006.001-002.

Single cell sequencing is the process of determining the sequences of nucleotides in a nucleic acid molecule, which usually includes the following steps: library generation and tagging of sequences; amplification; and sequencing. EX1002 ¶ 76.

1. DNA Tagging

Long before the earliest priority date of the '981 Patent, "tagging" was a known concept in genetics and molecular biology. Briefly, tagging involves adding synthetic polynucleotide to a sequence of interest by various methods, including ligation or annealing techniques. EX1002 ¶ 77. In fact, the '981 Patent acknowledges that various methods of tagging previously existed. EX1001 at 22:38-40 ("Any convenient method for tagging and/or counting individual nucleic acid molecules with unique tags may be employed").

It was common practice in the art 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 ¶ 78; 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.

2. Amplification

Amplification is the process of generating multiple copies of a specific polynucleotide. EX1002 ¶ 83. Polymerase Chain Reaction ("PCR") is a common method of amplification. *See* EX1008.001; EX1009.002; EX1004.001. PCR is a method of amplifying a polynucleotide of interest to generate a sufficient quantity for sequencing and analysis. EX1009.002.

PCR dates back to at least the early 1980s, and has been widely used in the art since then. *See* EX1008.001. Indeed, the '981 Patent acknowledges that PCR was known. EX1001 at 3:45-56 (incorporating by reference prior art references

discussing PCR). Without PCR, the amount of DNA retrievable from a sample would often be too small to provide reliable sequencing data. The accompanying declaration of Dr. Gregory Cooper summarizes the overall process of PCR. *See* EX1002 ¶¶ 85-89.

3. Amplification Bias and Molecular Tagging

By 2009, one problem with PCR had become apparent: amplification bias. EX1002, ¶ 90; EX1010.001-003. Due to random and preferential hybridization of primers, every target sequence is not duplicated in every PCR cycle. EX1002 ¶ 90; EX1022.001-002. Thus, the amplified end product may not accurately represent the relative quantity of each sequence that existed in the original sample. *Id*. This problem clouded the ability of researchers or clinicians to understand, for example, how much of a particular gene is being expressed in a particular cell of interest. EX1002 ¶ 38; EX1012.001-002, .012.

Prior to the ’981 Patent, researchers had developed methods of using molecular tagging to solve the problem of bias for gene expression analysis. EX1002 ¶ 92; EX1013.001. In such approaches, sample DNA molecules are first given a tag. Ideally, the number of different tags that are applied to the DNA sample is large enough so that every DNA molecule in the sample is given a unique tag relative to the tag that is applied to any other sample DNA molecule.

The tagged sample polynucleotides then undergo PCR amplification, and the resulting molecules are sequenced. EX1002 ¶ 92. For each molecule, the sequence data will include not just the sequence of the original DNA molecule, but also the tag that was added to the DNA molecule. Researchers could then count the number of unique tags that appear in the sequence data. *Id*.; EX 1013.001. Because every sample DNA molecule was given its own unique tag, the number of unique tags corresponds to the number of unique polynucleotides in the original sample. EX1002 ¶ 92. In this way, the tags allow one to avoid amplification bias and measure the number of unique molecules present in an original DNA sample. EX1013.001; EX1004.006.

4. Sequencing

Nucleic acid sequencing, loosely speaking, is the process of determining the sequence of nucleotides in a polynucleotide such as DNA. EX1002 ¶ 94. Amongst the nucleic acid sequencing technologies, Next Generation Sequencing ("NGS") emerged in the early 2000s. EX1045.002. NGS is a type of high-throughput sequencing technology that uses parallel sequencing of many fragments of DNA, enabling processing and detection of millions of sequence reads in a single run. *Id*. at .001. Sequencing is performed by alternating cycles of enzyme-driven processes and imaging steps.

D. Patent Owner's Admissions Regarding The Prior Art And The Novelty Of The Claimed Inventions

The well-known nature of the above-mentioned background technology has been acknowledged by Patent Owner. Indeed, Patent Owner's prior admissions confirm unequivocally that the claims of the '981 Patent are not remotely patentable.

In an unrelated case between Patent Owner and Becton, Dickinson and Company ("BD"),[2] Patent Owner challenged the eligibility of seven asserted patents (the "Fodor Patents"), which are directed to tagging DNA molecules for the purpose of tracking and counting individual molecules. EX1016.007-008. This is the exact thing to which the claims of the '981 Patent are directed. Petitioner's expert, Dr. Gregory Cooper, explains in detail the similarity between the claims at issue in the prior BD case and the claims at issue now. *See* EX1002 ¶¶ 38-42.

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.

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

And the Fodor Patents "[m]erely apply[] this 'old solution' of different labels in the particular technological environment of DNA." *Id.* at .016.

Patent Owner further argued that elements of the Fodor Patents—which also are claimed by the '981 Patent—are "***well-known and conventional***." *Id.* at .011. In Patent Owner's words, 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 was characterized as "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 (BD's complaint asserting claims 13 and 19 of the '659 Patent); EX1052.013-019, .031-039 (BD'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 ¶ 42 (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 also confirmed that detecting and sequencing DNA samples were nothing but "generic, routine, well-known laboratory techniques." EX1016.018; *compare with* EX1001 at Claim 1 ("(c) sequencing the plurality of

tagged polynucleotides"). Indeed, 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 '981 Patent are "[g]eneric, conventional [] techniques." EX1016.010-011.

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

Id. at .011. 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 '981 Patent.

V. OVERVIEW OF THE '981 PATENT

A. Priority Date of the '981 Patent

The '981 Patent, which was filed on August 15, 2017, identifies two provisional applications, the earlier of which was filed on August 20, 2009.

EX1001 at (60). Thus, the priority date of the ’981 Patent is no earlier than August 20, 2009.

B. Overview of the Challenged Claims and Specification

The Challenged Claims of the ’981 Patent are directed to methods for analyzing genetic sequences (*i.e.*, polynucleotides) from different single cells by appending “tags” to the polynucleotides.[3] EX1001 at Claim 1; *see also id.* at Abstract (“Aspects of the present invention include analyzing nucleic acids from single cells using methods that include using tagged polynucleotides containing multiplex identifier sequences.”). The Challenged Claims recite using two tags to track through amplification and sequencing two types of information available in the originating sample. The tags enable a researcher to distinguish (1) from which single cell the polynucleotide originates, and (2) one polynucleotide from another within that single cell.

As acknowledged by Applicants of the ’981 Patent, the features of these claims were already known in the art. 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

[3] A full listing of the claims of the ’981 Patent is available in the APPENDIX: CHALLENGED CLAIM LISTING.

use in identifying polynucleotides"); EX1002 ¶ 29. Likewise, the "multiplex identifier" (MID) of claim 1 is admittedly not novel. The specification explains that "[e]xemplary nucleic acid tags" from the prior art and incorporated by reference "find use as MIDs." EX1001 at 6:56-64; *see also id.* at 30:29-37, 6:33-36 (defining a "multiplex identifier" as "a tag or combination of tags associated with a polynucleotide whose identity can be used to differentiate polynucleotides in a sample."); EX1002 ¶¶ 30-32; EX1016.010 (explaining that methods of DNA tagging were "well-known and conventional before 2009.").

The '981 Patent specification describes attaching a tag through ligation or primer extension. EX1001 at 7:15-19. The specification confirms that such methods were well-known, citing ***nine*** references to this effect:

> In one aspect, template-driven reactions are ***primer extensions*** with a nucleic acid polymerase or ***oligonucleotide ligations*** with a nucleic acid ligase. Such reactions include, but are not limited to, polymerase chain reactions (PCRs), linear polymerase reactions, nucleic acid sequence-based amplification (NASBAs), rolling circle amplifications, and the like, ***disclosed in [the nine] references that are incorporated herein by reference***.

EX1001 at 3:42-56. Every single one these nine references predate the '981 Patent's earliest priority date of August 20, 2009. *Compare id.* at Claim 5 (reciting

"wherein the tagged polynucleotides are generated through at least one ligation reaction.").

The '981 Patent claims other conventional methods for preparing and sequencing tagged polynucleotides. For example, independent claim 1 recites "sequencing the plurality of tagged polynucleotides," yet the specification admits that methods for sequencing DNA was known in the art. EX1001 at 1:32-34 (discussing "existing DNA sequencing technologies"); *see also* EX1016.017 (describing sequencing methods as "generic, routine, well-known laboratory techniques.").

Similarly, the specification admits that methods for amplifying DNA sequences—as recited by dependent claim 6 of the '981 Patent—were well-known in the art. EX1001 at 14:53-56 ("Any convenient method for performing amplification reactions on a starting nucleic acid sample can be used in practicing the subject invention.").

C. Prosecution History Overview

During prosecution, the Examiner issued two rejections, finding that the pending claims were anticipated by Linnarsson. EX1005.154-162 – .193-202 . In response, the Applicants conceded that Linnarsson disclosed each and every limitation of the pending claims—which are substantially similar to the issued claims—except for a limitation requiring a second tag that distinguishes one sample

polynucleotide from other polynucleotides originating from the same single cell. EX1005.215-226.[4]

The Examiner ultimately allowed the claims, and in the Reasons for Allowance, reiterated that Linnarsson disclosed each and every element of the issued claims, except the claimed second tag. EX1005.238 ("The claimed identifier sequence comprises…a second tag sequence,…which is not taught by Linnarsson."). McCloskey, which was not before or expressly considered by the Examiner, discloses this missing limitation of including a second tag sequence to distinguish one polynucleotide from other polynucleotides from the same single cell. *See infra* Sections VII.A.1.e-i.

Notably, the Examiner also rejected all claims for being directed to an abstract idea and law of nature, "without significantly more." EX1005.152. The Examiner found that the method of tagging polynucleotides involves "mental step[s] of performing a correlation" and the "remaining steps in claim 1 were well-understood, routine steps," and the "dependent claims add elements…[that] are

[4] The only difference between the originally filed claims and the issued claims is that issued claim 1 additionally recites "wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells." *See* EX1005.178. The Applicant amended originally filed claim 1 to include this language after the Examiner issued the first rejection based on Linnarsson. EX1005.178 (March 26, 2018 amendment). The Examiner considered amended claim 1, which is identical to issued claim 1, in the second rejection. EX1005.195 (July 10, 2018 rejection finding that Linnarsson discloses "a different tag for each cell.").

routine, well-understood and conventional in molecular biology." EX1005.150-151; *see also id.* at .152. The Examiner subsequently withdrew the § 101 rejection, but maintained in the same office action that "tagging nucleic acid sample with identifier sequence [was] routinely practiced in the art as exemplified [by] Linnarsson." EX1005.199.

The '981 Patent then issued on December 18, 2018.

D. The Brenner Family and the Reflex Method

The subject matter of the '981 Patent was not developed by Patent Owner, but by PGT, a now-defunct company, in the 2009 timeframe. Patent Owner purchased the patent rights from PGT in 2016, and filed the application that resulted in the '981 Patent in 2017. EX1026; EX1005.074 (showing Patent Owner as the Applicant).

The '981 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 2016.[5] 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 a DNA strand within much larger fragments of genomic DNA. EX1001 at 1:32-37. As the Brenner Patents state, the "present invention

[5] 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.

removes the limitations imposed by current sequencing technologies as well as being 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 generally id.*, 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 invention is drawn to compositions and methods for intramolecular nucleic acid ***rearrangement*** that find use in various applications of genetic analysis, including sequencing, as well as general molecular biological manipulations of polynucleotide structures."). Indeed, 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.

Unsurprisingly, when the original inventors first sought patent protection in 2009, their claims closely tracked the "reflex" method in the specification. *See, e.g.*, EX1014 at Claim 1. Yet, years later, Patent Owner assumed control of the Brenner portfolio, and began drafting claims that had little, if anything, to do with the "reflex" method set forth in the Brenner Patents.

Rather than pertaining to the "reflex" method, Patent Owner's newly-drafted claims—illustrated by the Challenged Claims—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 above, the Brenner Patents characterize this tracking process not as an invention, but rather as a prior art technique that the inventors had previously accomplished. *See, e.g.*, EX1001 at 1:26-29 ("We have previously described methods that enable tagging each of a population of fragmented genomes and then combining them together to create a 'population library' that can be processed and eventually sequenced as a mixture.").

VI. LEVEL OF ORDINARY SKILL IN THE ART OF THE '981 PATENT

A person of ordinary skill in the art ("POSA") relating to the '981 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 ¶ 57. Further, a POSA would have been familiar with associated tools, methods, and techniques including: (1) polynucleotide tagging, *see* Section III.C.1; (2) amplification, *see* Section III.C.2; (3) use of tags to overcome amplification bias, *see*

Section III.C.3; (4) single cell analysis, *see* Section III.C; (5) ligation and primer extension, *see* Section III.B; and (6) sequencing, *see* Section III.C.4. EX1002 ¶ 58.

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 the 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)

Indeed, Linnarsson was cited as prior art during prosecution of the '981 Patent, and the Applicants did not contest its prior art status. Instead, the Applicants identified Linnarsson as prior art in an Information Disclosure Statement ("IDS"). EX1005.125. Therefore, Linnarsson is prior art to the challenged claims even if

the Challenged Claims of the ’981 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 Disclosure
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; *see also id.* at 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; *see also id.* 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 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;	“(ii) synthesising a first strand of cDNA from the mRNA in each individual mRNA sample and incorporating a tag 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; *see also id.* at 5:4-7, 5:24-32.
(iii) pooling the tagged cDNA samples; and	“pooling the tagged cDNA samples; and” EX1015 at 3:1; *see also id.* at 3:9-20.

Linnarsson	Linnarsson Provisional Application Disclosure
(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; *see also id.* 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 '981 Patent. *See Dynamic Drinkware; In re Giacomini, supra*. 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.

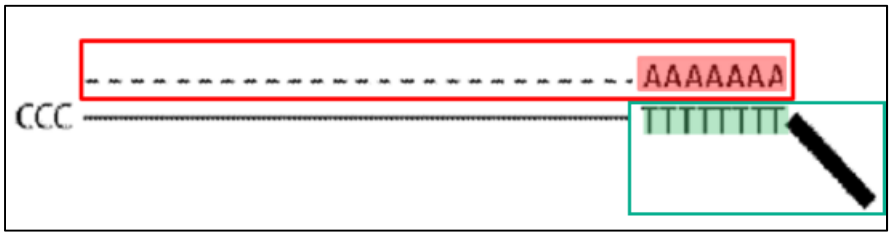
2. Linnarsson Overview

Linnarsson is directed to analyzing gene expression of a plurality of single cells. EX1003 at 1:6. In particular, 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. *Id.* 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-

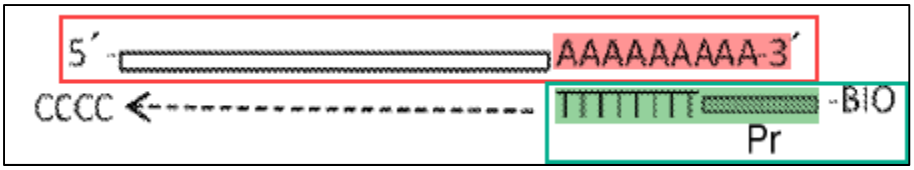
cell amplification bias. *Id.* at 37:28-29, 19:9-10 (disclosing that the tag acts as a barcode to "identify which single cell from each cDNA sample originated.").

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 ("In some aspects of the invention, a tag can be incorporated into the cDNA during its synthesis. For example, the CDS and/or the TSO can include a tag."). 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, below) that includes a sequence of thymines (highlighted in green, below) 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, below) of an mRNA strand (boxed in red, below). This is shown in both Figures 2 and 11 of Linnarrsson:

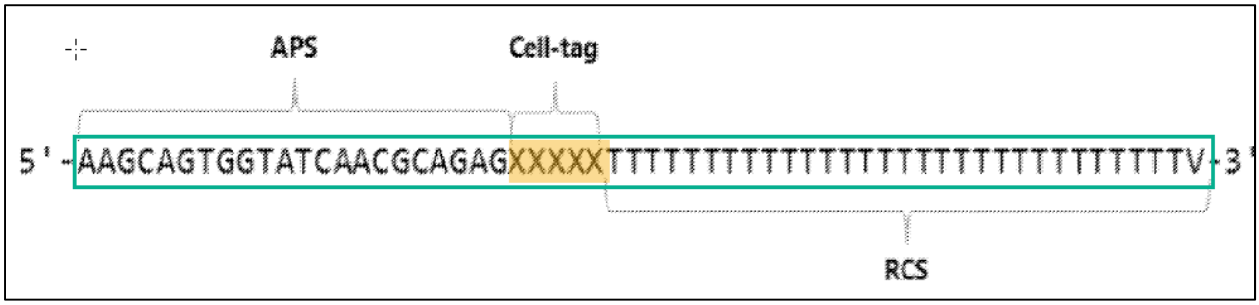


EX1003 at Fig. 2.



Id. at Fig. 11; *id*. at 5:29-31, 24:13-15; EX1002 ¶ 110. The resulting cDNA molecule also includes at its end a series of cytosine (C) nucleotides, which is added by the natural activity of the enzyme that is responsible for synthesizing the cDNA. EX1003 at 16:22-26.

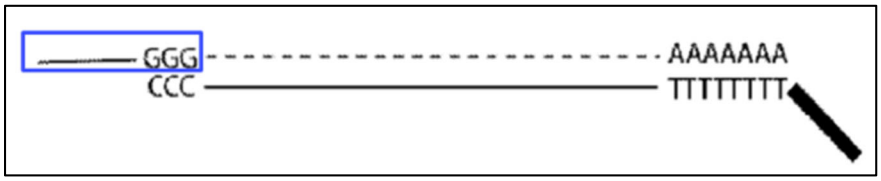
Figure 4 of Linnarsson depicts an example of a CDS (boxed in green, below) with a cell-tag (highlighted in yellow, below):



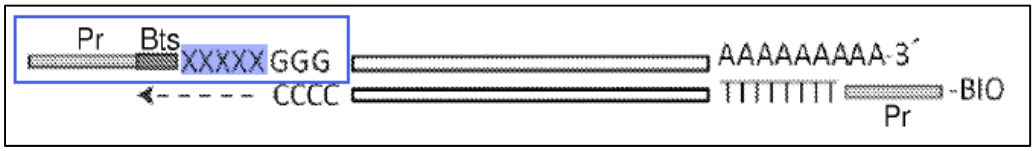
EX1003 at Fig. 4. Linnarsson discloses that the CDS cell-tag "can be incorporated into the cDNA" and can "be used to identify which single cell from each cDNA sample originated." EX1003 at 18:31, 19:9-10.

Linnarsson also discloses a template switching oligonucleotide ("TSO") (boxed in blue, below) that comprises the tag "XXXXX" (highlighted in blue), which "anneals transiently" to the series of cytosine nucleotides at the end of the

newly-synthesized strand "and cDNA synthesis proceeds using the oligo as template." This too is shown in both Figures 2 and 11 of Linnarsson:

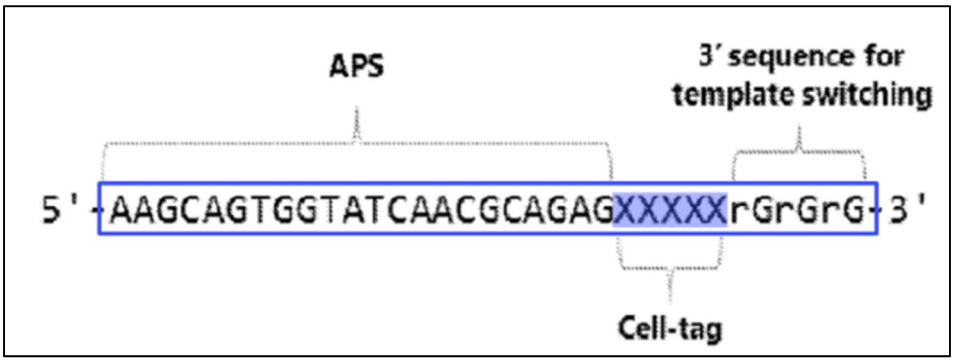


EX1003 at Fig. 2.



Id. at Fig. 11; *id.* at 5:31-33, 24:15-20 (explaining Figure 11); EX1002 ¶¶ 113-114.

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



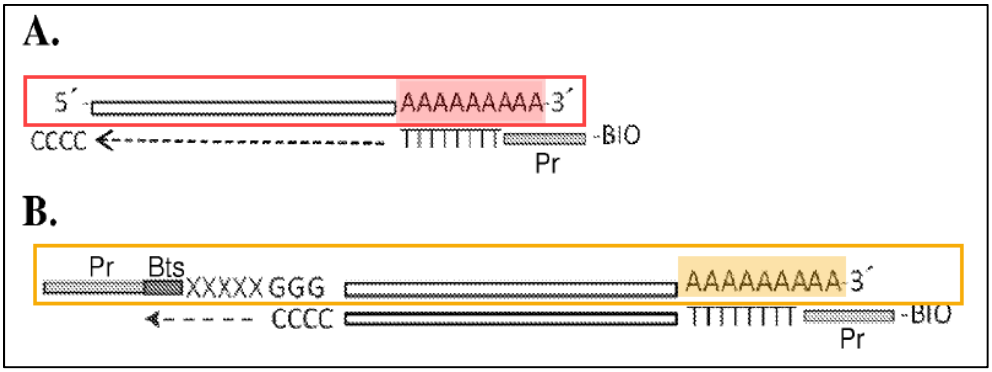
EX1003 at Fig. 3. Linnarsson discloses that the TSO cell-tag "can be incorporated into the cDNA" and can "be used to identify which single cell from each cDNA sample originated." *Id.* at 18:31, 19:9-10.

Thus, Linnarsson discloses 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 ("This cDNA library can be sequenced to provide an analysis of gene expression in single cells or in a plurality of single cells.").

Notably, during reverse transcription, the sample mRNA is denatured from the first synthesized cDNA strand and a new complementary strand of cDNA is formed along the first synthesized cDNA strand, generating a double-stranded cDNA. As a result, one strand of the double-stranded cDNA molecule (boxed in orange, below) has the same sequence as the original mRNA strand (boxed in red, below), including the same sequence of adenines (highlighted in orange, below) that made up the poly-A tail (highlighted in red, below) 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 ¶ 117.

B. McCloskey

The McCloskey reference, titled "Encoding PCR Products with Batch-Stamps and Barcodes," is a peer-reviewed scientific article 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). McCloskey was not considered by the Examiner during prosecution.[6]

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, below), which "distinguishes among sequences arising from different cell or allele copies." EX1004.002-004. Further, McCloskey teaches a second tag sequence, the "batch-stamp" (highlighted in red, below), that is unique to each experiment and is intended to associate a polynucleotide to "a specific sample run on a specific date." *Id*. at .004. The other regions on the encoding oligonucleotide include: "a genomic target-binding site" (highlighted in grey, below), "a primer-binding site for PCR" (highlighted in light blue, below), and "extra bases that serve as internal sentinels of recoding as well as tethering the oligonucleotide to itself" to minimize non-specific annealing (highlighted in purple, below). *Id.* at .003.

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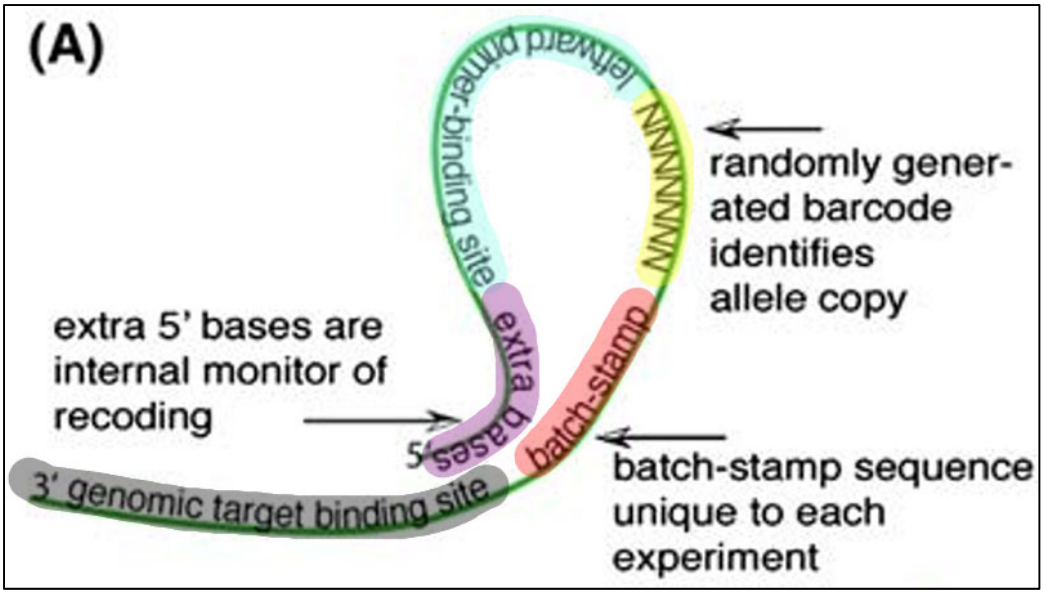
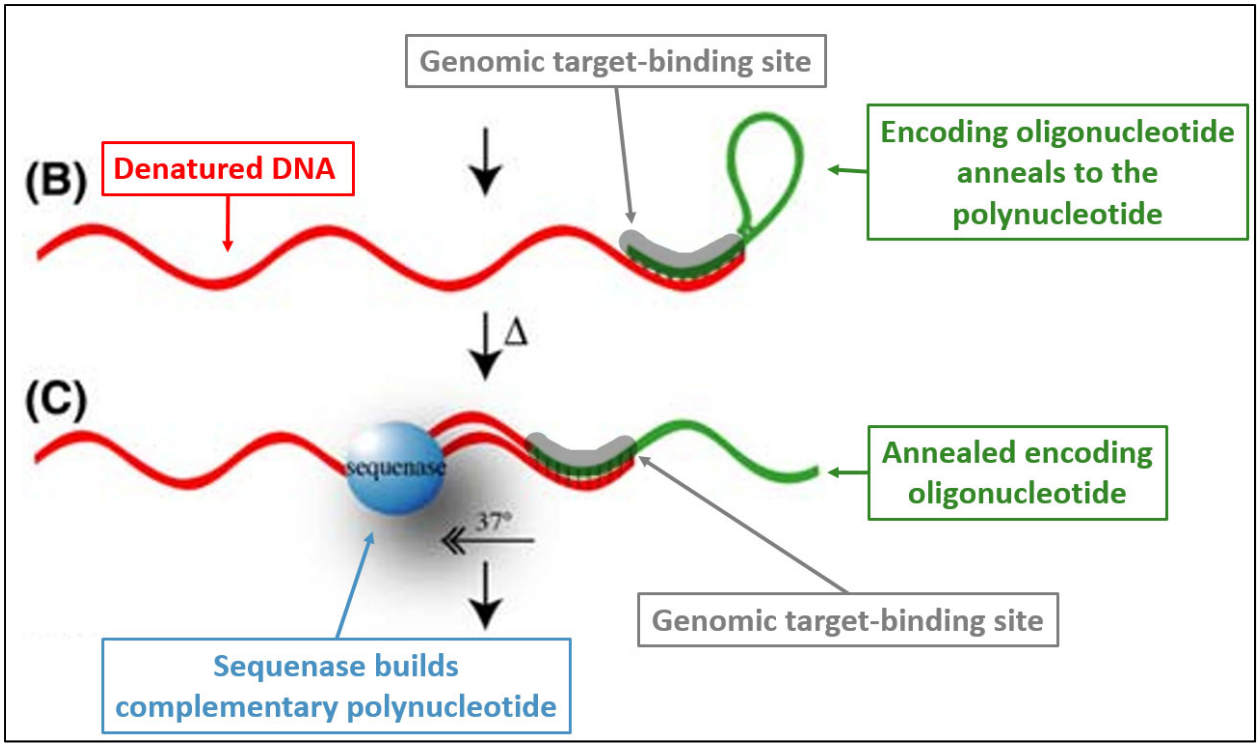
[6] In an IDS statement during prosecution, the Applicant identified a patent application publication ("the '640 Publication") with McCloskey's author being its first named inventor. EX1005.124. The Examiner raised no prior art rejection based on the '640 Publication, and the '640 Publication and McCloskey are different.



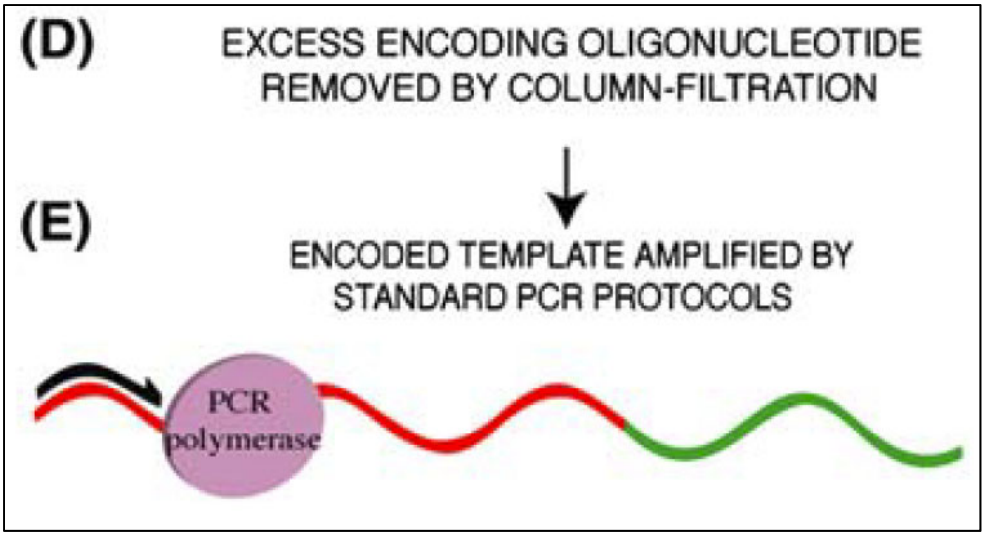
Id. at Fig. 1.

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.

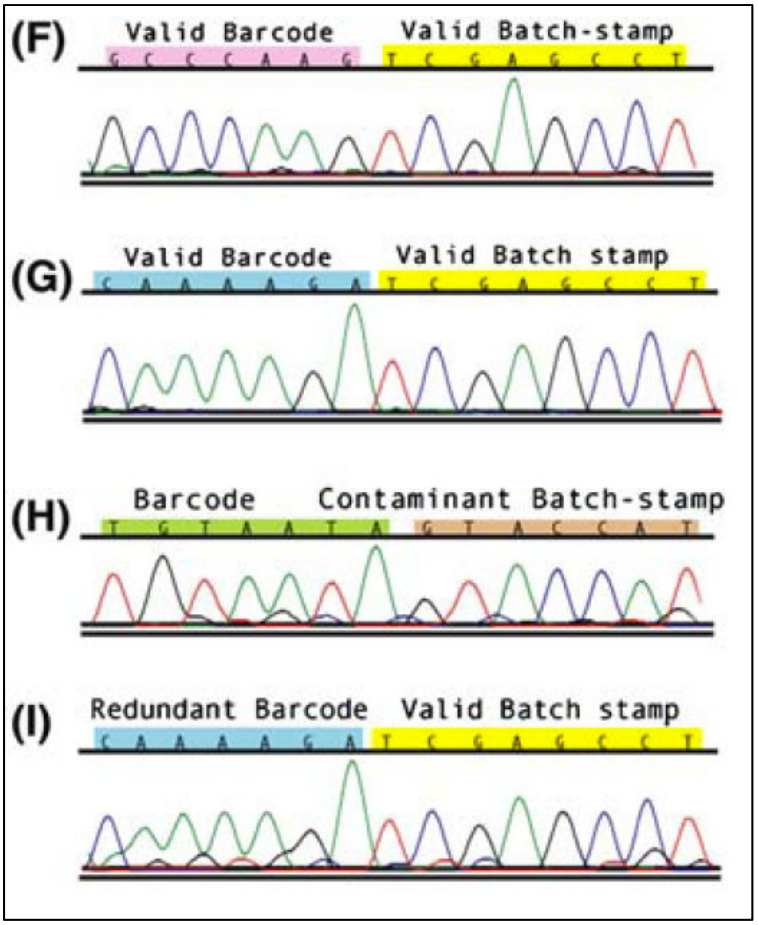
After the annealing and extension steps, McCloskey teaches purifying the sample to remove encoding oligonucleotides that were not annealed, followed by PCR amplification and sequencing. *Id.* at .005-007 ("Sequenase extension products were purified to remove any unincorporated encoding oligonucleotides 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 that are the result of PCR amplification from redundant sequences that existed in the sample before amplification. Two identical sequences that have the same barcode suggest that the redundancy is from PCR amplification, whereas two identical sequences that have a different barcode suggest that the redundancy existed 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 template diversity of the analyzed 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 another advantage of its method is the ability to detect contamination. Because the batch-stamp tag is unique to, and the same for, each experiment, one is able to tell from sequencing whether the results for one experiment contain any contaminant polynucleotides from another experiment, such as a test batch for a different cell. *Id*. at .004 ("The assigned batch-stamp is registered for a specific sample run on a specific date and is used only once."); *id*. at .006 ("The appearance of sequences bearing inappropriate batch-stamps enabled us to trace contaminating sequences to PCR reactions run either in parallel or previously in our laboratory …."). McCloskey depicts exemplary results from using its method that illustrate contaminant sequences and different barcodes:



EX1004 at Fig. 1.

McCloskey teaches that its 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.

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 person of ordinary skill in the art at the time of the invention. The following definitions are provided by the specification of the '981 patent. Further, these definitions are consistent with the ordinary understanding of a POSA. EX1002 at Section VIII, Claim Construction.

Claim 1 of the '981 patent recites "a multiplex identifier (MID) sequence." The specification defines "Multiplex Identifier" ("MID") as "a tag or combination of tags associated with a polynucleotide whose identity (e.g., the tag DNA sequence) can be used to differentiate polynucleotides in a sample. In certain embodiments, the MID on a polynucleotide is used to identify the source from which the polynucleotide is derived." EX1001 at 6:33-38.

Claim 1 of the '981 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 1-6 Are Unpatentable Under 35 U.S.C. § 103 Over Linnarsson in View Of McCloskey

As explained below, the Challenged Claims of the '981 Patent would have been obvious to a POSA over the combination of Linnarsson and McCloskey. This prior art combination discloses each and every one of the limitations of claims 1-6. Moreover, a POSA would have had a reason to combine Linnarsson's and McCloskey's teachings in the way claimed by the '981 Patent and would have had a reasonable expectation of success in doing so.

1. Claim 1:

a. [1A] A method of analyzing nucleic acids from a plurality of single cells, the method comprising:

To the extent the preamble is limiting, Linnarsson discloses this limitation. Applicant did not dispute that Linnarsson discloses this limitation during prosecution.

Linnarsson discloses a method of analyzing nucleic acids from a plurality of single cells: the "present invention provides methods and compositions for the analysis of gene expression in single cells or in a plurality of single cells." EX1003 at 9:23-25; EX1015 at 1:3-8; *see also* EX1003 at Abstract, 10:15-22, 22:22-28; EX1015 at 1:3-8, 2:27-3:3, 9:8-10, 11:8-17. In one embodiment, Linnarson's method comprises the following steps: "(A) the tissue of interest is dissected; (B) ***a***

plurality of single cells are selected; (C) single cells are placed in separate wells of a 96-well plate and lysed; tagged reverse transcription is performed on each sample to produce cDNA; (D) cDNA samples are pooled and amplified; (E) ***sequencing is performed*** to obtain 100 million reads; and (F) ***identification of expressed genes and identification of cells from which they originated***." EX1003 at 4:8-13; EX1015 at 9:35-10:6; *see also* EX1003 at Fig. 1; EX1015 at Fig. 1.

Therefore, to the extent the preamble is limiting, Linnarsson teaches this limitation.

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

Linnarsson discloses this claim element. Applicant did not dispute that Linnarsson discloses this during prosecution.

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 ("Figure 1…show an overview of a method of analyzing gene expression in a plurality of single cells….the tissue of interest is dissected;…a plurality of single cells are selected;…."); EX1015 at 9:35-37. 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 ("A single cell is placed in one well of a 96-well plate …."); EX1015 at 9:37-10:1, 11:10-11.

Second, Linnarsson teaches that each single cell of the plurality of single cells 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 ("…mRNA can be released from the cells by lysing the cells."); EX1015 at 4:12, 9:37-10:3; *see also* EX1003 at 22:24-26; EX1015 at 11:11-14. Linnarsson further teaches that cells contain a plurality of mRNA molecules. *See, e.g.*, EX1003 at 3:26-30 ("In one aspect, the method includes the steps of releasing mRNA from each single cell to provide a plurality of individual mRNA samples …."); EX1015 at 2:27-3:3.

Thus, Linnarsson teaches this limitation.

c. [1C] generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides,

Linnarsson discloses this claim element. Applicant did not dispute that Linnarsson discloses this limitation during prosecution. Further, as discussed

above in Section IV.D., Patent Owner previously challenged claims directed to a method for attaching a tag to a DNA sample as "well-known and conventional before 2009." EX1016.010.

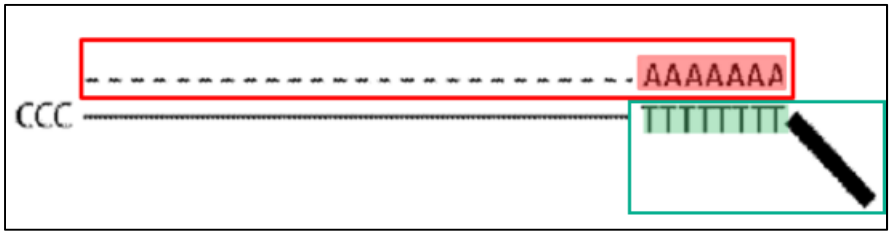
As explained above in Section IX.A.1.b, Linnarsson teaches a plurality of single cells comprising a plurality of sample polynucleotides (*i.e.*, mRNA). According to the method disclosed by Linnarsson, these sample mRNA are released from the single cells via lysis. *See* EX1003 at 4:10-11, 13:28 ("mRNA can be released from the cells by lysing the cells."); EX1015 at 4:12, 9:37-10:1.

Linnarsson 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 (describing reverse transcription methods to synthesize cDNA); EX1015 at 4:29-5:22.

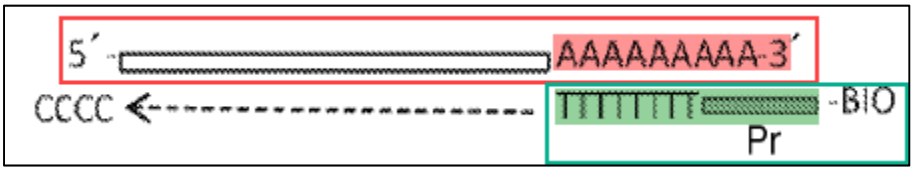
Furthermore, Linnarsson teaches that during cDNA synthesis, tagged oligonucleotides (*i.e.*, CDSs and/or TSOs) can be used to tag the cDNA. EX1003 at 19:4-7 ("As the tag is present in the CDS and/or the TSO it will be incorporated into the cDNA during its synthesis and can therefore act as a 'barcode' to identify

the cDNA."); 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):

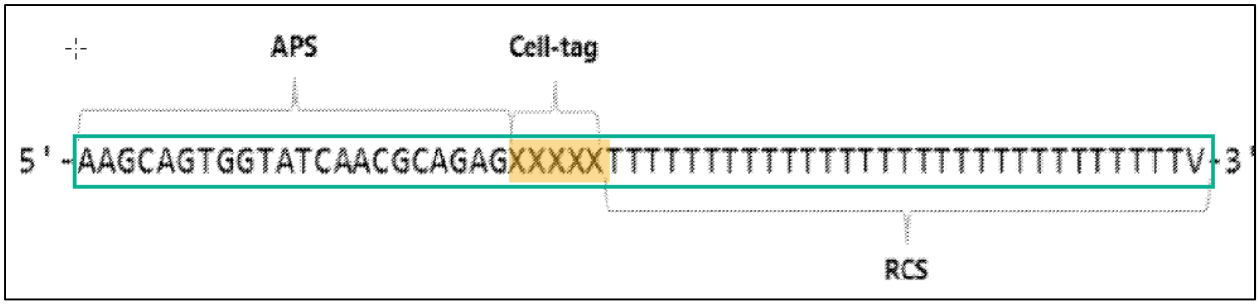


EX1003 at Fig. 2; *see also* EX1015 at Fig. 2. Figure 11 of Linnarsson discloses the same:



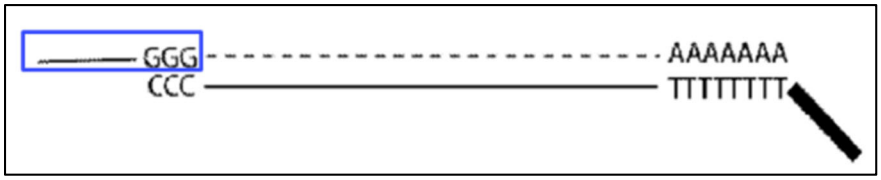
Id. at Fig. 11; *see also* EX1015 at Fig. 2; EX 1003 at 5:29-31 (explaining the disclosure of Figure 11); EX1015 at 5:24-32, 13:8-14 (same); EX1002 ¶ 140.

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

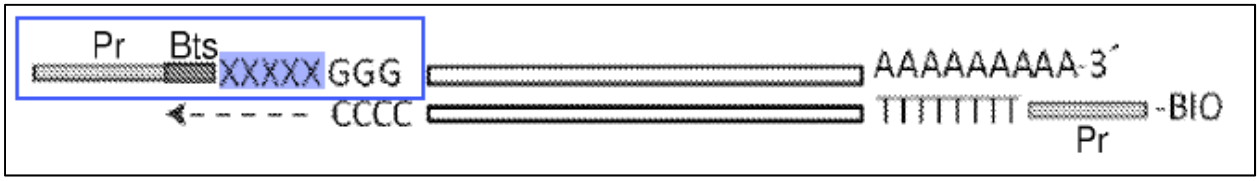


EX1003 at Fig. 4; *see also* EX1015 at Fig. 4.

Second, Linnarsson teaches using tagged TSO during reverse transcription to generate tagged cDNA. As shown in Figure 2 below, a TSO (boxed in blue, below) 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 ¶¶ 142-143.

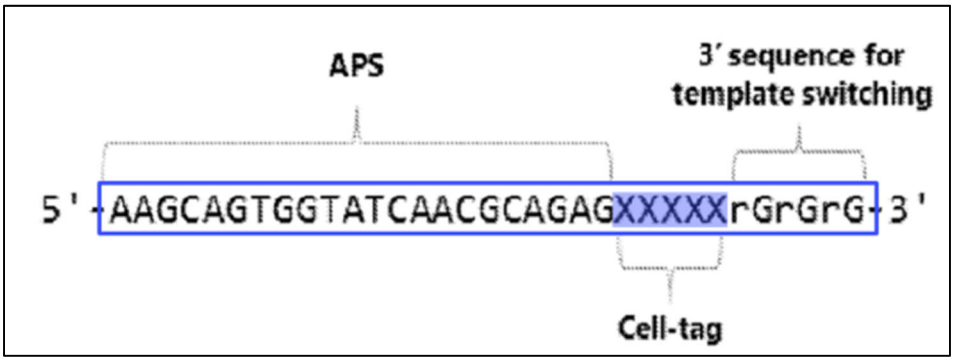


EX1003 at Fig. 2; *see also* EX1015 at Fig. 2. Linnarsson Figure 11 discloses the same:



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 (highlighted in blue, below):



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.

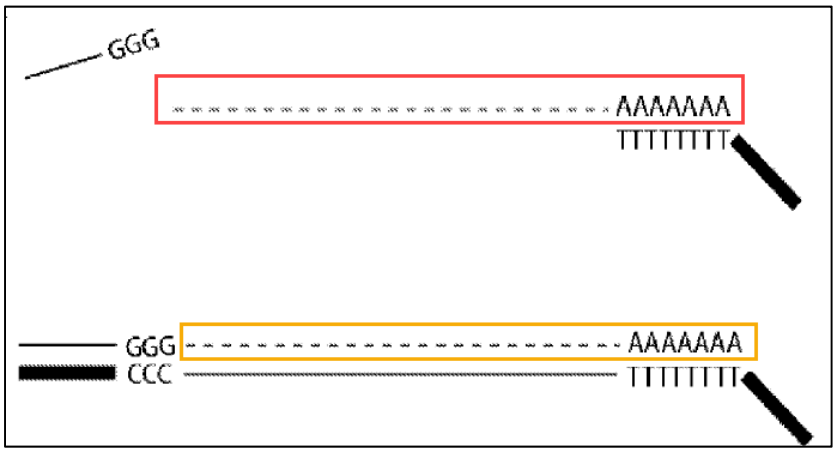
After cDNA synthesis, the plurality of tagged cDNA are then amplified to generate copies of each tagged double-stranded cDNA, and such copies are also the claimed "plurality of tagged polynucleotides." EX1003 at 10:20-22 ("…amplifying the pooled cDNA samples to generate a cDNA library comprising double-stranded cDNA."); 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) as required by this claim limitation.

d. [1D] wherein each tagged polynucleotide comprises: a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and

Linnarsson discloses this claim element. Applicant did not dispute that Linnarsson discloses this limitation during prosecution.

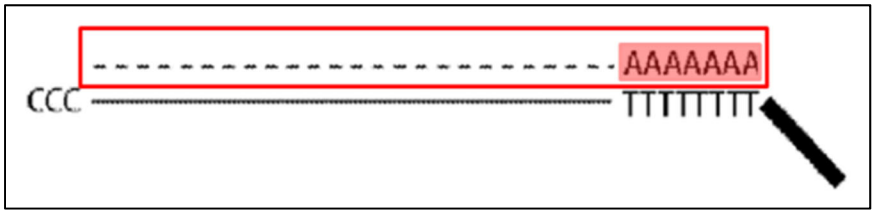
As explained above in Section IX.A.1.c., Linnarsson teaches generating a plurality of tagged polynucleotides (*i.e.*, tagged double-stranded cDNA and/or amplified copies) from the plurality of sample polynucleotides (*i.e.*, sample mRNA). As shown in Figure 2, Linnarsson further discloses that the resulting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



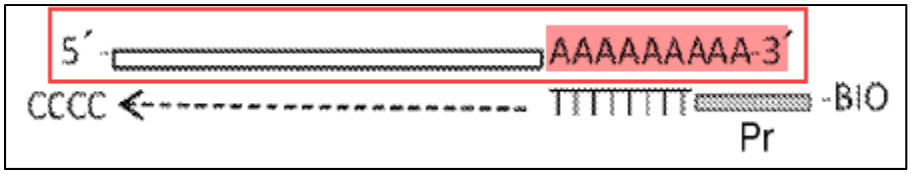
EX 1003 at Fig. 2. Indeed, because the cDNA is synthesized from the sample mRNA using reverse transcription, one strand of each cDNA is necessary identical to the sample mRNA. *See* EX1002 ¶ 152.

A POSA would have further concluded that a cDNA synthesized from a sample mRNA comprises the same sample sequence. EX1002 ¶ 152. 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.* ¶ 152.

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 ¶ 153 (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 ¶ 67. Figure 2 of Linnarsson, reproduced and annotated below, shows an mRNA molecule (boxed in red) with its poly-A tail (highlighted in red):



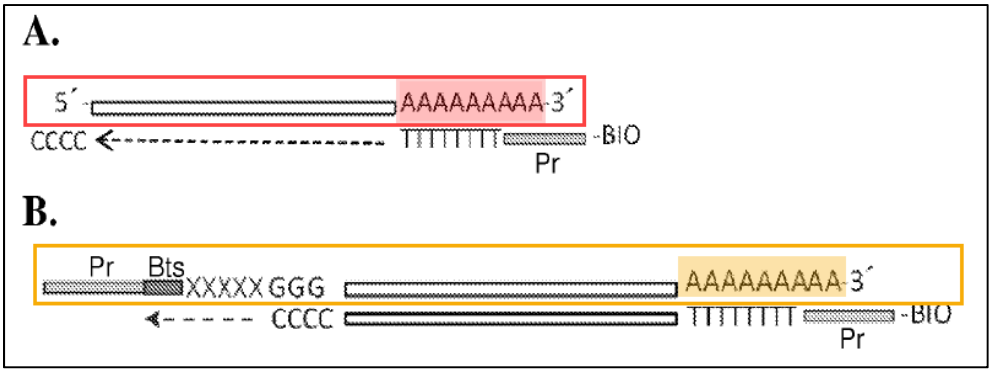
EX1003 at Fig. 2; EX1015 at Fig. 2; EX1003 at 4:14 (describing Fig. 2), 24:13-20 (same); EX1015 at 10:8, 13:8-18. Linnarsson's Figure 11 shows the same:



EX1003 at Fig. 11(A); EX1015 at Fig. 2; *see also* EX1002 ¶ 154.

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, below) shares the same sequence as the original mRNA strand (boxed in red, below), including a poly-A tail (highlighted in orange, below) that is the same as the poly-A tail (highlighted in red, below) 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 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.

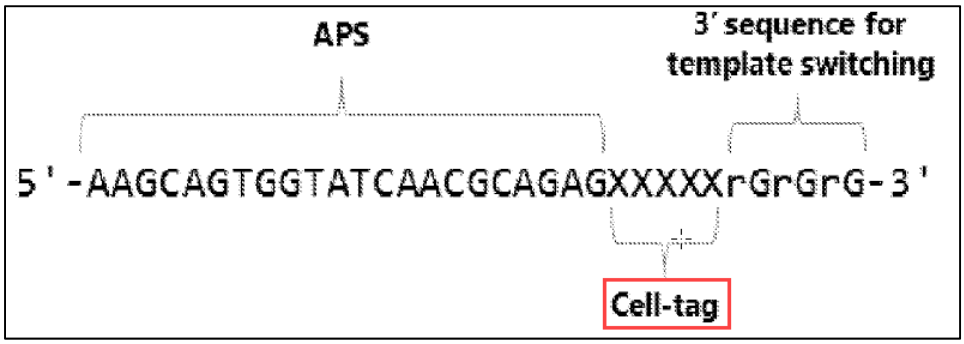
e. [1E] wherein each tagged polynucleotide comprises: … a multiplex identifier (MID) sequence comprising: I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and

Linnarsson discloses this claim element.

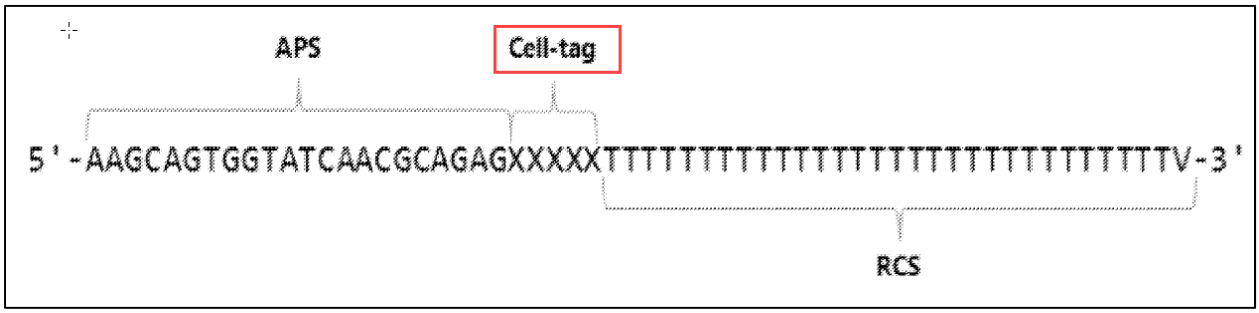
First, Linnarsson discloses that each tagged polynucleotide comprises a multiplex identifier ("MID") sequence. The '981 Patent expressly defines multiplex identifier (MID). EX1001 at 6:33-36; *see also* Section VII, *supra*.

Consistent with this definition, Linnarsson discloses "a tag…associated with a polynucleotide whose identity…can be used to differentiate polynucleotides in a sample." For example, Linnarsson discloses that in "some aspects of the invention,

a tag can be incorporated into the cDNA during its synthesis….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." EX1003 at 18:31-19:5; EX1015 at 7:17-26; *see also* EX1003 at 4:15-18, 10:15-22 ("incorporating a tag into the cDNA to provide a plurality of tagged cDNA samples…."). Figure 3 of Linnarsson depicts a TSO comprising a cell-tag:



EX1003 at Fig. 3. Figure 4 of Linnarsson similarly depicts a CDS comprising a cell tag:



EX1003 at Fig. 4; *see also* EX1015 at 2:27-3:3, 10:10-16, Figs. 3-4.

Second, Linnarsson discloses that the MID sequence (*i.e.* the cell-tag) comprises a first tag sequence associated with the single cell from which the sample

polynucleotide is derived, wherein that first tag sequence is a different sequence for different single cells in the plurality of single cells. 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 the cell-tags present in the CDS and/or the TSO and incorporated into the cDNA 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 multiplex identifier (MID) sequence (*i.e.*, the cell-tag in the CDS and/or TSO sequence) comprising a first tag sequence associated with the single cell from which the sample polynucleotide is derived ("the tag can be used to identify which single cell from each cDNA sample originated"), wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells ("a distinct tag, or a distinct combination of tags").

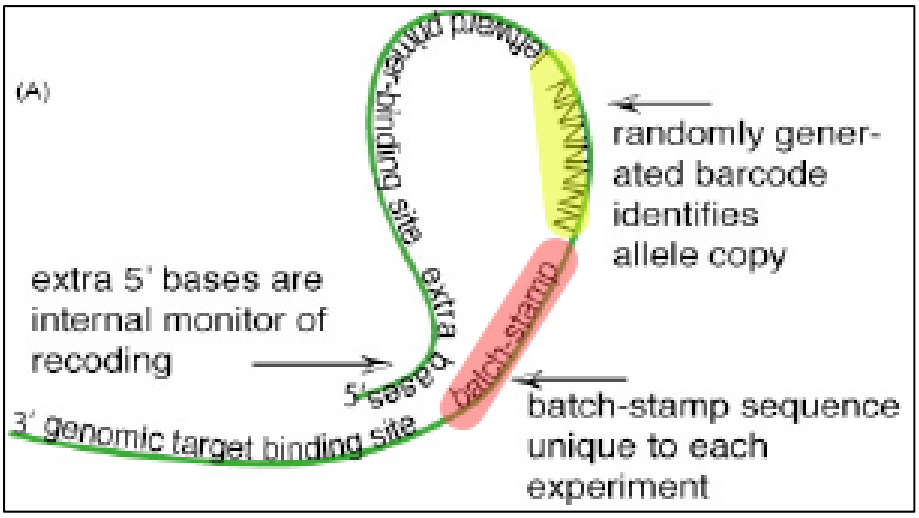
f. [1F] wherein each tagged polynucleotide comprises: … a multiplex identifier (MID) sequence comprising: … II. a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell;

(i) The Combination of Linnarsson and McCloskey Teaches This Limitation

The combination of Linnarsson and McCloskey teaches this claim element.

As explained above, during prosecution, the Patent Owner conceded that this limitation of "a second tag" is the only limitation missing from Linnarsson. EX1005.215-216; *see* Section V.C., *supra*. The examiner agreed. EX1005.238; *see* Section V.C., *supra*. However, McCloskey—which the Examiner did not discuss alone or in combination with Linnarsson—discloses the recited "second tag."

The MID sequence taught by McCloskey is depicted below in Figure 1 as an "encoding oligonucleotide":



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 ¶¶ 65, 184. 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 a MID (*i.e.*, 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), after which PCR amplification is 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.

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 a MID comprising a second tag to distinguish sample polynucleotides derived from the same single cell would have been an obvious design choice. EX1002 ¶¶ 187, 192. Indeed, as Patent Owner itself

acknowledged, "using different labels to differentiate and distinguish between different instances of similar objects is commonplace." EX1016.010. Just like the Fodor Patents that Patent Owner was addressing in the BD case, the '981 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 problem with its methods that McCloskey's teachings resolve. EX1002 ¶¶ 188-191. 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 MID 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 ¶¶ 85-89 (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 the cDNA: “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 ¶ 190.

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 ¶ 191.

Third, a POSA would have had a reasonable expectation of success incorporating McCloskey's teachings into Linnarsson's. Linnarsson discloses annealing oligonucleotides (*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 using 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 tagged oligonucleotides—CDS or TSO—could be modified through routine methods to incorporate a second tag to uniquely identify each sample polynucleotide according to McCloskey's teachings. EX1002 ¶¶ 192-193.

Indeed, as Dr. Cooper explains in the attached declaration, the method would be identical to the approach already set forth in Linnarsson, except that the tags 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 ¶ 192.

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 multiplex identifier (MID) sequence (*i.e.*, Linnarsson's CDS and/or TSO, and McCloskey's encoding oligonucleotide) comprising a second tag sequence (i.e., McCloskey's barcode) distinguishing the sample polynucleotide (i.e., mRNA/cDNA template) from other sample polynucleotides derived from the same single cell.

g. [1G] sequencing the plurality of tagged polynucleotides to obtain a plurality of identified polynucleotide sequences;

Linnarsson discloses this claim element. Applicant did not dispute that Linnarsson discloses this limitation during prosecution. Further, as discussed above in Section IV.D., Patent Owner previously challenged claims directed to detecting and sequencing DNA samples as nothing but "generic, routine, well-known laboratory techniques." EX1016.017.

Linnarsson teaches that after generating the tagged polynucleotides, "sequencing is performed" thereon. *See* EX1003 at 4:8-13, 19:28-32, 21:13-25 ("This cDNA library can be sequenced to provide an analysis of gene expression in single cells or in a plurality of single cells."); EX1015 at 8:22-28, 8:33-9:10, 9:35-10:6.

Thus, Linnarsson discloses this limitation.

h. [1H] using the first tag sequence to correlate the identified polynucleotide sequence with the single cell from which the identified polynucleotide sequence is derived; and

Linnarsson discloses this claim element.

As discussed above in Section IX.A.1.e., Linnarsson explains that the tags present in the CDS and/or the TSO and incorporated into the cDNA 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 comprising a first tag sequence (*i.e.*, the cell-tag) that correlates the identified polynucleotide with the single cell from which it is derived ("the tag can be used to identify which single cell from each cDNA sample originated"), wherein the first tag sequence is a different

sequence for different single cells in the plurality of single cells ("a distinct tag, or a distinct combination of tags").

i. [1I] using the second tag sequence to correlate the identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived.

The combination of Linnarsson and McCloskey discloses this claim element.

As discussed above in Section IX.A.1.f., McCloskey's encoding oligonucleotide comprises two tag sequences: (1) a "batch-stamp" sequence…and (2) a "barcode" to distinguish polynucleotide sequences "arising from different cell or allele copies." *See* EX1004.002-003 ("the random barcode distinguishes among sequences arising from different cell or allele copies …."); *id.* at .003 (describing the barcode tags).

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 using a second tag sequence (*i.e.*, the barcode) to correlate the identified polynucleotide sequence with the sample polynucleotide (*i.e.*, cDNA) from which it derived.

Additionally, it would have been obvious to a POSA to combine Linnarsson's and McCloskey's teachings. *See supra* Section IX.A.1.f.ii.

Thus, the combination of Linnarsson and McCloskey discloses and renders obvious using the second tag sequence (McCloskey's "barcode") to correlate the identified polynucleotide sequence with the sample polynucleotide (*i.e.*, mRNA or cDNA) from which the identified polynucleotide sequence is derived.

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

The combination of Linnarsson and McCloskey discloses and renders obvious the method of claim 1, further comprising the step of amplifying the tagged polynucleotides prior to sequencing. Applicant did not dispute that Linnarsson discloses this limitation during prosecution. Further, as discussed above in Section IV.D., Patent Owner previously challenged claims directed to amplifying tagged polynucleotide samples as nothing but "generic, routine, well-known laboratory techniques." EX1016.017.

According to Linnarsson's teachings, 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 then 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 ("cDNA samples are pooled and amplified"); EX1015 at 10:2-3. 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.

Thus, as is standard, Linnarsson discloses amplifying the tagged polynucleotides prior to sequencing.

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

The combination of Linnarsson and McCloskey discloses and renders obvious the method of claim 1, wherein the sample polynucleotides are selected from DNA and RNA. Applicant did not dispute that Linnarsson discloses this limitation during prosecution. Further, as discussed above in Section IV.D., Patent Owner previously challenged claims directed to tagging polynucleotide samples saying that "the application of that abstract idea to DNA (and other nucleic acid molecules) does not save the claims." EX1016.017.

As described above in Section IX.A.1.b., Linnarsson teaches sample polynucleotides that are mRNA. *See* EX1003 at 3:26-27 ("In one aspect, the method includes the steps of releasing mRNA from each single cell to provide a plurality of individual mRNA samples."); EX1015 at 2:27-31. As explained in Section IX.A.1.f., McCloskey teaches sample polynucleotides that are DNA and cDNA. *See* EX1004.001-002 ("We now report a method by which molecular codes are added to single-stranded DNA or cDNA templates…."), *id*. at .005 ("We

recommend that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs for…single cell…DNA analyses.”).

Thus, because Linnarsson and McCloskey disclose sample polynucleotides that are mRNA and cDNA, respectively, the combination of Linnarsson and McCloskey teach and render obvious sample polynucleotides are 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.”) (citing *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1380 (Fed.Cir.2003)).

4. Claim 4: The method of claim 3, wherein the sample polynucleotides comprise mRNA.

The combination of Linnarsson and McCloskey discloses and renders obvious the method of claim 3, wherein the sample polynucleotides comprise mRNA. As explained in Sections and IX.A.1.b. and IX.A.3., Linnarsson discloses sample polynucleotides that are mRNA. Applicant did not dispute that Linnarsson discloses this limitation during prosecution. Further, as discussed above in Section IV.D., Patent Owner previously challenged claims directed to tagging polynucleotide samples saying that “the application of that abstract idea to DNA (and other nucleic acid molecules) does not save the claims.” EX1016.017.

Thus, combination of Linnarsson and McCloskey discloses sample polynucleotides that comprise mRNA.

5. Claim 6: The method of claim 1, wherein the tagged polynucleotides are generated through PCR or linear amplification of the plurality of sample polynucleotides using an adapter sequence comprising the MID sequence and an amplification primer.

The combination of Linnarsson and McCloskey discloses and renders obvious the method of claim 1, wherein the tagged polynucleotides are generated through PCR or linear amplification of the plurality of sample polynucleotides using an adapter sequence comprising the MID sequence and an amplification primer. Applicant did not dispute that Linnarsson discloses this limitation during prosecution. Further, as discussed above in Section IV.D., Patent Owner previously challenged claims directed to tagging polynucleotide samples arguing that a PCR step to generate tagged polynucleotides was "indisputably routine." EX1017.012.

First, Linnarsson and McCloskey both teach generating the tagged polynucleotides through PCR of the plurality of sample polynucleotides. 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. As explained above, each cDNA copy generated through PCR is a recited “tagged polynucleotide.” *See supra* Section IX.A.1.c.

McCloskey similarly teaches generating tagged polynucleotides through PCR of the plurality of sample polynucleotides. After annealing the encoding oligonucleotide to the sample polynucleotide and performing extension by Sequenase, the “Sequenase-extension products are … amplified using standard PCR protocols.” EX1004.002; *see also id.* at .003 (describing and depicting the same).

Second, McCloskey and Linnarsson both teach generating the plurality of sample polynucleotides using (1) an adapter sequence comprising the MID sequence and (2) an amplification primer molecule. A POSA would understand that the recited “amplification primer” is a separate molecule from the recited “adapter sequence” because the specification defines a “primer” to mean “an oligonucleotide,” which is in turn defined as a “linear polymer of nucleotide monomers.” EX1001 at 9:52, 8:60-62.

As explained above, McCloskey’s encoding oligonucleotide comprises a MID. Section IX.A.1.f., *supra*. McCloskey further teaches that its encoding oligonucleotide is an adapter sequence. Specifically, McCloskey discloses that the encoding nucleotide is an adapter sequence as it comprises a “primer-binding site” and “genomic target-binding site,” which are adaptors that enable the

polynucleotides' extension and amplification via PCR. McCloskey at 762-763 (EX1004.002-003); EX1002 ¶¶ 228-229. The encoding oligonucleotide also comprises two tags—a "barcode" and a "batch-stamp"—and therefore comprises a MID according to the '981 Patent. *See* EX1004.001-004; *see also* EX1001, 6:33-36 (explaining that the term MID "refers to a tag or combination of tags ….").

McCloskey further discloses generating the tagged polynucleotides using an amplification primer molecule. The "primer-binding site" of McCloskey's encoding oligonucleotide "is the target of one of the primers used for PCR amplification." EX1004.004. These "primers used for PCR" are the claimed "amplification primer." *Id.*

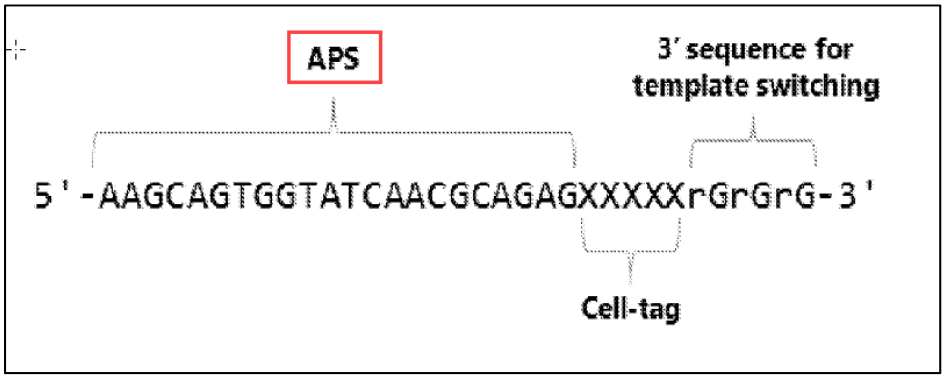
Linnarsson also discloses generating the plurality of tagged polynucleotides using an adapter sequence comprising the MID sequence. As explained above, Linnarsson discloses that its TSO and/or CDS can comprise a MID sequence. Section IX.A.1.e., *supra*. Linnarsson further discloses that the TSO and/or CDS is an adapter sequence. *See* EX1003 at 21:20-22 ("Adapters can be added to the cDNA, e.g. at one or both ends to facilitate sequencing of the library. The cDNA library can be further amplified, e.g. by PCR, to obtain a sufficient quantity of cDNA for sequencing."); EX1015 at 9:3-6.

Moreover, Linnarsson teaches generating the plurality of tagged polynucleotides using an amplification primer molecule. Specifically, Linnarsson

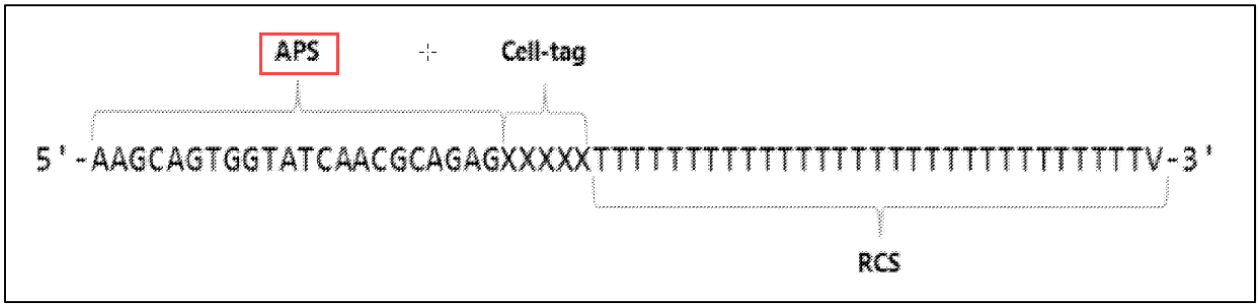
discloses that that each of the CDS and TSO comprises an "amplification primer sequence" ("APS"):

> The CDS can comprise a 5' amplification primer sequence (APS), which subsequently allows the first strand of cDNA to be amplified by PCR using a primer that is complementary to the 5' APS. The TSO can also comprise a 5' APS ….

EX1003 at 19:18-23; EX1015 at 8:9-12. The APS in the TSO is depicted in Linnarsson Figure 3:



EX1003 at Fig. 3. Figure 4 similarly depicts the APS for the CDS:



EX1003 at Fig. 4; *see also* EX1015 at Fig. 3-4.

As discussed above, Linnarsson discloses "a primer that is complementary to the 5' APS," which is the amplification primer sequence present on both the CDS and TSO. EX1003 at 19:18-23; *see also* EX1015 at 8:9-15. This primer, which binds to the APS, is the claimed "amplification primer."

Thus, the combination of McCloskey and Linnarsson teach and render obvious the method of claim 1, wherein the tagged polynucleotides (*i.e.*, cDNA) are generated through PCR or linear amplification of the plurality of sample polynucleotides using an adapter sequence (*i.e.*, Linnarsson's CDS and TSO, and McCloskey's encoding oligonucleotide) comprising the MID sequence and an amplification primer (*i.e.*, Linnarsson's primer which binds to the APS and McCloskey's "primers used for PCR").

B. Ground 2: Claim 5 is Unpatentable Under 35 U.S.C. § 103 Over Linnarsson in View of McCloskey, and Further in View of the Knowledge of a POSA

Claim 5 recites "The method of claim 1, wherein the tagged polynucleotides are generated through at least one ligation reaction." As explained above in Section IX.A.1, the combination of Linnarsson and McCloskey teaches and renders obvious claim 1. Further, as explained above in Section IX.1.f.ii, a POSA would have been motivated to adopt McCloskey's teachings and modify Linnarsson's design so that the tags include both a first portion designating the cell and a second portion distinguishing tagged 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 '981 Patent, it was well-known and routine in the art to attach tag sequences to other sequences by ligation. *See* EX1002 ¶ 238. As the Patent Owner admitted in prior litigation, 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 MID such that the MID is then ligated to the target polynucleotide. EX1007.008; *see also* EX1002 ¶¶ 241-242 (explaining Hug's methods in detail).

A POSA could use 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 ¶ 243 (describing the process in more detail). This approach was commonplace in the art at the time. *See id.* ¶¶ 240-243; *see also* Hug at 621 (EX1007.007); Okayama at 165 (EX1024.005); Shibata at 1250-51, Fig. 1 (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 Linnarrson 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. EX1002 ¶ 243. 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 id.*

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.

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. Although the Applicant identified a patent application ("the '640 Publication") with McCloskey's author being its first named inventor, the '640 Publication and McCloskey are different. EX1005.024. Even assuming that the '640 Publication and McCloskey contain similar disclosures, the '640 Publication was not cited or discussed in any rejection or in any remarks in response to a rejection.

Accordingly, with respect to McCloskey, "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 McCloskey or any similar reference disclosing an oligonucleotide with two tags. *See 3Shape A/S v. Align Tech., Inc.*, IPR2019-00160, Paper No. 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 No. 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").

Indeed, the Examiner only considered an anticipation rejection based on Linnarsson, and did not consider any obviousness rejections. Therefore, the

grounds in this Petition—obviousness based on Linnarsson and McCloskey—involve different tests for validity and different elements of proof and the Board should not exercise its discretion to deny institution. The Board regularly declines to apply § 325(d) in such circumstances. *See, e.g.*, *Caterpillar Inc., v. Wirtgen America, Inc.*, IPR2018-00155, Paper 8 at 11–13 (P.T.A.B. May 23, 2018) (declining to exercise discretion to deny institution under § 325(d) when the Examiner only considered an anticipation rejection and the petition involves a challenge under § 103, noting that the "tests for anticipation and obviousness are different" and that the "elements of proof for anticipation and obviousness are different."); *see also Delphi Tech., Inc. v. Microchip Tech. Inc.*, IPR2017-00861, Paper 14 at 15 (P.T.A.B. Aug. 29, 2017) (declining to exercise § 325(d) discretion when the challenged patent was allowed after overcoming an anticipation rejection, and the asserted ground in the petition is an obviousness ground).

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 '640 Publication.

In the Notice of Allowance, the Examiner did not discuss or cite any passage or disclosure of the '640 Publication. EX1005.238. Instead, the Examiner stated —with respect to the double patenting rejection—that "the instant claims are neither

obvious nor anticipated by the prior art" without expressly identifying any reference. 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 the '640 Publication "was not 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).

Additionally, the Examiner concluded in the Notice of Allowance that the only limitation missing from Linnarsson is the second tag sequence that distinguishes a sample polynucleotide from other sample polynucleotides derived from the same single cell. EX1005.238; *see also id.*, .217-222 (8/6/2018 Response to Final Rejection). As shown above, however, McCloskey discloses this missing limitation. Moreover, it would have been obvious to combine McCloskey's teachings with Linnarsson's in order to, among other things, solve Linnarsson's amplification bias problem. *See supra* Section IX.A.1.f.ii.. Therefore, the Examiner's cursory statement that "the instant claims are neither obvious nor anticipated by the prior art" was erroneous.

Accordingly, the Examiner erred by failing to acknowledge the teachings in McCloskey that disclose the second tag. *Amber.IO, Inc. v. 72LUX, Inc.*, IPR2020-00015, Paper No. 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. 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 approximately 2 months 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. 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 (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 '981 Patent are unpatentable, and therefore this factor weighs in favor of institution. Section IX, *supra*; *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: April 20, 2023

Respectfully submitted,

/Derek C. Walter/

Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656
Weil, Gotshal & Manges LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065

APPENDIX: CHALLENGED CLAIM LISTING

No.	Limitation
1	A method of analyzing nucleic acids from a plurality of single cells, the method comprising: (a) providing a sample comprising a plurality of single cells, wherein each single cell of the plurality of single cells comprises a plurality of sample polynucleotides; (b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides, wherein each tagged polynucleotide comprises: (i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and (ii) a multiplex identifier (MID) sequence comprising: I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and II. a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell; (c) sequencing the plurality of tagged polynucleotides to obtain a plurality of identified polynucleotide sequences; (d) using the first tag sequence to correlate the identified polynucleotide sequence with the single cell from which the identified polynucleotide sequence is derived; and (e) using the second tag sequence to correlate the identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived.
2	The method of claim 1, wherein the method further comprises amplifying the tagged polynucleotides prior to the sequencing step (c).
3	The method of claim 1, wherein the sample polynucleotides are selected from DNA and RNA.
4	The method of claim 3, wherein the sample polynucleotides comprise mRNA.
5	The method of claim 1, wherein the tagged polynucleotides are generated through at least one ligation reaction.

6	The method of claim 1, wherein the tagged polynucleotides are generated through PCR or linear amplification of the plurality of sample polynucleotides using an adapter sequence comprising the MID sequence and an amplification primer.

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 13,884 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: April 20, 2023

By: */Derek C. Walter/*
Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,155,981 WITH PARSE BIOSCIENCES, INC'S EXHIBIT LIST, POWER OF ATTORNEY AND EXHIBITS 1001-1053** are being served on April 20, 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:

Morgan, Lewis & Bockius LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

Patent Owner's Address of Record

Nicholas Groombridge
Jennifer H. Wu
Josephine Young
Jennifer Rea Deneault
PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
1285 Avenue of the Americas
New York, NY 10019

Additional Addresses Known as Likely to Effect Service

Dated: April 20, 2023

By: */Derek C. Walter/*

Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656