

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

10X GENOMICS, INC. and THE BOARD OF	)	
TRUSTEES OF THE LELAND STANFORD	)	
JUNIOR UNIVERSITY	)	
	)	
Plaintiffs,	)	
	)	
v.	)	
	)	C.A. No. 22-1117 (JHS)
PARSE BIOSCIENCES, INC.,	)	
	)	
Defendant.	)	

OPENING REPORT OF JOHN QUACKENBUSH, Ph.D.

May 17, 2024

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From https://www.researchgate.net/figure/Polymerase-Chain-Reaction-A-PCR-reaction-consists-of-three-phases-1-denaturation_fig4_362991666

81. PCR amplification is very commonly used in nucleic acid analysis (including that of DNA and cDNA derived from mRNA) because it increases the quantity of material available to be analyzed.

E. Polynucleotide Tags

82. One way to distinguish the DNA or mRNA in a biological sample is to use polynucleotide tags. Polynucleotide tags are typically synthetic nucleic acid sequences of varying lengths, which can be adjusted for the particular needs of the analysis being performed. As disclosed in the Brenner Patents, tags (also called barcodes or MIDs) can be used to differentiate the source cell and to differentiate the source molecular polynucleotide (sometimes called a “unique molecular identifier” or “UMI”); those two tags also can be combined into a single MID. For example, a polynucleotide tag with the sequence of **AGCGCAACCGG**TTTTAATTG**CGCGCAAACCC**AAAA could be used to track both the cell of origin and the polynucleotide of origin if the sequence “**AGCGCAACCGG**” were used as the cell-specific tag and was identical for every polynucleotide from that cell, and “**GCGCAAACCC**” were used as a UMI and appeared only once and differed for each oligonucleotide tag used to label nucleic acids from the cell of interest.

F. Single Cell DNA and mRNA Analysis

83. Both genomic (or DNA) analysis and transcriptome (or mRNA) analysis have become integral aspects of research, diagnostics, and therapeutic development. Until recently, most methods used nucleic acids derived from “bulk” tissue samples (macroscopic pieces of tissue or millions of cells collected together). While these analyses have given us insight into

the nature of disease, they fail to capture the diversity of the population of cells within that tissue and what that diversity might mean for understanding disease processes. Because the analysis of bulk tissue is not complete and actually results in a loss of information, scientists have developed novel techniques that could allow assessment of the genomes or transcriptomes of individual cells.

84. As an analogy to the information loss, think about identifying all the fruits in a fruit smoothie. While the identification of different types of fruit in the smoothie does capture some information, it loses considerable detail. For example, one will not know how many strawberries or blueberries are in the smoothie.

85. In the same way, being able to do genomic and transcriptome analysis at the single-cell level is especially powerful because it provides better resolution and information about the distribution of measurements. For example, while we know that above-average expression of the *HER2* gene is associated with an aggressive form of cancer, in the early stages of cancer, there may be only a few cancerous cells present in a bulk tissue sample. Further, these cancer cells, identifiable by their expression of abnormal levels of *HER2*, might not be appreciated in an aggregate sample due large number of cells under-expressing *HER2*, or even expressing it at normal levels.

86. For example, in a sample of 100 normal breast cells, each expressing 10 copies of the mRNA encoding *HER2*, the average number of copies of the *HER2* mRNA expressed across that group of cells would be ten. But, if we had an early- stage breast cancer in which a biopsy captured 1 cancer cell expressing 100 copies of *HER2*, and 99 normal cells each expressing only 10 copies, then the average across all 100 cells would be 10.9 copies—just a little above “normal” and likely with the range of normal values and experimental error. By

averaging over the population, one would miss the presence of the cancer cell, and potentially miss diagnosing an aggressive cancer.

87. Analysis of genomic DNA at the single-cell level is also extremely powerful. Because each cell contains two copies of each chromosome, it also contains two copies of each gene—one copy from one’s mother and one copy from one’s father. These paired maternal and paternal chromosomes are homologous chromosomes and the paired genes on each are referred to as maternal and paternal alleles. However, in some diseases including cancer, a maternal or paternal allele might be altered or lost in some but not all cells. Understanding where and how this happens is particularly important in understanding the development and progression of disease.

88. In addition to being able to trace a polynucleotide sequence back to its cell of origin, it is also extremely useful to be able to trace it to its *molecule*, or polynucleotide, of origin. In the context of genomic DNA analysis, being able to trace DNA fragments back to their starting molecule (regardless of whether that molecule was subsequently fragmented or otherwise altered prior to sequencing) makes it possible to track, for example, different DNA fragments as belonging to the same gene, even accounting for experimental errors and biases that are introduced during processing of samples for analysis. Similarly, being able to count each unique mRNA molecule makes it possible to determine expression levels of a particular gene in the cell even allowing for experimental biases to occur during processing of samples. Further, being able to count how many molecules of a specific mRNA in a cell compared to another cell allows one to capture the diversity of the population of cells within that tissue and what that diversity might mean for understanding disease processes.

89. Performing single-cell analysis generally requires: (a) separating the cell’s polynucleotides from the polynucleotides of other cells in the sample; (b) tagging the polynucleotides to distinguish the cellular source of the polynucleotide as well as the molecular source; and (c) amplification, sequencing, and analysis.

90. Single-cell analysis generally requires that the polynucleotides from the cells be separated from each other in some fashion. This separation allows the polynucleotides from each individual cell to be tagged with the same distinct tag, or set of tags, that identifies the cell from which a polynucleotide originated (*e.g.*, a *cell-specific* tag). There are variety ways of achieving separation. One way to do this is to isolate the cells in an array of very small wells called “microwells.” Another way to do this is using a “microfluidic” system that can send sample cells and tags through microscopic channels where each cell is partitioned into its own droplet with its own tags. This is the approach used in the droplet-based methods, including in 10x’s methods.

91. Another way to do this is to keep the polynucleotides within the cell from which they originated such that each polynucleotide in a given cell can be tagged with the same source-identifying tag(s). This can be done by permeabilizing the cell such that tags can be introduced to the polynucleotides within the cell. This is the approach used in the split-pool based method, including in Parse’s methods.

92. Single-cell analysis also requires tagging the polynucleotide with a tag that distinguishes the polynucleotide from other polynucleotide molecules as well as the cellular source of the polynucleotide. This tagging can be accomplished in a variety of ways (*e.g.*, primer extension or ligation) and the tag(s) can be added in one step or multiple steps. All cell-specific tags must be the same so that all polynucleotides from a cell can receive the same cell

tag, thus making it possible to track them to their cell of origin. On the other hand, molecule-specific tags need to all be different so that each molecule to which the tags attach receives a unique tag.

93. For example, when using a droplet-based method, one way to do this is to attach the polynucleotide tags to small “beads,” which can be made of a variety of materials. Each bead can carry millions of polynucleotide tags in some implementations. The beads can be delivered into the droplets in which the cells have been partitioned to ensure, to the extent possible, that each well contains one cell and one bead. In addition to the cell tag, these tags can include a second sequence that functions as the molecular tag. This allows both tags to be added in a single step, and is the approach used in 10x’s methods.

94. When using a split-pool based method, one way to deliver the tags is to add a first set of tags to a first group of cells in one well, and a second set of tags to a second group of cells in a second well (and so on and so forth for the number of wells employed in a particular protocol). After a first round of tagging, the cells in each well are combined and randomly redistributed to a new set of wells for a second round of tagging. Through this process, each cell ideally should be tagged with a unique set of well-specific barcodes. The result is that, to the extent possible, each polynucleotide from a particular cell is tagged with the same set of tags that permit users to identify the cell from which the polynucleotides originated. The molecular tag can be added with a well-specific barcode, which is the approach used in Parse’s methods, or can be added separately.

95. Regardless of the methods employed or the number of steps in which the tag(s) are added, the result is that polynucleotides from each cell are tagged with two functional

sequences, the first identifying the cellular source of the polynucleotide and the second identifying the molecular source.

96. Once the polynucleotides of interest are tagged, and, if analyzing mRNA, the tagged mRNAs have been converted to cDNAs through a reverse transcription reaction, the tagged polynucleotides (either genomic DNA or cDNA) are amplified to create a sufficient number of molecules for them to be sequenced and analyzed.

97. After the tagged polynucleotides are amplified, they are sequenced. The details of sequencing technology are beyond the scope of this report, but the process is now more or less routine and widely available. As discussed above, sequencers, however, remain limited in the length of the individual polynucleotides that can be sequenced in one “run.” The most widely used sequencing instruments today (and in 2009) are generally limited to around 300 nucleotides from one end of a polynucleotide template.

98. Once the tagged polynucleotides have been sequenced, the resulting sequences can be analyzed. Importantly, the sequencing data will include the sequences of the tags that were attached to the polynucleotides. The presence of these tags makes it possible to trace the sequenced polynucleotides to their cell of origin and to the specific molecule within that cell, and to perform quantitative analysis on the resulting sequences.

G. ATAC-seq

99. ATAC-seq is technique for mapping chromatin accessibility genome-wide. The technique was first published in 2013 by the inventors of the Giresi Patents.

10X_PARSE_000701260 (Buenrostro *Nature Methods* 2013). Soon after the publication, ATAC-seq became the industry standard for epigenomic analysis, including single-cell epigenomic analysis.

210. In my opinion, Parse infringes a method of generating tagged polynucleotides with a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides from the single cell satisfying this claim element of claim 1 of the '197 Patent.

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

(a) providing a sample comprising a plurality of cells, wherein a cell of the plurality of cells comprises a plurality of sample polynucleotides;

(b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides of said cell and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises:

(i) a sample sequence from a sample polynucleotide of the plurality of sample polynucleotides;

(ii) a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells; and

(iii) a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell;

(c) sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence; and

(d) using the first tag sequence and the second tag sequence to count a number of sample polynucleotides in said plurality of sample polynucleotides of said cell.

211. Claim 1 of the '197 Patent requires sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence. The '197 Patent states that “the nucleic acid may be sequenced directly using a sequencing primer specific for the primer site. This sequencing reaction will read through the MID and desired site in the insert.” '197 Patent at 19:29-32.

212. In my opinion, Parse’s Evercode Products require sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence. The Evercode Products require “[a]fter sequencing, each single cell transcriptome is

assembled by combining reads containing the same four-barcode combination.” *See, e.g.*, PARSE10X0000412, at 424, 456 (Evercode WT v2 Manual); *see also* PARSE10X0000343, at 355, 387 (Evercode WT Mini v2 Manual); PARSE10X0000481, at 493, 525 (Evercode WT Mega v2 Manual) 493, 525; WT v3 at 5-7, 33-35, 63-65; PARSE10X0000097, at 109, 141 (Evercode TCR Mega, Human TCR + WT Manual); *see also* PARSE10X0000179, at 191, 223 (Evercode TCR Mini, Human TCR + WT Manual); PARSE10X0000261, at 273, 305 (Evercode TCR, Human TCR + WT Manual). Parse’s Evercode Products require the use of sequencing machines. *See, e.g.*, PARSE10X0000012, at 028 ([REDACTED]) (sequencing machine); PARSE10X0000046, at 050 (Evercode Brochure) (sequencing data); PARSE10X0662818, at 826 ([REDACTED]); PARSE10X0061542, at 614 ([REDACTED]); *see also* Parse Biosciences, *Evercode Combinatorial Barcoding* (2024), <https://www.parsebiosciences.com/technology/>.

213. In my opinion, Parse’s Evercode Products require sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence. The Evercode Products require “[a]fter sequencing, each single cell transcriptome is assembled by combining reads containing the same four-barcode combination.” *See, e.g.*, PARSE10X0000412, at 424; *see also* PARSE10X0000343, at 355 (Evercode WT Mini v2 Manual); PARSE10X0000481, at 493 (Evercode WT Mega v2 Manual); WT v3 at 5-7, 33-35, 63-65; PARSE10X0000097, at 109 (Evercode TCR Mega, Human TCR + WT Manual); *see also* PARSE10X0000179, at 191 (Evercode TCR Mini, Human TCR + WT Manual); PARSE10X0000261, at 273. Parse’s Evercode Products require the use of sequencing machines. *See, e.g.*, PARSE10X0000012, at 028 ([REDACTED]) (sequencing machine); PARSE10X0000046, at 050 (Evercode Brochure) (sequencing data);

PARSE10X0662818, at 826 ([REDACTED]); PARSE10X0000097, at 110 (Evercode TCR Mega, Human TCR + WT Manual); *see also* PARSE10X0000179, at 192 (Evercode TCR Mini, Human TCR + WT Manual); PARSE10X0000261, at 274 (Evercode TCR, Human TCR + WT Manual); PARSE10X0061542, at 614 ([REDACTED]); PARSE10X0000012, at 017, 035 ([REDACTED]); 10X_PARSE_000001588 (Parse Support Suite); PARSE10X0000412, at 413 (Evercode WT v2 Manual); *see also* PARSE10X0000343, at 344 (Evercode WT Mini v2 Manual); PARSE10X0000481, at 482 (Evercode WT Mega v2 Manual); PARSE10X0000097, at 098 (Evercode TCR Mega, Human TCR + WT Manual); PARSE10X0000179, at 180 (Evercode TCR Mini, Human TCR + WT Manual); PARSE10X0000261, at 262 (Evercode TCR, Human TCR + WT Manual); 10X_PARSE_000001635, at 657, 644 (’065 patent at 15:32-35; ’065 patent Fig. 13); 10X_PARSE_000001627, at 628 (Rosenberg Article); 10X_PARSE_000796587, at 871 (Xperience Presentation); WT v3 at 5-7, 33-35, 63. *See also* Parse Biosciences, *Evercode Combinatorial Barcoding* (2024), <https://www.parsebiosciences.com/technology/>. Thus, Parse teaches, instructs, promotes, recommends, and/or encourages to sequence the four rounds of barcodes, which include the first and second tag sequences, and enough of the sample sequence to identify the transcript and analyze gene expression.

214. To the extent Parse argues it does not infringe because it sequences fragments of the tagged polynucleotides, this is incorrect. The claims do not require sequencing the entirety of the tagged polynucleotides.

215. In my opinion, Parse infringes the tagged polynucleotides to sequence the tagged polynucleotides satisfying this claim element of claim 1 of the ’197 Patent.

(Evercode WT Mini v2 Manual); PARSE10X0000481, at 542 (Evercode WT Mega v2 Manual); Parse Biosciences, *Evercode Combinatorial Barcoding* (2024), <https://www.parsebiosciences.com/technology>.

298. In my opinion, Parse infringes a method amplifying tagged polynucleotides to generate amplified polynucleotides corresponding to the tagged polynucleotides satisfying this claim element of claim 1 of the '013 Patent.

Claim 1. A method for multiplexed analysis of nucleic acids from single cells, the method comprising:

(a) providing a sample comprising a plurality of cells, wherein a single cell of the plurality of cells comprises a plurality of sample polynucleotides;

(b) performing combinatorial tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:

(A) providing an extension product by primer extension using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and

(B) ligating a second oligonucleotide tag to said extension product, and

wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises:

(i) a sample sequence corresponding to said sample polynucleotide of the plurality of sample polynucleotides;

(ii) a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells; and

(iii) a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell;

(c) amplifying said tagged polynucleotide, thereby generating a plurality of amplified polynucleotides corresponding to the tagged polynucleotide; and

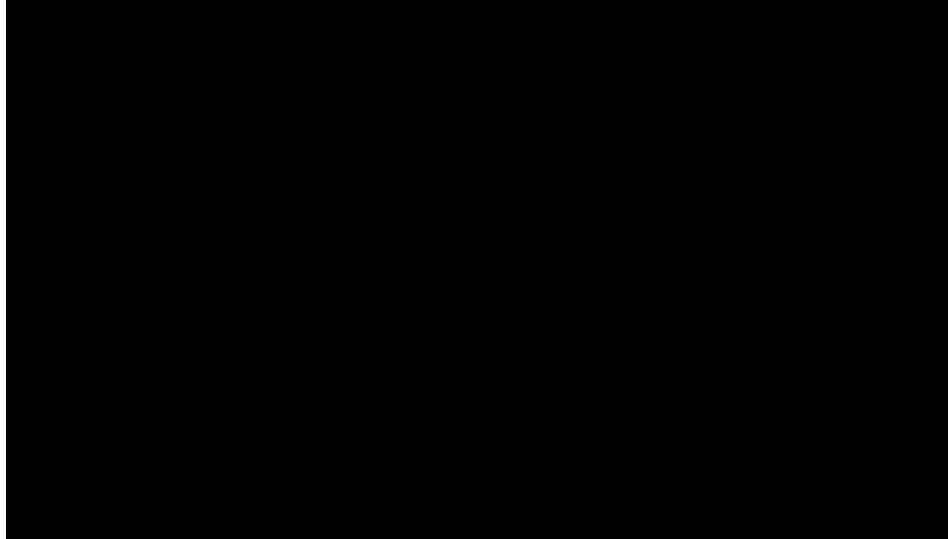
(d) sequencing said plurality of amplified polynucleotides to determine sequences of the amplified polynucleotides corresponding to the sample sequence, the first tag sequence, and the second tag sequence of the tagged polynucleotide; and

(e) using the sequences determined in step (d) to count sample polynucleotides for multiple different sample polynucleotides of multiple different single cells of said plurality of cells.

299. Claim 1 of the '013 Patent requires sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence. The '013 Patent states that “the nucleic acid may be sequenced directly using a sequencing primer specific for the primer site. This sequencing reaction will read through the MID and desired site in the insert.” '013 Patent at 19:38-41.

300. In my opinion, Parse’s Evercode Products require sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence. The Evercode Products require “[a]fter sequencing, each single cell transcriptome is assembled by combining reads containing the same four-barcode combination.” *See, e.g.*, PARSE10X0000412, at 424, 456 (Evercode WT v2 Manual); *see also* PARSE10X0000343, at 355, 387 (Evercode WT Mini v2 Manual); PARSE10X0000481, at 493, 525 (Evercode WT Mega v2 Manual); WT v3 at 5-7, 33-35, 63-65; PARSE10X0000097, at 109, 141 (Evercode TCR Mega, Human TCR + WT Manual); *see also* PARSE10X0000179, at 191, 223 (Evercode TCR Mini, Human TCR + WT Manual); PARSE10X0000261, at 273, 305 (Evercode TCR, Human TCR + WT Manual); PARSE10X0061542, at 614 ([REDACTED]); PARSE10X0662818, at 826 ([REDACTED]). Parse’s Evercode Products require the use of sequencing machines. *See, e.g.*, PARSE10X0000012, at 028 ([REDACTED]) ([REDACTED]) (sequencing machine); PARSE10X0000046, at 050 (Evercode

Brochure) (sequencing data); PARSE10X0662818, at 826 ([REDACTED]);
PARSE10X0000097, at 110 (Evercode TCR Mega, Human TCR + WT Manual); *see also*
PARSE10X0000179, at 192 (Evercode TCR Mini, Human TCR + WT Manual);
PARSE10X0000261, at 274 (Evercode TCR, Human TCR + WT Manual);
PARSE10X0000012, at 017, 035 ([REDACTED]);
10X_PARSE_000001588 (Parse Support Suite); PARSE10X0000412, at 413 (Evercode WT v2
Manual); *see also* PARSE10X0000343, at 344 (Evercode WT Mini v2 Manual);
PARSE10X0000481, at 482 (Evercode WT Mega v2 Manual); PARSE10X0000097, at 098
(Evercode TCR Mega, Human TCR + WT Manual); PARSE10X0000179, at 180 (Evercode
TCR Mini, Human TCR + WT Manual); PARSE10X0000261, at 262 (Evercode TCR, Human
TCR + WT Manual); 10X_PARSE_000001635, at 657, 644 ('065 patent at 15:32-35; '065
patent Fig. 13); 10X_PARSE_000001627, at 628 (Rosenberg Article);
10X_PARSE_000796587, at 871 (Xperience Presentation); WT v3 at 5-7, 33-35, 63. *See also*
Parse Biosciences, *Evercode Combinatorial Barcoding* (2024),
<https://www.parsebiosciences.com/technology/>. Thus, Parse teaches, instructs, promotes,
recommends, and/or encourages that it sequences the four rounds of barcodes, which include the
first and second tag sequences, and enough of the sample sequence to identify the transcript and
analyze gene expression. PARSE10X0662818, at 826 ([REDACTED]).



301. To the extent Parse argues it does not infringe because it sequences fragments of the tagged polynucleotides, this is incorrect. The claims do not require sequencing the entirety of the tagged polynucleotides.

302. In my opinion, Parse infringes a method the tagged polynucleotides to sequence the tagged polynucleotides satisfying this claim element of claim 1 of the '013 Patent.

Claim 1. A method for multiplexed analysis of nucleic acids from single cells, the method comprising:

(a) providing a sample comprising a plurality of cells, wherein a single cell of the plurality of cells comprises a plurality of sample polynucleotides;

(b) performing combinatorial tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:

(A) providing an extension product by primer extension using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and

exists between the Giresi Patents and my opinions regarding long-felt unmet need, failure of others, industry praise, and copying.

XV. Supplementation

595. I reserve the right to consider additional materials and to amend or supplement my opinions in light of additional information that may come to my attention, including any Court rulings and/or new arguments raised by Parse directly or through its experts or any critique of my report or opinions advanced by or on behalf of Parse.

596. If I am called to testify, I may explain principles and terminology referred to in this report as well as documents referenced or cited herein. I reserve the right to utilize visual aids, animations, demonstrative exhibits, trial exhibits, and other such testimonial aids in support of my testimony to illustrate the bases for my opinions.

HIGHLY CONFIDENTIAL – ATTORNEYS’ EYES ONLY

I declare under penalty of perjury that the foregoing is true and correct.

Dated: May 17, 2024.

A handwritten signature in black ink, appearing to read 'J. Quackenbush', is positioned above a horizontal line.

JOHN QUACKENBUSH, Ph.D.