IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BECTON, DICKINSON AND COMPANY and CELLULAR RESEARCH, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 18-1800 (RGA)
10X GENOMICS, INC.,	)	**DEMAND FOR JURY TRIAL**
Defendant.	)	

FIRST AMENDED COMPLAINT

Becton, Dickinson and Company ("BD") and Cellular Research, Inc. ("Cellular Research" and collectively with BD, "Plaintiffs") hereby allege for their First Amended Complaint against Defendant 10X Genomics, Inc. ("10X," or "Defendant"), as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the United States Patent Act, 35 U.S.C. §§1 *et seq.,* including 35 U.S.C. § 271.

2. BD and Cellular Research bring this action to seek relief for 10X's infringement of Plaintiffs' rights arising under the Patent Laws of the United States 35 U.S.C. §1, *et. seq.,* from U.S. Patent Nos. 8,835,358, 9,845,502, 9,315,857, 9,816,137, 9,708,659, 9,290,808, and 9,290,809 (collectively the "Fodor patents"), and from U.S. Patent Nos. 9,567,645, 9,567,646, 9,598,736, and 9,637,799 (collectively the "Fan patents" and collectively with the Fodor patents, "the Asserted Patents").

PARSE EX1051.001

THE PARTIES

3. BD is a corporation organized and existing under the laws of New Jersey, with its principal place of business at 1 Becton Drive, Franklin Lakes, NY 07417. BD is the current owner by assignment of each of the Fodor and Fan patents.

4. Cellular Research is a corporation organized and existing under the laws of Delaware, with its principal place of business at 4040 Campbell Avenue, Suite 110, Menlo Park, CA 94025. Cellular Research was the previous owner by assignment of each of the Fodor and Fan patents.

5. Upon information and belief, 10X is a company organized and existing under the laws of Delaware, with its principal place of business at 7068 Koll Center Parkway, Suite 401, Pleasanton, CA, 94566.

JURISDICTION AND VENUE

6. This action for patent infringement arises under the patent laws of the United States, Title 35 of the United States Code.

7. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. This Court has personal jurisdiction over defendant 10X because, *inter alia*, 10X is incorporated in Delaware, and committed, aided, abetted, induced, contributed to, and/or participated in the commission of tortious acts of patent infringement that have led to foreseeable harm and injury to Plaintiffs in Delaware, 10X has substantial contacts with the forum as a consequence of conducting business in Delaware.

9. Venue is proper in this District under 28 U.S.C. § 1400(b) because 10X is a Delaware corporation.

PARSE EX1051.002

BACKGROUND

10. Cellular Research is a pioneering biotechnology research and development company founded in 2011 by innovators from Silicon Valley and Stanford University. Cellular Research's mission is to revolutionize life science research by enabling high resolution investigation of single cells and limited biological samples. Cellular Research developed advanced tools for massively parallel single cell genetic analysis based on their proprietary Molecular Indexing™ technology to produce gene expression profiles from single cells. Its first two product lines Pixel™ and Precise™ delivered the power of Molecular Indexing™ to customers interested in high accuracy and precision for gene expression studies.

11. BD is a global medical technology company that is advancing the world of health by improving medical discovery, diagnostics and the delivery of care. BD leads in patient and healthcare worker safety and the technologies that enable medical research and clinical laboratories. The company provides innovative solutions, including products that help advance medical research and genomics, and enhance the diagnosis of infectious disease and cancer.

12. In 2015, BD acquired Cellular Research, which set the stage for the next generation of commercial tools in the field of single cell genomic analysis, widely acknowledged by leading academic and industry researchers as the next frontier of biological discovery and clinical advancement.

13. The BD Rhapsody™ Single Cell Analysis System leverages innovations from Cellular Research. The BD Rhapsody™ system enables digital quantitation of hundreds of expressed genes across tens of thousands of single cells, provides customized assays that are flexible enough to meet any experimental need, and comprises an efficient system that reduces experimentation time and sequencing costs.

14. BD's past and future success as a company rests on its ability to continuously bring new innovations to market, including innovations such as the BD Rhapsody™ system for genomic and gene expression analysis, and in protecting those innovations, including the inventions claimed in the Fodor and Fan patents.

15. The Asserted Patents relate to fundamental technologies for single molecule digital counting (Fodor patents) and single-cell multiplex analysis (Fan patents) platforms. The Asserted Patents contribute to BD's reputation as an industry leader in single molecule counting and single cell analysis technologies and help protect BD's significant investment to design and develop innovative solutions for its customers.

16. 10X has infringed and continues to infringe the Asserted Patents by making, using (including during research and development activities and product testing), offering for sale, selling and/or importing at least 10X's single cell solutions and workflows, or inducing or contributing to such acts.

17. 10X's infringement has been and continues to be willful. At least since about May 2017, 10X has had knowledge of the Asserted Patents, has recognized their value, and has also recognized that it needs a license to the Asserted Patents in order to make, use, sell, offer to sell and/or import at least its single cell solutions and workflows. 10X has not obtained such a license. Nevertheless, 10X has continued its infringement with knowledge of the Asserted Patents and recognition of its need for a license.

OVERVIEW OF 10X INFRINGING PRODUCTS

18. As examples, set forth below are preliminary exemplary descriptions detailing 10X's infringing products. These descriptions are not intended to limit Plaintiffs' right to amend, supplement or modify these descriptions or any other analysis, description, or claim chart

PARSE EX1051.004

or allege that other activities of 10X infringe the identified claims or any other claims of these patents or any other patents.

19. Defendant manufactures, uses, sells, offers for sale and/or imports instruments, kits, reagents, software, and parts and training kits combined into, *inter alia*, a "Single Cell Gene Expression Solution" (hereinafter "Single Cell 3' Workflow"), a "Single Cell Immune Profiling Solution" (hereinafter "Single Cell 5' Workflow"), and a "Spatial Transcriptomics" product (hereinafter "Spatial Transcriptomics Workflow"). Defendant manufactures, uses, sells, offers for sale and/or imports the Spatial Transcriptomics Workflow as indicated on its website.[1] The website for the Spatial Transcriptomics products indicates that it is "[p]art of 10x Genomics" identifies its "[c]ontact" as "10x Genomics," and states that it is "pleased to announce that we are now part of 10x Genomics."[2] In addition, upon information and belief, 10X acquired Spatial Transcriptomics AB in or around December 2018, and 10x controls, manages, supervises and directs the companies' efforts relating to the Spatial Transcriptomics Workflow.

20. Defendant's Single Cell 3' Workflow and the Single Cell 5' Workflow are for profiling gene expression of single cells by assessing nucleic acid contents of cells and involve steps of labelling cellular nucleic acids with barcode nucleic acids, to thereby obtain information relating to mRNA expression profiles for individual genes in a cell. Defendant's Spatial Transcriptomics Workflow is for spatial gene expression profiling from biological samples involving steps of labelling cellular nucleic acids with barcode nucleic acids to thereby obtain information relating to spatial mRNA expression profiles for individual genes in a sample. BD reserves the right to assert infringement against other of Defendant's products, including its

[1] *See* https://www.10xgenomics.com.
[2] *See* https://spatialtranscriptomics.com.

PARSE EX1051.005

ATAC and CNV products, to the extent evidence of such infringement is obtained through discovery.

SINGLE CELL 3' WORKFLOW ACCUSED PRODUCTS

21. Defendant's Single Cell 3' Workflow provides a "scalable solution for cell characterization and gene expression profiling of hundreds to millions of cells" that is used to perform "millions of parallel reactions to enable gene expression profiling at scale with single cell resolution."[3]

22. Defendant's Single Cell 3' Workflow is also known as "Single Cell Gene Expression," and "Chromium Single Cell 3'." On information and belief, Defendant's Single Cell 3' Workflow is sold in two "Gene Expression Versions" called "Gene Expression v2" and "Gene Expression v3."

23. As shown in Defendant's own literature, Defendant itself markets, and sells various instruments, reagents, software, and parts and training kits as a single "solution" for the Single Cell 3' Workflow Gene Expression v2 product and describes that "solution" in a single "Product Sheet."[4]

[3] https://www.10xgenomics.com/solutions/single-cell/
[4] ProductSheet_PS016_SingleCell3PrimeGE_ProductSheet.pdf; *see also* **Exhibit 32**.

THE CHROMIUM SINGLE CELL GENE EXPRESSION SOLUTION

PRODUCTS	PRODUCT CODE
Chromium Single Cell 3' Library & Gel Bead Kit v2, 16 rxns	120237
Chromium Single Cell 3' Library & Gel Bead Kit v2, 4 rxns	120267
Chromium Single Cell A Chip Kit, 48 rxns	120236
Chromium Single Cell A Chip Kit, 16 rxns	1000009
Chromium i7 Multiplex Kit, 96 rxns	120262
Chromium Single Cell Controller & Accessory Kit, 12 Mo. Warranty	120263
Chromium Single Cell Controller & Accessory Kit, 24 Mo. Warranty	120212
Chromium Controller & Accessory Kit, 24 Mo. Warranty	120246
Chromium Controller & Accessory Kit, 12 Mo. Warranty	120223
Cell Ranger Analysis Pipelines go.10xgenomics.com/scRNA-3/cell-ranger	DOWNLOAD
Loupe Cell Browser go.10xgenomics.com/scRNA-3/loupe-cell	DOWNLOAD

24. On information and belief, reagents sold by Defendant for the Single Cell 3' Workflow Gene Expression v2 include the "Chromium Single Cell 3' Library & Gel Bead Kit v2, 16 rxns" (Product ID 120237), the "Chromium Single Cell 3' Library & Gel Bead Kit v2, 4 rxns" (Product ID 120267), "Chromium Single Cell 3' Library Kit" (Product ID 120230), and the "Chromium Single Cell 3' Gel Bead Kit" (Product ID 120231).

25. On information and belief, the "Chromium Single Cell 3' Library & Gel Bead Kit v2, 16 rxns" (Product ID 120237) comprises the "Chromium Single Cell 3' Library Kit

v2, 16 rxns" (Product ID 120234) and the "Chromium Single Cell 3' Gel Bead Kit v2, 16 rxns" (Product ID 120235).

26. On information and belief, the "Chromium Single Cell 3' Library Kit v2, 16 rxns" (Product ID 120234) comprises RT Reagent Mix (Product ID 220089), RT Enzyme Mix (Product ID 220079), Additive A (Product ID 220074), RT Primer (Product ID 310354), Buffer Sample Clean Up 1 (Product ID 220020), Amplification Master Mix (Product ID 220125), cDNA Primer Mix 1 (Product ID 220106), cDNA Additive 1 (Product ID 220067), Fragmentation Enzyme Blend (Product ID 220107), Fragmentation Buffer (Product ID 220108), Ligation Buffer (Product ID 220109), DNA Ligase (Product ID 220110), Adaptor Mix (Product ID 220026), and SI-PCR Primer (Product ID 220111).

27. On information and belief, the "Chromium Single Cell 3' Gel Bead Kit v2, 16 rxns" (Product ID 120235) comprises Single Cell 3' Gel Beads (Product ID 220104).

28. On information and belief, the "Chromium Single Cell 3' Library Kit" (Product ID 120230) comprises RT Reagent Mix (Product ID 220071), RT Enzyme Mix (Product ID 220070), RNase Inhibitor (Product ID 220065), Additive A (Product ID 220074), RT Primer (Product ID 310354), Buffer for Sample Clean Up (Product ID 220020), cDNA Primer Mix 1 (Product ID 220066), cDNA Additive 1 (Product ID 220067), Amplification Master Mix (Product ID 220073), End Repair and A-tailing Buffer (Product ID 220046), End Repair and A-tailing Enzyme (Product ID 220047), Ligation Buffer (Product ID 220048), DNA Ligase (Product ID 220049), R1 Adaptor Mix (Product ID 220064), and SI-PCR Primer (Product ID 220068), and Surrogate Fluid (Product ID 220021).

29. On information and belief, the "Chromium Single Cell 3' Gel Bead Kit" (Product ID 120231) comprises Single Cell 3' Gel Bead Strip (Product ID 220063).

30. On information and belief, the "Chromium Single Cell 3' Library & Gel Bead Kit v2, 4 rxns" (Product ID 120267) comprises the "Chromium™ Single Cell 3' Library Kit v2, 4 rxns" (Product ID 120264) and the "Chromium Single Cell 3' Gel Bead Kit v2, 4 rxns" (Product ID 120265).

31. On information and belief, the "Chromium™ Single Cell 3' Library Kit v2, 4 rxns" (Product ID 120264) comprises RT Reagent Mix (Product ID 220089), RT Enzyme Mix (Product ID 220127), Additive A (Product ID 220074), RT Primer (Product ID 310354), Buffer Sample Clean Up 1 (Product ID 220020), Amplification Master Mix 1 (Product ID 220129), cDNA Primer Mix 1 (Product ID 220106), cDNA Additive 1 (Product ID 220067), Fragmentation Enzyme Blend (Product ID 220130), Fragmentation Buffer (Product ID 220108), Ligation Buffer (Product ID 220109), DNA Ligase (Product ID 220131), Adaptor Mix (Product ID 220026), and SI-PCR Primer (Product ID 220111).

32. On information and belief, the "Chromium Single Cell 3' Gel Bead Kit v2, 4 rxns" (Product ID 120265) comprises Single Cell 3' Gel Beads (Product ID 220104).

33. On information and belief, additional reagents sold by Defendant for the Single Cell 3' Workflow Gene Expression v2 include, the "Chromium Single Cell A Chip Kit, 48 rxns" (Product ID 120236), the "Chromium Single Cell A Chip Kit, 16 rxns" (Product ID 1000009), the "Chromium Multiplex Kit, 96 rxns" (Product ID 120262), the "Chromium Single Cell 3' Chip Kit" (Product ID 120232).

34. On information and belief, the "Chromium Single Cell A Chip Kit, 48 rxns" (Product ID 120236) comprises Single Cell A Chip (Product ID 230027), Gaskets (Product ID 370017), Partitioning Oil (Product ID 220088), and Recovery Agent (Product ID 220016).

35. On information and belief, the "Chromium Single Cell A Chip Kit, 16 rxns" (Product ID 1000009) comprises Single Cell A Chip (Product ID 2000019), Gaskets (Product ID 3000072), Partitioning Oil (Product ID 220088), and Recovery Agent (Product ID 220016).

36. On information and belief, the "Chromium Multiplex Kit, 96 rxns" (Product ID 120262) comprises the Chromium™ i7 Sample Index Plate (Product ID 220103).

37. On information and belief, the "Chromium Single Cell 3' Chip Kit" (Product ID 120232) comprises Single Cell 3' Chips (Product ID 230008), Gaskets (Product ID 370017), Partitioning Oil (Product ID 220017), and Recovery Agent (Product ID 220016).

38. On information and belief, parts and training kits sold by Defendant for the Single Cell 3' Workflow Gene Expression v2 include the "Chromium Training Chip Kit" (Product ID 120244), and the "Chromium Training Reagents and Gel Bead Kit" (Product ID 120238).

39. On information and belief, instruments sold by Defendant for the Single Cell 3' Workflow Gene Expression v2 include the "Chromium Controller & Accessory Kit" with 12- or 24-month warranty (Product ID 120223 or 120246) and the "Chromium Single Cell Controller & Accessory Kit" with 12 or 24 month warranty (Product ID 120263 or 120212).

40. On information and belief, the "Chromium Controller Accessory Kit" (Product ID 110204) comprises Power Cord (Product ID 34000X), 10x™ Vortex Adapter (Product ID 330002), 10x™ Chip Holder (Product ID 330019), 10x™ Vortex Clip (Product ID 230002), 10x™ Magnetic Separator (Product ID 230003), and Chromium Test Chip V1 (Product ID 230024).

41. As shown in Defendant's own literature, Defendant itself markets and sells various instruments, reagents, software, and parts and training kits as a single "solution" for the Single Cell 3' Workflow Gene Expression v3 product and describes that "solution" on its website.[5] The "Gene Expression v3" workflow is sold with or without "Feature Barcode Selection." The "Feature Barcode Selection" is sold as either "Cell Surface Protein," "CRISPR Screening," or "Other."[6]

[5] https://www.10xgenomics.com/product-list/
[6] https://www.10xgenomics.com/product-list/ as of November 2018; *see also* **Exhibit 32**

Chromium Single Cell Gene Expression Solution

To view a list of products by application type, first select your desired version of the Single Cell Gene Expression Solution. If you would like to combine this solution with Feature Barcoding technology, select Feature Barcode type(s).

Gene Expression Version

- ● Gene Expression v3
- Gene Expression v2

Feature Barcode Selection

- None
- Cell Surface Protein
- CRISPR Screening
- Other

Reagents & Consumables	Reactions	Product Code
Chromium Chip B Single Cell Kit	48 rxns	1000073
Chromium Chip B Single Cell Kit	16 rxns	1000074
Chromium i7 Multiplex Kit	96 rxns	120262
Chromium Single Cell 3′ Feature Barcode Library Kit	16 rxns	1000079
Chromium Single Cell 3′ Library & Gel Bead Kit v3	4 rxns	1000092
Chromium Single Cell 3′ Library & Gel Bead Kit v3	16 rxns	1000075

Compatible Partner Products	
Biolegend TotalSeq™- B	Learn More

Instruments	Warranty	Product Code
Chromium Controller & Accessory Kit	12 months	120223
Chromium Controller & Accessory Kit	24 months	120246
Chromium Single Cell Controller & Accessory Kit	12 months	120263
Chromium Single Cell Controller & Accessory Kit	24 months	120212

Analysis Software	
Cell Ranger Analysis Pipelines	Download
Loupe Cell Browser	Download

Documentation	
Demonstrated Protocol – Antibody Staining of Cells	Coming soon
User Guide for Gene Expression & CRISPR Screening	Coming soon
User Guide for Gene Expression v3	Coming soon

42. On information and belief, reagents sold by Defendant for the Single Cell 3' Workflow Gene Expression v3 include the "Chromium Single Cell 3' Feature Barcode Library Kit 16 rxns" (Product ID 1000079), the "Chromium Single Cell 3' Library & Gel Bead Kit v3, 4 rxns" (Product ID 1000092), and the "Chromium Single Cell 3' Library & Gel Bead Kit v3, 16 rxns" (Product ID 1000075).

43. On information and belief, the "Chromium Single Cell 3' Feature Barcode Library Kit 16 rxns" (Product ID 1000079) comprises Feature cDNA Primers 1 (Product ID 2000096), Feature cDNA Primers 2 (Product ID 2000097), Feature SI Primers 1 (Product ID 2000098), Feature SI Primers 2 (Product ID 2000099), and Amp Mix 1 (Product ID 2000047).

44. On information and belief, the "Chromium Single Cell 3' Library & Gel Bead Kit v3, 4 rxns" (Product ID 1000092) comprises the "Chromium Single Cell 3' GEM Kit v3, 4 rxns" (Product ID 100094), the "Chromium Single Cell 3' Library Kit v3, 4 rxns" (Product ID 1000095), the "Chromium Single Cell 3' Gel Bead Kit v3, 4 rxns" (Product ID 1000093), and "Dynabeads MyOne SILANE" (Product ID 2000048).

45. On information and belief, the "Chromium Single Cell 3' GEM Kit v3, 4 rxns" (Product ID 100094) comprises RT Reagent (Product ID 2000086), RT Enzyme C (Product ID 2000102), Template Switch Oligo (Product ID 3000228), Reducing Agent B (2000087), Cleanup Buffer (Product ID 2000088), cDNA Primers (Product ID 2000089), and Amp Mix (Product ID 2000103).

46. On information and belief, the "Chromium Single Cell 3' Library Kit v3, 4 rxns" (Product ID 1000095) comprises Fragmentation Enzyme (Product ID 2000104), Fragmentation Buffer (Product ID 2000091), Ligation Buffer (Product ID 2000092), DNA

Ligase (Product ID 220131), Adaptor Oligos (Product ID 2000094), and SI Primer (Product ID 2000095).

47. On information and belief, the "Chromium Single Cell 3' Gel Bead Kit v3, 4 rxns" (Product ID 1000093) comprises Single Cell 3' v3 Gel Beads (Product ID 2000059).

48. On information and belief, the "Chromium Single Cell 3' Library & Gel Bead Kit v3, 16 rxns" (Product ID 1000075) comprises the "Chromium Single Cell 3' GEM Kit v3, 16 rxns" (Product ID 100077), the "Chromium Single Cell 3' Library Kit v3, 16 rxns" (Product ID 1000078), the "Chromium Single Cell 3' Gel Bead Kit v3, 16 rxns" (Product ID 1000076), and "Dynabeads MyOne SILANE" (Product ID 2000048).

49. On information and belief, the "Chromium Single Cell 3' GEM Kit v3, 16 rxns" (Product ID 100077) comprises RT Reagent (Product ID 2000086), RT Enzyme C (Product ID 2000085), Template Switch Oligo (Product ID 3000228), Reducing Agent B (2000087), Cleanup Buffer (Product ID 2000088), cDNA Primers (Product ID 2000089), and Amp Mix (Product ID 2000047).

50. On information and belief, the "Chromium Single Cell 3' Library Kit v3, 16 rxns" (Product ID 1000078) comprises Fragmentation Enzyme (Product ID 2000090), Fragmentation Buffer (Product ID 2000091), Ligation Buffer (Product ID 2000092), DNA Ligase (Product ID 220110), Adaptor Oligos (Product ID 2000094), SI Primer (Product ID 2000095), and Amp Mix (Product ID 200047).

51. On information and belief, the "Chromium Single Cell 3' Gel Bead Kit v3, 16 rxns" (Product ID 1000076) comprises Single Cell 3' v3 Gel Beads (Product ID 2000059).

52. On information and belief, additional reagents sold by Defendant for the Single Cell 3' Workflow Gene Expression v3 include, the "Chromium Chip B Single Cell Kit 48

rxns" (Product ID 1000073), the "Chromium Chip B Single Cell Kit 16 rxns" (Product ID 1000074), and the "Chromium i7 Multiplex Kit 96 rxns" (Product ID 120262).

53. On information and belief, the "Chromium Chip B Single Cell Kit 48 rxns" (Product ID 1000073) comprises Chromium Partitioning Oil (Product ID 220088), Chromium Recovery Agent (Product ID 220016), Chip B Single Cell (Product ID 2000060), and Gasket 6 pack (Product ID 370017).

54. On information and belief, the "Chromium Chip B Single Cell Kit 16 rxns" (Product ID 1000074) comprises Chromium Partitioning Oil (Product ID 220088), Chromium Recovery Agent (Product ID 220016), Chip B Single Cell (Product ID 2000060), and Gasket 2 pack (Product ID 370072).

55. On information and belief, the "Chromium Multiplex Kit, 96 rxns" (Product ID 120262) comprises the Chromium™ i7 Sample Index Plate (Product ID 220103).

56. On information and belief, parts and training kits sold by Defendant for the Single Cell 3' Workflow Gene Expression v3 include the "Chromium Training Chip Kit" (Product ID 120244), and the "Chromium Training Reagents and Gel Bead Kit" (Product ID 120238).

57. On information and belief, instruments sold by Defendant for the Single Cell 3' Workflow Gene Expression v3 include the "Chromium Controller & Accessory Kit" with 12- or 24-month warranty (Product ID 120223 or 120246) and the "Chromium Single Cell Controller & Accessory Kit" with 12 or 24 month warranty (Product ID 120263 or 120212).

58. On information and belief, the "Chromium Controller Accessory Kit" (Product ID 110204) comprises Power Cord (Product ID 34000X), 10x™ Vortex Adapter (Product ID 330002), 10x™ Chip Holder (Product ID 330019), 10x™ Vortex Clip (Product ID

230002), 10x™ Magnetic Separator (Product ID 230003), and Chromium Test Chip V1 (Product ID 230024).

59. The term "**Single Cell 3' Workflow Accused Products**" is used hereinafter to refer to the foregoing instruments, reagents, software, and parts and training kits sold or provided by Defendant for the Single Cell 3' Workflow.

SINGLE CELL 5' WORKFLOW ACCUSED PRODUCTS

60. On information and belief, Defendant's Single Cell 5' Workflow provides an "approach to simultaneously examine the cellular context of the adaptive immune response and the immune repertoires of hundreds to millions of T and B cells on a cell-by-cell basis" that is used to "identify cell-type-specific immune repertoires on a cell-by-cell basis."[7]

61. On information and belief, Defendant's Single Cell 5' Workflow is also known as "Single Cell Immune Profiling," and "Chromium Single Cell V(D)J."

62. As shown in Defendant's own literature, Defendant itself markets, and sells various instruments, reagents, software, and parts and training kits as a single "solution" and describes that "solution" in a single "Product Sheet."[8]

[7] https://www.10xgenomics.com/solutions/vdj/
[8] PS033_SingleCellImmune_FeatureBarcoding_Rev_A_digital.pdf; 20180601_PS017_ImmuneRepertoireProfiling_Rev_D_FINAL.pdf; *see also* **Exhibit 32.**

THE CHROMIUM SINGLE CELL IMMUNE PROFILING SOLUTION

Gene Expression & Immune Repertoire Profiling

REAGENT KITS	PRODUCT CODE
Chromium Single Cell 5' Library & Gel Bead Kit, 16 rxns	1000006
Chromium Single Cell 5' Library & Gel Bead Kit, 4 rxns	1000014
Chromium Single Cell A Chip Kit, 48 rxns	120236
Chromium Single Cell A Chip Kit, 16 rxns	1000009
Chromium i7 Multiplex Kit, 96 rxns	120262
Chromium Single Cell 5' Library Construction Kit, 16 rxns*	1000020
Target Enrichment Kits	*See Enrichment Kits*

* Library & Gel Bead Kit contains reagents to generate one library type (Gene Expression, TCR or Ig) from one Gel Bead reaction. Each additional library type from the same Gel Bead reaction requires additional reactions from the 5' Library Construction Kit

Target Enrichment Kits

SPECIES & TARGET	ENRICHMENT KITS	PRODUCT CODE
Human T cells	Chromium Single Cell V(D)J Enrichment Kit, Human T Cell, 96 rxns	1000005
Human B Cells	Chromium Single Cell V(D)J Enrichment Kit, Human B Cell, 96 rxns	1000016
Mouse T Cells	Chromium Single Cell V(D)J Enrichment Kit, Mouse T Cell, 96 rxns	1000071
Mouse B Cells	Chromium Single Cell V(D)J Enrichment Kit, Mouse B Cell, 96 rxns	1000072

Immune Repertoire Profiling

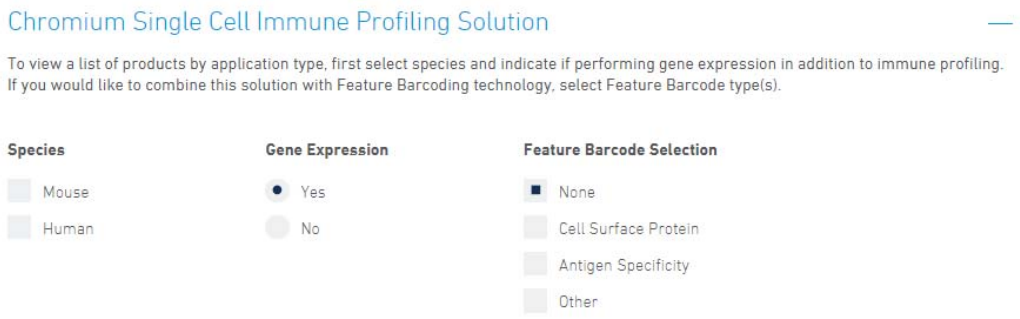
REAGENT KITS	PRODUCT CODE
Chromium Single Cell 5' Library & Gel Bead Kit, 16 rxns	1000006
Chromium Single Cell 5' Library & Gel Bead Kit, 4 rxns	1000014
Chromium Single Cell A Chip Kit, 48 rxns	120236
Chromium Single Cell A Chip Kit, 16 rxns	1000009
Chromium i7 Multiplex Kit, 96 rxns	120262
Target Enrichment Kits	*See Enrichment Kits*

CONTROLLERS & SOFTWARE	PRODUCT CODE
Chromium Single Cell Controller & Accessory Kit, 12 Mo. Warranty	120263
Chromium Single Cell Controller & Accessory Kit, 24 Mo. Warranty	120212
Chromium Controller & Accessory Kit, 24 Mo. Warranty	120246
Chromium Controller & Accessory Kit, 12 Mo. Warranty	120223
Cell Ranger Analysis Pipelines go.10xgenomics.com/vdj/cell-ranger	DOWNLOAD
Loupe V(D)J Browser go.10xgenomics.com/vdj/loupe-vdj	DOWNLOAD
Loupe Cell Browser go.10xgenomics.com/vdj/loupe-cell	DOWNLOAD

PRODUCTS	PRODUCT CODE
Chromium Single Cell 5' Library Construction Kit, 16 rxns	1000020
Chromium Single Cell 5' Library & Gel Bead Kit, 16 rxns	1000006
Chromium Single Cell 5' Library & Gel Bead Kit, 4 rxns	1000014
Chromium Single Cell V(D)J Enrichment Kit, Human T Cell, 96 rxns	1000005
Chromium Single Cell V(D)J Enrichment Kit, Human B Cell, 96 rxns	1000016
Chromium Single Cell V(D)J Enrichment Kit, Mouse T Cell, 96 rxns	1000071
Chromium Single Cell V(D)J Enrichment Kit, Mouse B Cell, 96 rxns	1000072
Chromium i7 Multiplex Kit, 96 rxns	120262
Chromium i7 Multiplex Kit N, Set A, 96 rxns	1000084
Chromium Single Cell A Chip Kit, 16 rxns	1000009
Chromium Single Cell A Chip Kit, 48 rxns	120236
Chromium Single Cell 5' Feature Barcode Library Kit, 16 rxns	1000080
Chromium Single Cell Controller & Accessory Kit, 12 Mo. Warranty	120263
Chromium Single Cell Controller & Accessory Kit, 24 Mo. Warranty	120212
Chromium Controller & Accessory Kit, 12 Mo. Warranty	120223
Chromium Controller & Accessory Kit, 24 Mo. Warranty	120246
Cell Ranger	go.10xgenomics.com/vdj/cell-ranger
Loupe Cell Browser	go.10xgenomics.com/vdj/loupe-cell
Loupe V(D)J Browser	go.10xgenomics.com/vdj/loupe-vdj
Compatible Partner Product: Biolegend TotalSeq™-C	go.10xgenomics.com/totalseq-C
Compatible Partner Product: Immudex dCODE™ Dextramers®	go.10xgenomics.com/dCODE-Dextramers

63. On information and belief, Defendant's Single Cell 5' Workflow is sold as "Chromium Single Cell Immune Profiling Solution," with or without "Gene Expression" and with or without "Feature Barcode Selection." The "Feature Barcode Selection" is sold as either "Cell Surface Protein," "Antigen Specificity," or "Other." The "Chromium Single Cell Immune

Profiling Solution" is also sold with the "Species" optionally designated as "Mouse" or "Human."[9]



64. On information and belief, reagents sold by Defendant for the Single Cell 5' Workflow include the "Chromium Single Cell 5' Library & Gel Bead Kit, 16 rxns" (Product ID 1000006), the "Chromium Single Cell 5' Library & Gel Bead Kit, 4 rxns" (Product ID 1000014).

65. On information and belief, the "Chromium Single Cell 5' Library & Gel Bead Kit, 16 rxns" (Product ID 1000006) comprises the "Chromium™ Single Cell 5' Library Kit, 16 rxns" (Product ID 1000002), the "Chromium™ Single Cell 5' Gel Bead Kit, 16 rxns" (Product ID 1000003), and Dynabeads MyOne SILANE (Product ID 2000048).

66. On information and belief, the "Chromium™ Single Cell 5' Library Kit, 16 rxns" (Product ID 1000002) comprises RT Reagent Mix 1 (Product ID 220089), RT Enzyme Mix B (Product ID 2000010), Additive A (Product ID 220074), Poly-dT RT Primer (Product ID 2000007), Buffer Sample Clean Up 1 (Product ID 220020), Amplification Master Mix (Product ID 220125), cDNA Primer Mix (Product ID 220106), cDNA Additive (Product ID 220067) , Fragmentation Enzyme Blend (Product ID 220107), Fragmentation Buffer (Product ID 220108),

[9] https://www.10xgenomics.com/product-list/ as of February 2019

Ligation Buffer (Product ID 220109), DNA Ligase (Product ID 220110), Adaptor Mix (Product ID 220026), and SI-PCR Primer (Product ID 220111).

67. On information and belief, the "Chromium™ Single Cell 5' Gel Bead Kit, 16 rxns" (Product ID 1000003) comprises Single Cell 5' Gel Beads (Product ID 220112).

68. On information and belief, the "Chromium Single Cell 5' Library & Gel Bead Kit, 4 rxns" (Product ID 1000014) comprises the Chromium™ Single Cell 5' Library Kit, 4 rxns (Product ID 1000011), the Chromium™ Single Cell 5' Gel Bead Kit, 4 rxns (Product ID 1000010), and Dynabeads MyOne SILANE (Product ID 2000048).

69. On information and belief, the "Chromium™ Single Cell 5' Library Kit, 4 rxns" (Product ID 1000011) comprises RT Reagent Mix 1 (Product ID 220089), RT Enzyme Mix B (Product ID 2000021), Additive A (Product ID 220074), Poly-dT RT Primer (Product ID 2000007), Buffer Sample Clean Up 1 (Product ID 220020), Amplification Master Mix (Product ID 220125), cDNA Primer Mix (Product ID 220106), cDNA Additive (Product ID 220067) , Fragmentation Enzyme Blend (Product ID 220130), Fragmentation Buffer (Product ID 220108), Ligation Buffer (Product ID 220109), DNA Ligase (Product ID 220131), Adaptor Mix (Product ID 220026), and SI-PCR Primer (Product ID 220111).

70. On information and belief, the "Chromium™ Single Cell 5' Gel Bead Kit, 4 rxns" (Product ID 1000010) comprises Single Cell 5' Gel Beads (Product ID 220112).

71. On information and belief, additional reagents sold by Defendant for the Single Cell 5' Workflow include, the "Chromium Single Cell 3'/5' Library Construction Kit, 16 rxns" (Product ID 1000020), the "Chromium Single Cell V(D)J Enrichment Kit, Human T Cell, 96 rxns" (Product ID 1000005), the "Chromium Single Cell V(D)J Enrichment Kit, Human B Cell, 96 rxns" (Product ID 1000016), the "Chromium Single Cell A Chip Kit, 48 rxns" (Product

ID 120236), the "Chromium Single Cell A Chip Kit, 16 rxns" (Product ID 1000009), the "Chromium Multiplex Kit, 96 rxns" (Product ID 120262), the "Chromium i7 Multiplex Kit N, Set A, 96 rxns" (Product ID 1000084), the "Chromium Single Cell V(D)J Enrichment Kit, Mouse B Cell, 96 rxns" (Product ID 1000072), the "Chromium Single Cell V(D)J Enrichment Kit, Mouse T Cell, 96 rxns" (Product ID 1000071), and the "Chromium Single Cell 5' Feature Barcode Library Kit, 16 rxns" (Product ID 1000080).

72. On information and belief, the "Chromium Single Cell 3'/5' Library Construction Kit, 16 rxns" (Product ID 1000020) comprises "cDNA Additive" (Product ID 220067), Fragmentation Enzyme Blend (Product ID 220107), "Fragmentation Buffer (Product ID 220108), Ligation Buffer (Product ID 220109), DNA Ligase (Product ID 220110), Amplification Master Mix (Product ID 220125), Adapter Mix (Product ID 220026), and SI-PCR Primer (Product ID 220111).

73. On information and belief, the "Chromium Single Cell V(D)J Enrichment Kit, Human T Cell, 96 rxns" (Product ID 1000005) comprises "Human T Cell Mix 1" (Product ID 2000008), and "Human T Cell Mix 2" (Product ID 2000009).

74. On information and belief, the "Chromium Single Cell V(D)J Enrichment Kit, Human B Cell, 96 rxns" (Product ID 1000016) comprises "Human B Cell Mix 1" (Product ID 2000035), and "Human B Cell Mix 2" (Product ID 2000036).

75. On information and belief, the "Chromium Single Cell A Chip Kit, 48 rxns" (Product ID 120236) comprises Single Cell A Chip (Product ID 230027), Gaskets (Product ID 370017), Partitioning Oil (Product ID 220088), and Recovery Agent (Product ID 220016).

76. On information and belief, the "Chromium Single Cell A Chip Kit, 16 rxns" (Product ID 1000009) comprises Single Cell A Chip (Product ID 2000019), Gaskets

(Product ID 3000072), Partitioning Oil (Product ID 220088), and Recovery Agent (Product ID 220016).

77. On information and belief, the "Chromium Multiplex Kit, 96 rxns" (Product ID 120262) comprises the Chromium™ i7 Sample Index Plate (Product ID 220103).

78. On information and belief, the "Chromium i7 Multiplex Kit N, Set A, 96 rxns" (Product ID 1000084) comprises the Chromium i7 Sample Index Plate N, Set A (Product ID 3000262).

79. On information and belief, the "Chromium Single Cell V(D)J Enrichment Kit, Mouse B Cell, 96 rxns" (Product ID 1000072) comprises "Mouse B Cell Mix 1" (Product ID 2000080), and "Mouse B Cell Mix 2" (Product ID 2000081).

80. On information and belief, the "Chromium Single Cell V(D)J Enrichment Kit, Mouse T Cell, 96 rxns" (Product ID 1000071) comprises "Mouse T Cell Mix 1" (Product ID 2000075), and "Mouse T Cell Mix 2" (Product ID 2000079).

81. On information and belief, the "Chromium Single Cell 5' Feature Barcode Library Kit, 16 rxns" (Product ID 1000080) comprises SC5' Feature cDNA Primers (Product ID 2000119), Amplification Master Mix (Product ID 22015), and SI Primer (Product ID 2000095).

82. On information and belief, parts and training kits sold by Defendant for the Single Cell 5' Workflow include the "Chromium Training Chip Kit" (Product ID 120244), and the Chromium Training Reagents and Gel Bead Kit" (Product ID 120238).

83. On information and belief, instruments sold by Defendant for the Single Cell 5' Workflow include the "Chromium Controller & Accessory Kit" with 12- or 24-month warranty (Product ID 120223 or 120246) and the "Chromium Single Cell Controller & Accessory Kit" with 12 or 24 month warranty (Product ID 120263 or 120212).

84. On information and belief, the "Chromium Controller Accessory Kit" (Product ID 110204) comprises Power Cord (Product ID 34000X), 10x™ Vortex Adapter (Product ID 330002), 10x™ Chip Holder (Product ID 330019), 10x™ Vortex Clip (Product ID 230002), 10x™ Magnetic Separator (Product ID 230003), and Chromium Test Chip V1 (Product ID 230024).

85. On information and belief, Defendant also make available software for use in connection with the Single Cell 3' Workflow and Single Cell 5' Workflow including "Cell Ranger," "Loupe Cell Browser," and "Loupe V(D)J Browser."

86. The term "**Single Cell 5' Workflow Accused Products**" is used hereinafter to refer to the foregoing instruments, reagents, software, and parts and training kits sold or provided by Defendant for the Single Cell 5' Workflow.

SPATIAL TRANSCRIPTOMICS

87. Defendant's Spatial Transcriptomics Workflow "generates spatially barcoded ready-to-load sequencing libraries from fresh frozen tissue sections."[10]

88. As shown on Defendant's website, Defendant itself markets and sells "ST Tissue Optimization Slide" and "ST Library Preparation Slide."[11]

[10] Library Preparation Manual, Version 180611
[11] https://spatialtranscriptomics.com/products/ as of February 2019; *see also* **Exhibit 32**

ST TISSUE OPTIMIZATION SLIDE

The ***ST Tissue Optimization Slide*** gets you started with your new Spatial Transcriptomics Workflow. Adapt your protocol to your tissue of interest.

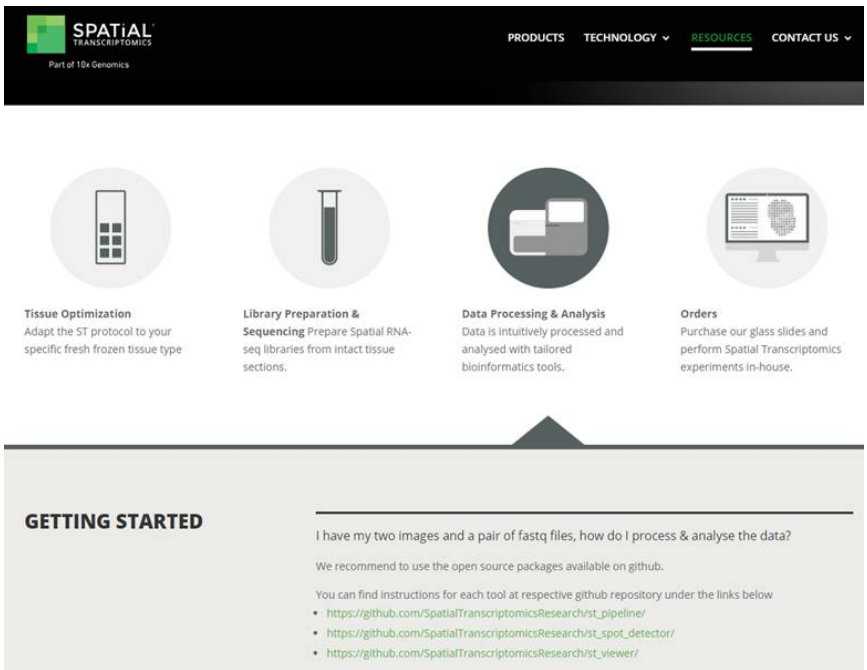
REQUEST A QUOTE EXPLORE

ST LIBRARY PREPARATION SLIDE

With the ***ST Library Preparation Slide*** you capture complete multidimensional RNA-seq images of the intact tissue samples you have selected.

REQUEST A QUOTE EXPLORE

89. On information and belief, Defendant also makes available software for use in connection with the Spatial Transcriptomics Workflow.



90. The term "Spatial Transcriptomics Accused Products" is used hereinafter to refer to the foregoing reagents, software, and parts sold or provided by Defendant for the Spatial Transcriptomics Workflow.

91. The term "Representative Accused Products" or "Accused Products" is used herein to refer to "Single Cell 3' Workflow Accused Products," "Single Cell 5' Workflow Accused Products," and "Spatial Transcriptomics Accused Products." 10X has infringed and continues to infringe directly and/or indirectly, literally or under the doctrine of equivalents, the Asserted Patents by making, using (including during research and development activities and product testing), offering for sale, selling and/or importing at least the Accused Products, or inducing or contributing to such acts.

COUNT 1
(INFRINGEMENT OF THE '358 PATENT)

92. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

93. U.S. Patent No. 8,835,358 (the "'358 patent"), entitled "Digital Counting of Individual Molecules by Stochastic Attachment of Diverse Labels," was duly and legally issued on September 16, 2014 to inventors Stephen P. A. Fodor and Glenn K. Fu. A true and accurate copy of the '358 patent is attached as **Exhibit 1**.

94. Skilled artisans would understand that, prior to the inventions of the '358 patent, numerous problems existed in the prior art relating to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample. Analytical methods for measuring the abundance of different molecules in a sample (*e.g.*, nucleic acids) existed, but were generally comparative techniques and were limited by signal to noise issues. Prior art techniques offered limited utility in cases where samples comprised a large number of different molecules or where the number of

molecules of interest was low in comparison to the number of background molecules. *See, e.g.*, ’358 patent at 2:49-53, 2:64-66; 3:7-16; 3:21-25. Other drawbacks and limitations in prior art methods included, for example:

- A requirement for one-to-one correspondence between probe sequences and oligonucleotide tag sequences in techniques where oligonucleotide tags are hybridized to their complements;
- A requirement for customizing dilutions for each type of molecule in digital methods, which generally limited the practice to analysis of a small number of different molecules and required physical separation of molecules;
- An inability to ensure that all sequences are captured in microarray and sequencing based technologies;
- A limited ability to correlate intensity of hybridization signal (or signal intensity) to the concentration of target molecules in hybridization-based methods;
- Variability relating to probe hybridization differences and cross-reactivity;
- Limitations on the ability to stochastically attach labels to known targets, in a known location, in the context of sequencing and amplification-based methodologies; and
- Dynamic range limitations in array-based methods.

See, e.g., *id.* at 1:64-2:5; 2:35-3:12; 3:21-25; 13:18-22; 17:56-65; 20:42-45; 20:63-21:3; 21:14-18; 21:66-22:3; 22:27-40; 30:46-56; 31:15-33.

95. Skilled artisans would understand that the inventions as recited in the common specifications of the Fodor patents are generally directed to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules. *See, e.g.*, ’358 patent at 3:29-63 (“High-sensitivity single molecule digital counting by the stochastic labeling of a collection of identical molecules is disclosed. Each copy of a molecule randomly chooses from a non-depleting reservoir of diverse labels. . . . The labeled fragments for

a target molecule of choice are detected with high specificity using a microarray readout system, and with DNA sequencing. The results are consistent with a stochastic process, and yield highly precise relative and absolute counting statistics of selected molecules within a vast background of other molecules. . . . The attachment of the label confers a separate, determinable identity to each occurrence of targets that may otherwise be indistinguishable."). The claimed inventions of the '358 patent are directed in general to methods for attaching diverse nucleic acid label tags to nucleic acid molecules in a sample, optionally including amplifying the newly-generated, distinct labeled nucleic acid molecules, and detecting or counting at least a portion of those nucleic acid molecules and attached diverse nucleic acid label tags. In certain aspects of the invention, the attaching can comprise reverse transcription. More specifically, skilled artisans would understand that the asserted independent claims of the '358 patent are directed to specific implementations of the inventions of the Fodor patents, reciting "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," "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," "amplifying at least a portion of the label-tag-target nucleic acid molecules," and "detecting an amplified product" ('358 patent, cl. 6) and "attaching by a species-independent manner to each occurrence of the first target molecule a label from a set of diverse labels . . . , thereby generating for each occurrence of the first target molecule, a new molecule that comprises a copy of the first target molecule and a label, wherein more than 90% of the new molecules have a label that is different from the labels on the other new molecules," "detecting each new molecule by detecting each label present on the new molecule,"

and "counting a number of new molecules" ('358 patent, cl. 1). They would further understand that asserted dependent claims are directed to further specific implementations of the methods recited in the independent claims, including "wherein the attaching is stochastic" ('358 patent, cls. 7, 16).

96. Skilled artisans would further understand that (1) quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, is not an abstract idea but rather a concrete and tangible method for manipulating molecules and generating new molecules that provide an improved method of quantitation; (2) the specific implementations of the inventions of the Fodor patents recited in the claims of the '358 patent are not directed to an abstract idea, nor are the claims directed merely to labeling different molecules or objects with different labels or all implementations thereof; (3) labeling nucleic acids with different labels is not an abstract idea; (4) the claims do not describe concepts long-practiced in society but rather claim novel and innovative methods used for quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, that improved upon prior art methods; and (5) the claims do not merely limit an abstract idea to a specific technological environment, *e.g.*, DNA and nucleic acids.

97. Skilled artisans would further understand that the inventions claimed in the '358 patent provide numerous improvements and benefits over prior art methods. In addition

to addressing the aforementioned drawbacks and limitations of the prior art, the inventions of the '358 patent also:

- Confer a separate, determinable identity to occurrences of targets that may otherwise be indistinguishable as a result of the diverse labels or label-tags in the newly-generated molecule;
- Allow simultaneous quantitation of multiple target sequences;
- Take quantitative measurements of copies of identical target molecules in a solution by transformation of the information into a digital process for detecting the presence of different or diverse labels or label-tags that are attached to the identical target molecules in a manner that is extremely sensitive and can be multiplexed to high levels;
- Allow newly-generated molecules comprising targets and diverse labels or label-tags to be amplified freely without impacting quantitation of the targets; and
- Convert an analog readout of hybridization signal intensities on arrays into a measurable process that can be scored digitally on the arrays by leveraging the diverse label-tags found in each newly-generated molecule, providing a clear cost-advantage over existing techniques.

See, e.g., '358 patent at 3:29-31; 3:41-54; 3:60-63; 3:67-4:4; 13:18-22; 19:38-41; 20:63-21:3; 21:6-9; 21:14-18; 21:22-29; 21:66-22:3; 23:32-35; 29:53-54; 30:35-38; 31:4-14. Skilled artisans would understand that these benefits inure from the claimed inventions and inventive concepts (alone or in combination with the other limitations), including the diverse labels or label-tags being attached to target molecules to generate new molecules comprising targets and diverse labels or label-tags, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, the amplification of those newly-generated molecules, and the other limitations (alone or in combination) of the independent and dependent claims, including as described above and below.

98. Skilled artisans would further understand that quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of

diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, was not well-understood, routine, or conventional at the time of the invention. They would further understand that the steps recited in the claims of the ’358 patent, either alone or in combination and including those recited above and below, were not well-understood, routine, or conventional at the time of the inventions and are integral to addressing the problems in the prior art remedied by the improved functionality of the claimed inventions and inventive concepts. They would further understand that the specific structures and manipulations recited in the claims of the ’358 patent, including distinct target nucleic acid molecules, nucleic acid label-tags with different sequences, label-tag-target nucleic acid molecules generated from attaching nucleic acid labels tags with different sequences to target nucleic acid molecules, target molecules, diverse labels, and new molecules generated by attaching diverse labels or label-tags to target molecules, including wherein more than 90% of the new molecules have a label that is different from the labels on the other new molecules, including through stochastic attachment of diverse labels, species-independent attachment, and/or by multiplexing to allow simultaneous quantitation of multiple molecules, are essential to addressing the problems remedied by the improved functionality of the claimed inventions. *See also supra* ¶ 97.

99. They would further understand that the additional limitations (alone or in combination) of at least dependent claims 2-5, 7-11, 16, 18-24, 26-27, 29-30, 32-37, 42-50, 53-54, 56-61, 66-70, 72-75, 77-83, 88-91, and 94-95 are not directed to an abstract idea and recite inventive concepts for additional reasons, including that the claims recite additional structure; are not routine, conventional, or well-known; improve upon prior art methods by providing increased functionality; and do not risk preemption as a result of the additional limitations in those claims.

100. They would further understand that claim 6 of the ’358 patent is not substantially similar to nor linked to any abstract idea, much less the same abstract idea as all claims of the ’358 patent, including because the other claims of the ’358 patent recite additional, tangible structures and manipulations, provide further improvements and innovations, address additional technological problems, add one or more inventive concepts, and involve different facts relating to issues of preemption and patentability that are not reflected in claim 6 of the ’358 patent. *See also supra* at ¶¶ 97-99.

101. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the ’358 patent, including at least claim 6 of the ’358 patent, directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

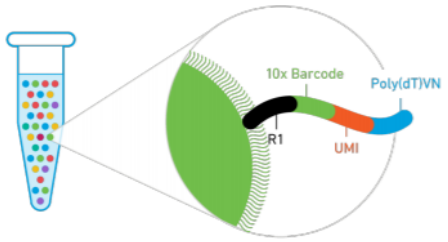
102. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 6 of the ’358 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD’s ability to demonstrate Defendant’s direct, indirect, literal, or equivalent infringement of additional ’358 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

103. In the **Single Cell 3’ Workflow** and **Single Cell 5’ Workflow** Accused Products, “combining a mixture comprising at least two distinct target nucleic acid molecules with a pool of nucleic acid label-tags” as recited in step (a) of claim 6 of the ’358 patent occurs

because "[t]he 10x™ GemCode™ Technology… partition[s] thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs),"[12] and "[o]nce partitioned, the Gel Bead dissolves and its oligo primers are released into the aqueous environment of the GEM."[13] The "combining" recited in step (a) of claim 6 of the '358 patent occurs when "the cell captured in the GEM is […] lysed" (thereby releasing the "at least two distinct target nucleic acid molecules" in the cell) and "[t]he contents of the GEM (oligos, lysed cell components and Master Mix) are incubated in an RT reaction"[14] which is "a mixture comprising at least two distinct target nucleic acid molecules with a pool of nucleic acid label-tags."

104. The oligos of the Gel Beads for the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are shown below[15]:

Each Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1):



i. Partial Illumina Read 1 sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 30 nt Poly(dT) primer sequence

Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

[12] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[13] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[14] *Id.*
[15] *Id.*

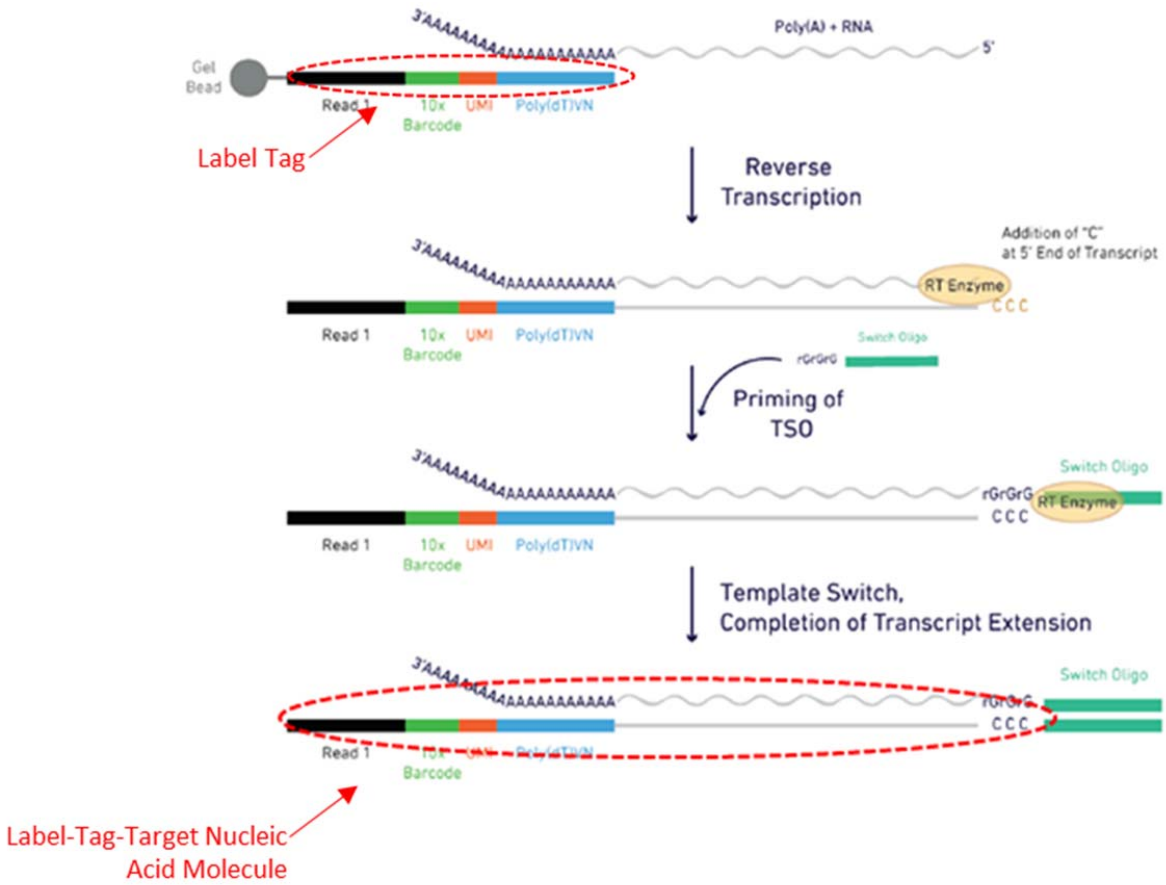
Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

105. In the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products "wherein the pool of nucleic acid label-tags comprises a plurality of nucleic acid label-tags with different sequences" as recited in step (a) of claim 6 exists because each of the GEMs "contain millions of oligo primers that comprise different Unique Molecular Identifiers"[16] that make up "a pool of ~ 750000 barcodes to separately index each cell's transcriptome."[17]

106. In the **Single Cell 3' Workflow** Accused Products, the "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" recited in step (b) of the '358 patent occurs when "[t]he contents of the GEM (oligos, lysed cell components and Master Mix) are incubated in an RT reaction to generate full-length, barcoded cDNA from the poly A-tailed mRNA transcripts" and a "reverse transcription reaction is primed by the barcoded Gel Bead oligo and the reverse transcriptase incorporates the template switch oligo via a template switching reaction at the 5' end of the transcript."[18] As illustrated below[19], this reverse transcription reaction is primed by a poly(dT) sequence on the oligo, thus yielding

[16] *Id.*
[17] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf; "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[18] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[19] *Id.* at Figure 3 (cropped, markings added)

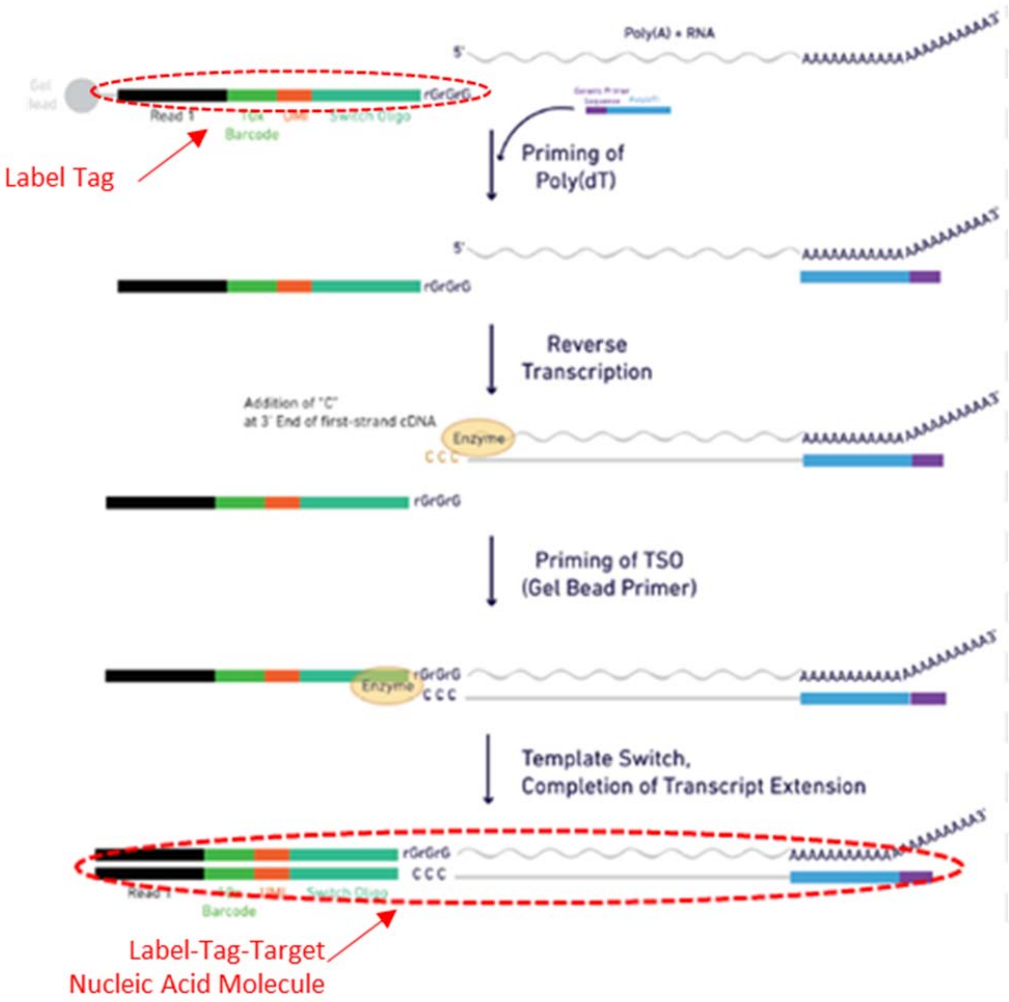
"at least two label-tag-target nucleic acid molecules, wherein the distinct target nucleic acid molecules have different sequences from one another."



107. In the **Single Cell 5' Workflow** Accused Products, the "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" recited in step (b) of the '358 patent occurs when "[t]he contents of the GEM (oligos, lysed cell components and Master Mix that contains the Poly-dT RT primer) are incubated in a reverse

transcription (RT) reaction to generate full-length, barcoded cDNA from the poly-adenylated mRNA" and "[t]he reverse transcriptase incorporates the Gel Bead oligo via a template switching reaction at the 5' end of the transcript."[20] Here, as shown below,[21] the reverse transcription product comprises a polyC tail which is hybridized to the barcoded Gel Bead oligo to thereby result in attachment to "distinct target nucleic acid molecules have different sequences from one another."

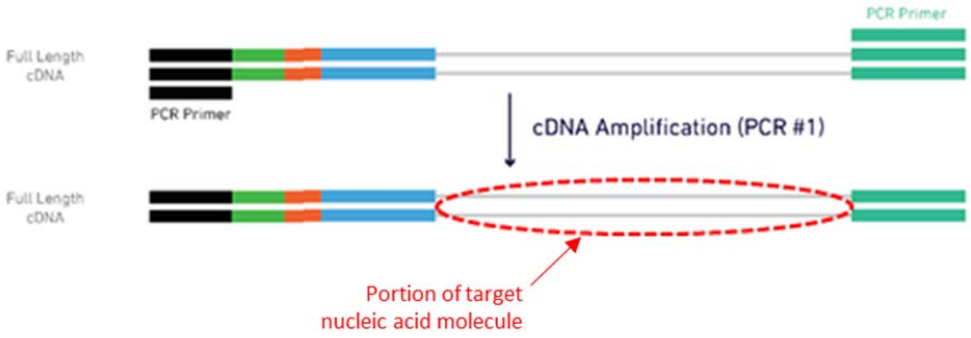
[20] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[21] *Id.* at Figure 3 (cropped, markings added)



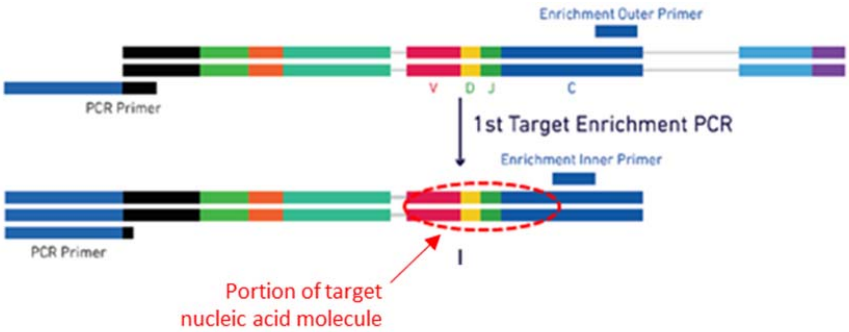
108. In the **Single Cell 3' Workflow** Accused Products, the "amplifying at least a portion of the label-tag-target nucleic acid molecules wherein an amplified portion of the label-tag-target nucleic acid molecules comprises at least a portion of said target nucleic acid molecule" as recited in step (c) of claim 6 of the '358 patent occurs because "[t]he GEMs are then 'broken', pooling single-stranded, barcoded cDNA molecules from every cell" and "[a] bulk PCR-amplification and Enzymatic Fragmentation" follows.[22] As illustrated below[23], this

[22] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[23] *Id.* at Figure 3 (cropped, markings added)

amplification step results in products wherein "an amplified portion of the label-tag-target nucleic acid molecules comprises at least a portion of said target nucleic acid molecule."

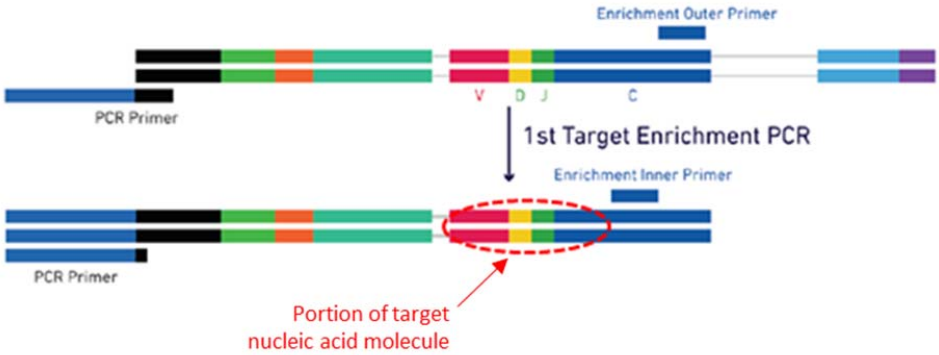


109. In the **Single Cell 5' Workflow** Accused Products, the "amplifying at least a portion of the label-tag-target nucleic acid molecules wherein an amplified portion of the label-tag-target nucleic acid molecules comprises at least a portion of said target nucleic acid molecule" as recited in step (c) of claim 6 of the '358 patent occurs because "[t]he Single Cell V(D)J Solution offers the option to generate" by PCR amplification, "Direct Target Enrichment" or "cDNA Amplification followed by Target Enrichment."[24] As illustrated below[25], the Direct Target Enrichment option results in products wherein "an amplified portion of the label-tag-target nucleic acid molecules comprises at least a portion of said target nucleic acid molecule."



[24] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[25] *Id.* at Figure 3 (cropped, markings added)

110. As illustrated below[26], the cDNA Amplification followed by Target Enrichment option in the **Single Cell 5' Workflow** Accused Products also results in products wherein "an amplified portion of the label-tag-target nucleic acid molecules comprises at least a portion of said target nucleic acid molecule."



111. In the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products, the "detecting an amplified product of step (c)" as recited in step (d) occurs because "[t]he Single Cell 3' Protocol produces Illumina-ready sequencing libraries"[27] and "[t]he Single Cell V(D)J Solutions produce V(D)J enriched and 5' gene expression Illumina-ready sequencing libraries."[28] Once these libraries are "generated and sequenced," "the 10x Barcodes are used to associate individual reads back to the individual partitions."[29]

112. As demonstrated in **Exhibit 12**, the **Single Cell 3' Workflow** Accused Products satisfy the claim limitations of at least claims 6-11, 58-59, 66-70, 75, 77-83, 88-91, and

[26] *Id.* at Figure 4 (cropped, markings added)
[27] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[28] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[29] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

94-95 of the ’358 patent. As demonstrated in **Exhibit 13**, the **Single Cell 5’ Workflow** Accused Products satisfy the claim limitations of at least claims 6-11, 58-59, 66-68, 75, 77-83, 88-91, and 94-95 of the ’358 patent. As demonstrated in **Exhibit 14**, the **Spatial Transcriptomics** Accused Products satisfy the claim limitations of at least claims 1-11, 16, 18-24, 26-27, 29-30, 32-37, 42-50, 53-54, 56-61, 66-70, 72-75, 77-82, 88-91, and 94 of the ’358 patent. The demonstration of infringement illustrated in **Exhibits 12, 13, and 14** is offered by way of example only and without limitation to BD’s ability to demonstrate Defendant’s direct, indirect, literal, or equivalent infringement of additional ’358 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

113. 10X has also induced and currently induces infringement of at least claim 6 of the ‘358 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, 10X knows infringes at least claim 6 of the ‘358 patent.[30] 10X has known of the ’358 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the ’358 patent.

114. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 6 of the ‘358 patent. 10X has designed the Accused Products specifically to be used in a manner as claimed at least claim 6 of the ‘358 patent.[31] As such, the Accused Products are a material component of the patented combination, specifically designed to be used according to at least claim 6 of the ‘358 patent, and especially made and

[30] See, e.g., “Chromium™ Single Cell 3’ Reagent Kits v2 User Guide” (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); “Chromium™ Single Cell V(D)J Reagent Kits User Guide” (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[31] See, e.g., “Chromium™ Single Cell 3’ Reagent Kits v2 User Guide” (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); “Chromium™ Single Cell V(D)J Reagent Kits User Guide” (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

adapted for use in a manner that infringes at least claim 6 of the '358 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 6 of the '358 patent. 10X has knowledge of the '358 patent and is aware that the Accused Products are especially made to be used in a system that infringes the '358 patent.

115. Defendant's infringement has been willful and deliberate because Defendant has known of the '358 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the '358 patent.

116. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages, injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 2
(INFRINGEMENT OF THE '857 PATENT)

117. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

118. U.S. Patent No. 9,315,857 (the "'857 patent"), entitled "Digital Counting of Individual Molecules by Stochastic Attachment of Diverse Labels," was duly and legally issued on April 19, 2016 to inventors Stephen P. A. Fodor and Glenn K. Fu. A true and accurate copy of the '857 patent is attached as **Exhibit 2**.

119. Skilled artisans would understand that, prior to the inventions of the ’857 patent, numerous problems existed in the prior art relating to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample. Analytical methods for measuring the abundance of different molecules in a sample (*e.g.*, nucleic acids) existed, but were generally comparative techniques and were limited by signal to noise issues. Prior art techniques offered limited utility in cases where samples comprised a large number of different molecules or where the number of molecules of interest was low in comparison to the number of background molecules. *See, e.g.*, ’857 patent at 3:13-17; 3:28-30; 3:38-47; 3:53-57. Other drawbacks and limitations in prior art methods included, for example:

- A requirement for one-to-one correspondence between probe sequences and oligonucleotide tag sequences in techniques where oligonucleotide tags are hybridized to their complements;
- A requirement for customizing dilutions for each type of molecule in digital methods, which generally limited the practice to analysis of a small number of different molecules and required physical separation of molecules;
- An inability to ensure that all sequences are captured in microarray and sequencing based technologies;
- A limited ability to correlate intensity of hybridization signal (or signal intensity) to the concentration of target molecules in hybridization-based methods;
- Variability relating to probe hybridization differences and cross-reactivity;
- Limitations on the ability to stochastically attach labels to known targets, in a known location, in the context of sequencing and amplification-based methodologies; and
- Dynamic range limitations in array-based methods.

See, e.g., *id.* at 2:14-22; 2:32-44; 2:66-3:44; 3:53-57; 14:53-57; 19:9-18; 27:21-24; 27:44-52; 27:63-67; 28:47-60; 29:19-24; 38:43-53.

120. Skilled artisans would understand that the inventions as recited in the common specifications of the Fodor patents are generally directed to quantitation of the

abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules. *See, e.g.*, '857 patent at 3:61-4:30 ("High-sensitivity single molecule digital counting by the stochastic labeling of a collection of identical molecules is disclosed. Each copy of a molecule randomly chooses from a non-depleting reservoir of diverse labels. . . . The labeled fragments for a target molecule of choice are detected with high specificity using a microarray readout system, and with DNA sequencing. The results are consistent with a stochastic process, and yield highly precise relative and absolute counting statistics of selected molecules within a vast background of other molecules. . . . The attachment of the label confers a separate, determinable identity to each occurrence of targets that may otherwise be indistinguishable."). The claimed inventions of the '857 patent are directed in general to methods for determining the number of copies of a nucleic acid target by attaching a plurality of diverse label-tags, comprising nucleotides, to a nucleic acid target from a sample, amplifying the plurality of labeled-targets, and detecting by sequencing the plurality of amplified labeled-targets. More specifically, skilled artisans would understand that the asserted independent claim of the '857 patent is directed to a specific implementation of the inventions of the Fodor patents, reciting "attaching a plurality of diverse label-tags to a nucleic acid target from a sample that contains multiple copies of the nucleic acid target, thereby producing a plurality of labeled targets," wherein "a label-tag of the plurality of diverse label-tags comprises nucleotides" and "a labeled target of the plurality of labeled targets comprises a distinct label-tag and at least a portion of a nucleic acid target, or its complementary sequence," "amplifying the plurality of labeled-targets to produce a plurality of amplified labeled-targets, wherein an amplified labeled-target of the plurality of amplified labeled-targets

comprises a copy of at least a portion of the nucleic acid target, or its complementary sequence, and a copy of the label-tag," "detecting the plurality of amplified labeled-targets by sequencing at least a portion of the target and the label-tag," and "determining the number of copies of the nucleic acid target" ('857 patent, cl. 1). They would further understand that asserted dependent claims are directed to further specific implementations of the methods recited in the independent claims, including "wherein the attaching step occurs in a stochastic manner" ('857 patent, cl. 17).

121. Skilled artisans would further understand that (1) quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, is not an abstract idea but rather a concrete and tangible method for manipulating molecules and generating new molecules that provide an improved method of quantitation; (2) the specific implementations of the inventions of the Fodor patents recited in the claims of the '857 patent are not directed to an abstract idea, nor are the claims directed merely to labeling different molecules or objects with different labels or all implementations thereof; (3) labeling nucleic acids with different labels is not an abstract idea; (4) the claims do not describe concepts long-practiced in society but rather claim novel and innovative methods used for quantitation of the abundance of genetic material in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, that improved upon prior art methods; and (5) the claims do not merely limit an abstract idea to a specific technological environment, *e.g.*, DNA and nucleic acids.

122. Skilled artisans would further understand that the inventions claimed in the ’857 patent provide numerous improvements and benefits over prior art methods. In addition to addressing the aforementioned drawbacks and limitations of the prior art, the inventions of the ’857 patent also:

- Confer a separate, determinable identity to occurrences of targets that may otherwise be indistinguishable as a result of the diverse labels or label-tags in the newly-generated molecule;
- Allow simultaneous quantitation of multiple target sequences;
- Take quantitative measurements of copies of identical target molecules in a solution by transformation of the information into a digital process for detecting the presence of different or diverse labels or label-tags that are attached to the identical target molecules in a manner that is extremely sensitive and can be multiplexed to high levels;
- Allow newly-generated molecules comprising targets and diverse labels or label-tags to be amplified freely without impacting quantitation of the targets; and
- Convert an analog readout of hybridization signal intensities on arrays into a measurable process that can be scored digitally on the arrays by leveraging the diverse label-tags found in each newly-generated molecule, providing a clear cost-advantage over existing techniques.

See, e.g., ’857 patent at 3:61-63; 4:6-20; 4:28-30; 4:35-38; 14:53-57; 19:46-47; 27:44-52; 27:53-57; 27:63-67; 28:3-10; 29:19-24; 29:42-48; 37:33-34; 38:23-26; 39:1-11. Skilled artisans would understand that these benefits inure from the claimed inventions and inventive concepts (alone or in combination with the other limitations), including the diverse label-tags being attached to nucleic acid targets from a sample that contains multiple copies of the nucleic acid target to generate a plurality of new labeled targets comprising distinct label-tags and at least a portion of a nucleic acid targets, including through stochastic attachment of diverse label-tags and/or by multiplexing to allow simultaneous quantitation of multiple nucleic acid targets, the amplification of those newly-generated molecules, and the other limitations (alone or in combination) of the independent and dependent claims, including as described above and below.

123. Skilled artisans would further understand that quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, was not well-understood, routine, or conventional at the time of the invention. They would further understand that the steps recited in the claims of the '857 patent, either alone or in combination and including those recited above and below, were not well-understood, routine, or conventional at the time of the inventions and are integral to addressing the problems in the prior art remedied by the improved functionality of the claimed inventions and inventive concepts. They would further understand that the specific structures and manipulations recited in the claims of the '857 patent, including a plurality of diverse label-tags, wherein the label-tags comprise nucleotides, a nucleic acid target from a sample that contains multiple copies of the nucleic acid target, a newly-generated labeled target that comprises a distinct label-tag and at least a portion of a nucleic acid target or its complementary sequence, generated by attaching a diverse label to a target molecule, including through stochastic attachment of distinct label-tags and/or by multiplexing to allow simultaneous quantitation of multiple nucleic acid targets, amplified labeled-targets comprising a copy of at least a portion of the nucleic acid target, or its complementary sequence, and a copy of the label-tag, are essential to addressing the problems remedied by the improved functionality of the claimed inventions. *See also supra* ¶ 122.

124. They would further understand that the additional limitations (alone or in combination) of at least dependent claims 2-6, 10, 12, 15, and 17-21 are not directed to an abstract idea and recite inventive concepts for additional reasons, including that they recite additional structure; are not routine, conventional, or well-known; improve upon prior art

methods by providing increased functionality; and do not risk preemption as a result of the additional limitations in those claims.

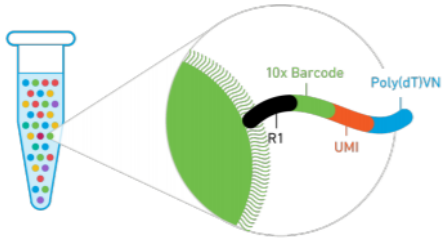
125. They would further understand that claim 6 of the ’358 patent is not substantially similar to nor linked to any abstract idea, much less the same abstract idea as all claims of the ’857 patent, including because the claims of the ’857 patent recite additional, tangible structures and manipulations, provide further improvements and innovations, address additional technological problems, add one or more inventive concepts, and involve different facts relating to issues of preemption and patentability that are not reflected in claim 6 of the ’358 patent. *See also supra* at ¶¶ 122-124.

126. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the ’857 patent, including at least claim 1 of the ’857 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

127. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the ’857 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD’s ability to demonstrate Defendant’s direct, indirect, literal, or equivalent infringement of additional ’857 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

128. In the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products, the "attaching a plurality of diverse label-tags to a nucleic acid target from a sample that contains multiple copies of the nucleic acid target" as recited in step (a) of claim 1 occurs because the label tags employed in the attaching step are from GEMs that "contain millions of oligo primers"[32] that comprise different "Unique Molecular Identifiers" that make up "a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[33] and because "[t]he cell captured in the GEM is also lysed."[34] The poly A-tailed mRNA transcripts[35] of a cell are the "multiple copies of the nucleic acid target." The oligos of the Gel Beads for the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are shown below[36]:

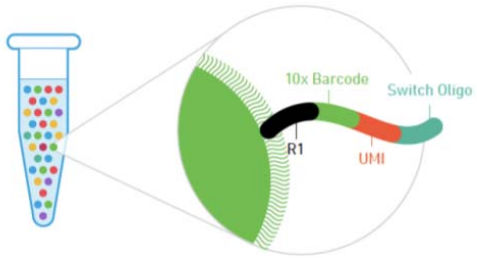
Each Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1):



i. Partial Illumina Read 1 sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 30 nt Poly(dT) primer sequence

Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

[32] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[33] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[34] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[35] *Id.*
[36] *Id.*

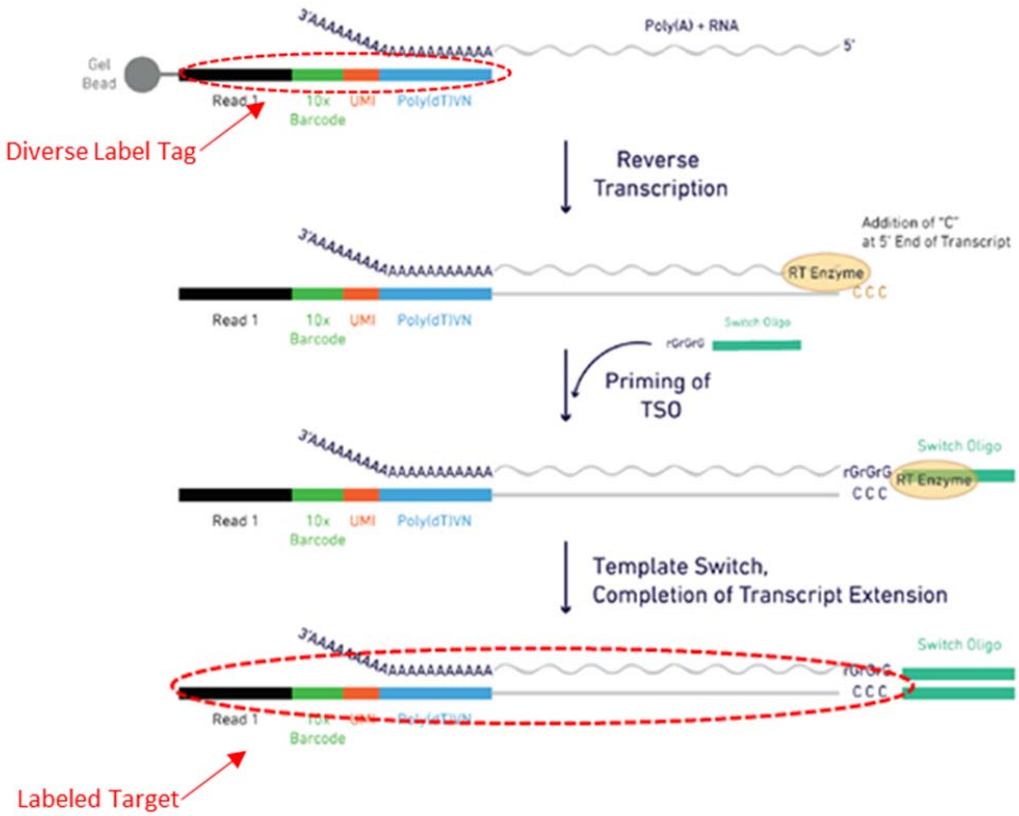


i. Partial Illumina Read 1 Sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 13 nt Switch Oligo

Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

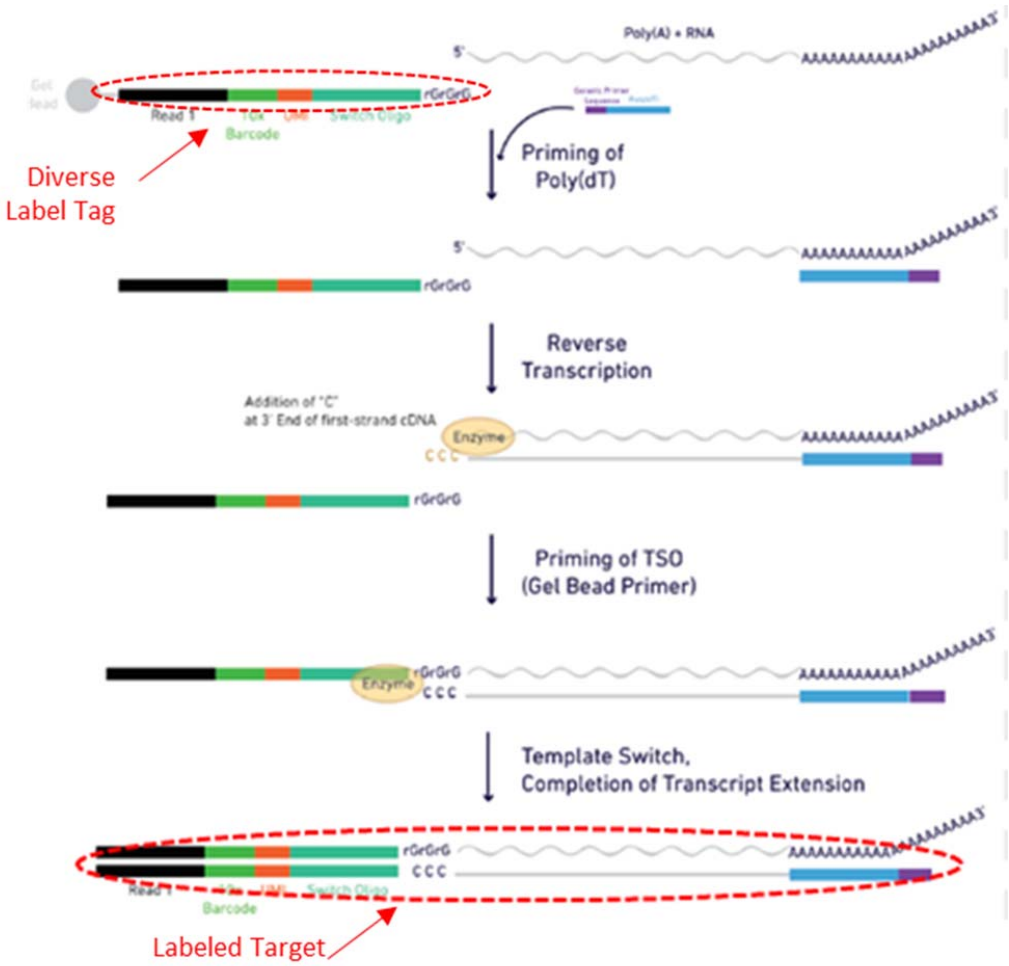
129. In the **Single Cell 3' Workflow** Accused Products, the "thereby producing a plurality of labeled targets" recited in step (a) occurs when a "[t]he contents of the GEM (oligos, lysed cell components and Master Mix) are incubated in an RT reaction to generate full-length, barcoded cDNA from the poly A-tailed mRNA transcripts."[37] As illustrated below[38], this step produces "a plurality of labelled targets."

[37] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[38] *Id.* at Figure 3 (cropped, markings added)



130. In the **Single Cell 5' Workflow** Accused Products, the "thereby producing a plurality of labeled targets" recited in step (a) occurs when "[t]he contents of the GEM […] are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA from poly-adenylated mRNA."[39] As illustrated below[40], this step produces "a plurality of labelled targets."

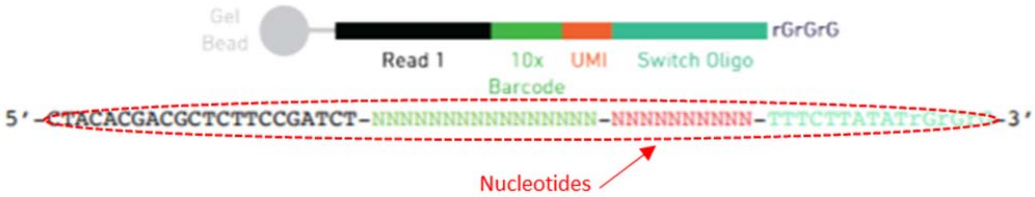
[39] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[40] *Id.* at Figure 3 (cropped, markings added)



131. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products comprise "a label-tag of the plurality of diverse label-tags comprises nucleotides selected from purine bases, pyrimidine bases, natural nucleotide bases, chemically modified nucleotide bases, biochemically modified nucleotide bases, non-natural nucleotide bases" as recited in substep (i) of step (a). As shown below[41], label tags of the **Single Cell 3' Workflow** Accused Products comprise A, C, G, and T purine bases and pyrimidine bases.

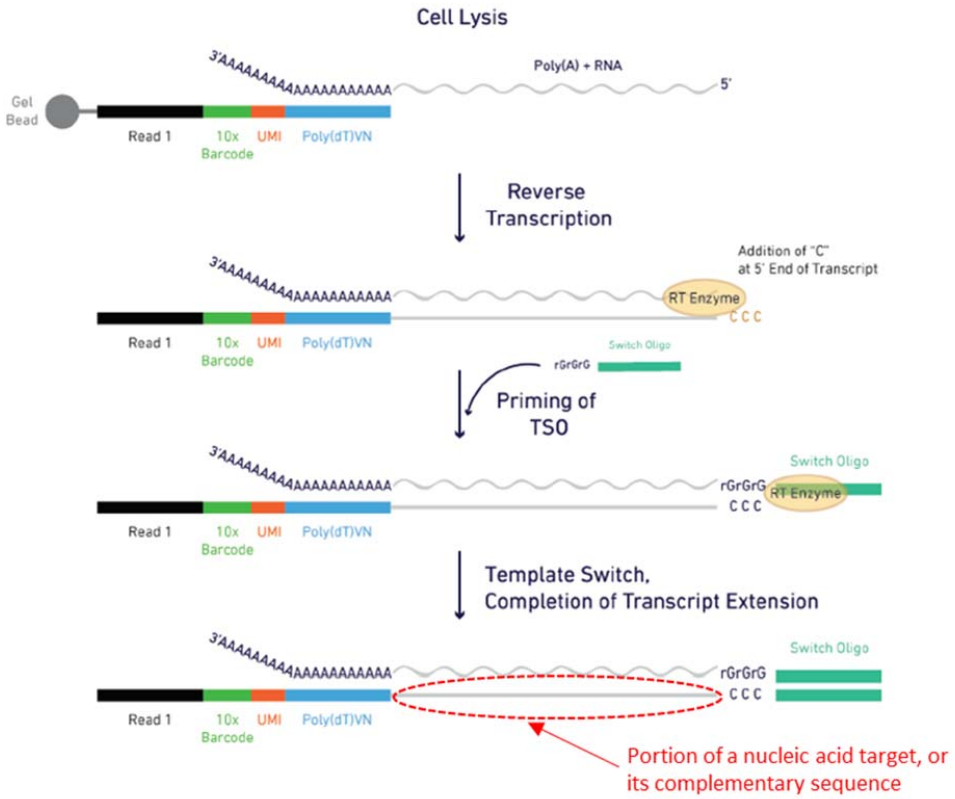
[41] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 4 (cropped)

132. As shown below[42], label tags of the **Single Cell 5' Workflow** Accused Products comprise A, C, G, and T purine bases and pyrimidine bases.



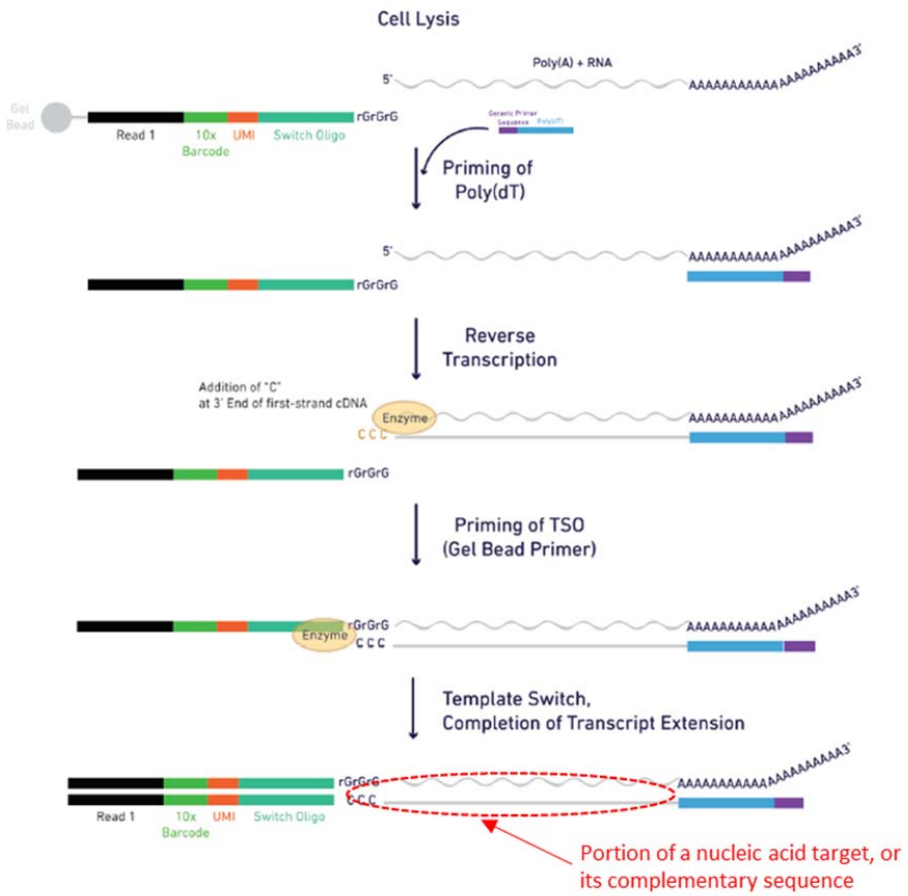
133. As illustrated below[43], in the **Single Cell 3' Workflow** Accused Products, the reverse transcription reaction produces "a labeled target of the plurality of labeled targets" comprising "a distinct label-tag and at least a portion of a nucleic acid target, or its complementary sequence" as recited in substep (ii) of step (a) when "[t]he contents of the GEM (oligos, lysed cell components and Master Mix) are incubated in an RT reaction to generate full-length, barcoded cDNA from the poly A-tailed mRNA transcripts."[44]

[42] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Table 1 (cropped)
[43] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 3 (cropped, markings added)
[44] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)



134. As illustrated below[45], in the **Single Cell 5' Workflow** Accused Products, the reverse transcription reaction produces "a labeled target of the plurality of labeled targets" comprising "a distinct label-tag and at least a portion of a nucleic acid target, or its complementary sequence" as recited in substep (ii) of step (a) when "[t]he contents of the GEM […] are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA from poly-adenylated mRNA."[46]

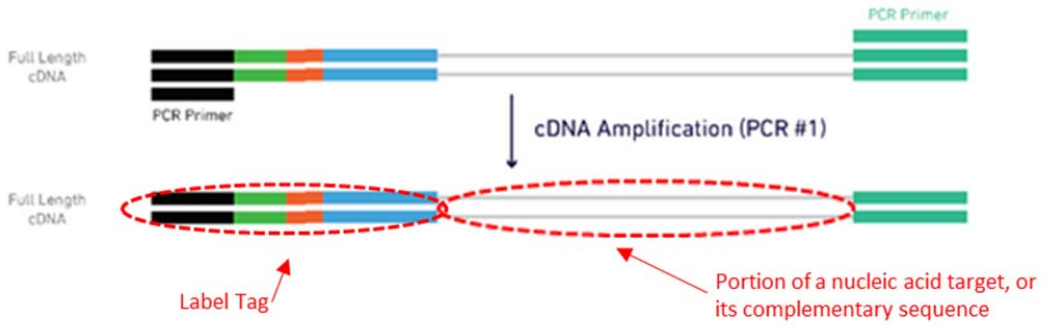
[45] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Figure 3 (cropped, markings added)
[46] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)



135. In the **Single Cell 3' Workflow** Accused Products, the "amplifying the plurality of labeled-targets to produce a plurality of amplified labeled-targets, wherein an amplified labeled-target of the plurality of amplified labeled-targets comprises a copy of at least a portion of the nucleic acid target, or its complementary sequence, and a copy of the label-tag" recited in step (b) occurs because "[t]he GEMs are then 'broken', pooling single-stranded, barcoded cDNA molecules from every cell" and "[a] bulk PCR-amplification and Enzymatic Fragmentation" follows.[47] As illustrated below[48], this amplification step results in the "amplified

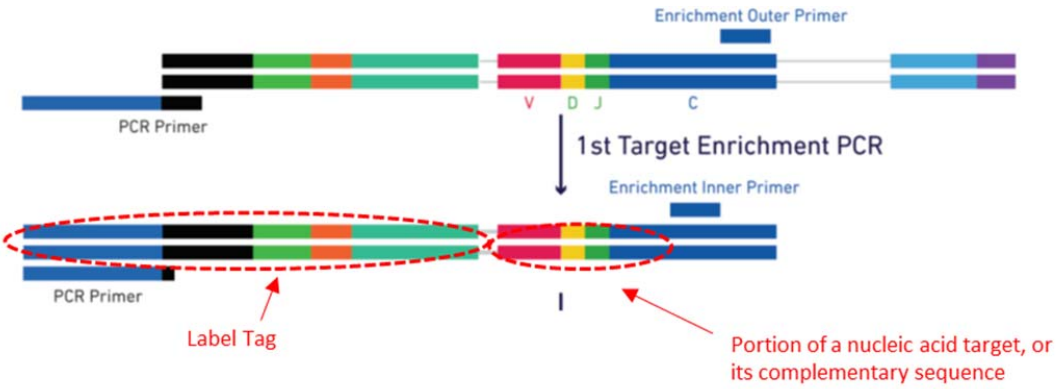
[47] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[48] *Id.* at Figure 3 (cropped, markings added)

labeled-target of the plurality of amplified labeled-targets" that "comprises a copy of at least a portion of the nucleic acid target, or its complementary sequence, and a copy of the label-tag."

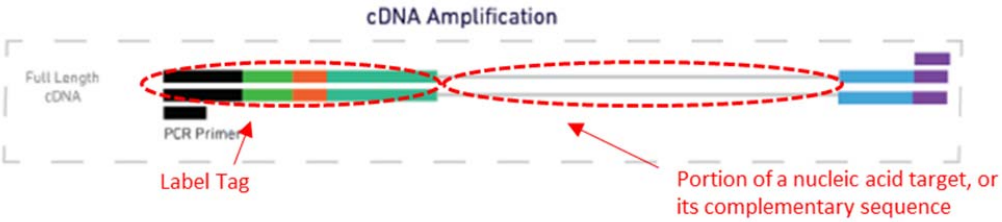


136. In the **Single Cell 5' Workflow** Accused Products, "amplifying the plurality of labeled-targets to produce a plurality of amplified labeled-targets, wherein an amplified labeled-target of the plurality of amplified labeled-targets comprises a copy of at least a portion of the nucleic acid target, or its complementary sequence, and a copy of the label-tag" recited in step (b) occurs because "[t]he Single Cell V(D)J Solution offers the option to generate" by PCR amplification, "Direct Target Enrichment" or "cDNA Amplification followed by Target Enrichment."[49] As illustrated below[50], the Direct Target Enrichment option results in the "amplified labeled-target of the plurality of amplified labeled-targets" that "comprises a copy of at least a portion of the nucleic acid target, or its complementary sequence, and a copy of the label-tag."

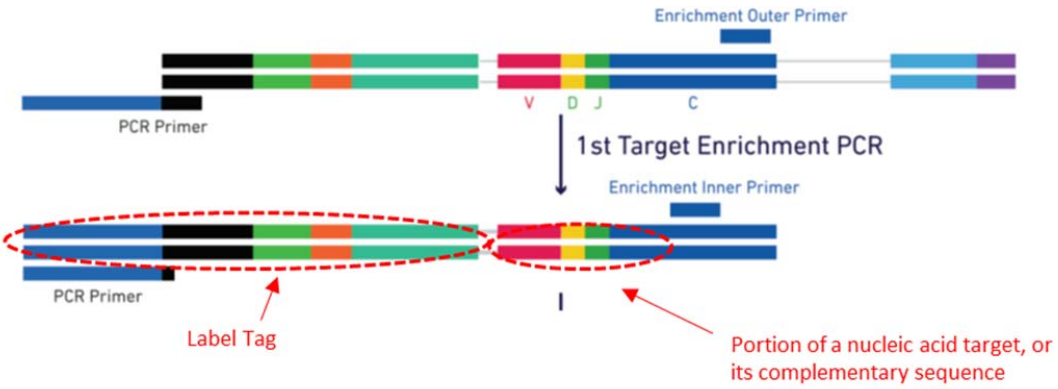
[49] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[50] *Id.* at Figure 3 (cropped, markings added)



137. As illustrated below[51], the cDNA Amplification followed by Target Enrichment option in the **Single Cell 5' Workflow** Accused Products also results in the "amplified labeled-target of the plurality of amplified labeled-targets" that "comprises a copy of at least a portion of the nucleic acid target, or its complementary sequence, and a copy of the label-tag."



[51] *Id.* at Figure 4 (cropped, markings added)



138. In the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products, the "detecting the plurality of amplified labeled-targets by sequencing at least a portion of the target and the label-tag" recited in step (c) occurs because "[d]uring library preparation, sequence components essential for Illumina sequencing and downstream data analysis are incorporated into the final library construct,"[52] and because "[t]he Single Cell 3' Protocol produces Illumina-ready sequencing libraries" [53] and "[t]he Single Cell V(D)J Solutions produce V(D)J enriched and 5' gene expression Illumina-ready sequencing libraries."[54] Once these libraries are "generated and sequenced," "the 10x Barcodes are used to associate individual reads back to the individual partitions."[55]

139. In the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products, the "determining the number of copies of the nucleic acid target, as indicated by the number of different label-tags that are associated with the nucleic acid target" recited in step (d) occurs because the amplified products of step (c) are processed with "Cell Ranger™" analysis

[52] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[53] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf)
[54] "Chromium™ Single Cell V(D)J Reagent Kits User Guide"(CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[55] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

software to perform "demultiplexing, alignment, and gene counting."[56] The information generated with the Cell Ranger™ software is used for "cell clustering, cell type classification, and differential gene expression at a scale of hundreds to millions of cells."[57] "Cell Ranger is a set of analysis pipelines [that perform gene expression analysis by] alignment, filtering, barcode counting, and UMI counting,"[58] which is "determining the number of copies of the nucleic acid target, as indicated by the number of different label-tags that are associated with the nucleic acid target."

140. As demonstrated in **Exhibit 15**, the **Single Cell 3' Workflow** Accused Products satisfy the claim limitations of at least claims 1-6, 10, 12, 15, 17-20 of the '857 patent. As demonstrated in **Exhibit 16**, the **Single Cell 5' Workflow** Accused Products satisfy the claim limitations of at least claims 1-6, 10, 12, 17-20 of the '857 patent. As demonstrated in **Exhibit 17**, the **Spatial Transcriptomics** Accused Products satisfy the claim limitations of at least claims 1-6, 10, 12, 15, 17-21 of the '857 patent. The demonstration of infringement illustrated in **Exhibits 15, 16, and 17** is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '857 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

141. 10X has also induced and currently induces infringement of at least claim 1 of the '857 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of

[56] *Id.*
[57] *Id.*
[58] https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger

operation, 10X knows infringes at least claim 1 of the '857 patent.[59] 10X has known of the '857 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the '857 patent.

142. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the '857 patent. 10X has designed the Accused Products specifically to be used in a manner as claimed at least claim 1 of the '857 patent.[60] As such, the Accused Products are a material component of the patented combination, specifically designed to be used according at least claim 1 of the '857 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the '857 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the '857 patent. 10X has knowledge of the '857 patent and is aware that the Accused Products are especially made to be used in a system that infringes the '857 patent.

143. Defendant's infringement has been willful and deliberate because Defendant has known of the '857 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the '857 patent.

144. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because

[59] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[60] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages, and injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 3
(INFRINGEMENT OF THE '137 PATENT)

145. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

146. U.S. Patent No. 9,816,137 (the "'137 patent"), entitled "Digital Counting of Individual Molecules by Stochastic Attachment of Diverse Labels," was duly and legally issued on November 14, 2017 to inventors Stephen P. A. Fodor and Glenn K. Fu. A true and accurate copy of the '137 patent is attached as **Exhibit 3**.

147. Skilled artisans would understand that, prior to the inventions of the '137 patent, numerous problems existed in the prior art relating to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample. Analytical methods for measuring the abundance of different molecules in a sample (*e.g.*, nucleic acids) existed, but were generally comparative techniques and were limited by signal to noise issues. Prior art techniques offered limited utility in cases where samples comprised a large number of different molecules or where the number of molecules of interest was low in comparison to the number of background molecules. *See, e.g.*, '137 patent at 2:59-63; 3:7-10; 3:18-28; 3:33-37. Other drawbacks and limitations in prior art methods included, for example:

- A requirement for one-to-one correspondence between probe sequences and oligonucleotide tag sequences in techniques where oligonucleotide tags are hybridized to their complements;
- A requirement for customizing dilutions for each type of molecule in digital methods, which generally limited the practice to analysis of a small number of different molecules and required physical separation of molecules;

- An inability to ensure that all sequences are captured in microarray and sequencing based technologies;
- A limited ability to correlate intensity of hybridization signal (or signal intensity) to the concentration of target molecules in hybridization-based methods;
- Variability relating to probe hybridization differences and cross-reactivity;
- Limitations on the ability to stochastically attach labels to known targets, in a known location, in the context of sequencing and amplification-based methodologies; and
- Dynamic range limitations in array-based methods.

See, e.g., *id.* at 2:7-15; 2:45-3:24; 3:33-37; 14:44-48; 19:50-59; 22:58-61; 23:13-20; 23:32-36; 24:18-22; 24:46-60; 33:7-17; 33:44-62.

148. Skilled artisans would understand that the inventions as recited in the common specifications of the Fodor patents are generally directed to quantitation of the abundance of molecules, e.g., nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules. *See, e.g.*, '137 patent at 3:41-4:9 ("High-sensitivity single molecule digital counting by the stochastic labeling of a collection of identical molecules is disclosed. Each copy of a molecule randomly chooses from a non-depleting reservoir of diverse labels. . . . The labeled fragments for a target molecule of choice are detected with high specificity using a microarray readout system, and with DNA sequencing. The results are consistent with a stochastic process, and yield highly precise relative and absolute counting statistics of selected molecules within a vast background of other molecules. . . . The attachment of the label confers a separate, determinable identity to each occurrence of targets that may otherwise be indistinguishable."). The claimed inventions of the '137 patent are directed in general to a method of analyzing a sample comprising a plurality of nucleic acids by attaching a plurality of primers comprising different variable label regions to

the plurality of nucleic acids from the sample, extending the primers to produce a plurality of labeled nucleic acids comprising different variable label regions and complementary copies of the nucleic acids, and attaching second primers to produce double-stranded labeled nucleic acids. More specifically, skilled artisans would understand that the asserted independent claims of the ’137 patent are directed to specific implementations of the inventions of the Fodor patents, reciting “attaching a plurality of primers to the plurality of nucleic acids from the sample, wherein each primer of the plurality of primers comprises a different variable label region, and the plurality of nucleic acids comprises multiple occurrences of a target nucleic acid,” “extending the plurality of primers attached to the plurality of nucleic acids to produce a plurality of labeled nucleic acids, wherein each one of the plurality of labeled nucleic acids comprises (i) a variable label region; and (ii) a complementary copy of a nucleic acid that was attached to a primer,” and “attaching a plurality of second primers to the plurality of labeled nucleic acids and extending the plurality of second primers to produce a plurality of double-stranded labeled nucleic acids” (’137 patent, cl. 1). They would further understand that asserted dependent claims are directed to further specific implementations of the methods recited in the independent claims, including “wherein attaching the plurality of primers to the plurality of nucleic acids occurs in a stochastic manner” (’137 patent, cl. 32).

149. Skilled artisans would further understand that (1) quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, is not an abstract idea but rather a concrete and tangible method for manipulating molecules and generating new molecules that provides an improved method of quantitation; (2) the specific

implementations of the inventions of the Fodor patents recited in the claims of the ’137 patent are not directed to an abstract idea, nor are the claims directed merely to labeling different molecules or objects with different labels or all implementations thereof; (3) labeling nucleic acids with different labels is not an abstract idea; (4) the claims do not describe concepts long-practiced in society but rather claim novel and innovative methods used for quantitation of the abundance of genetic material in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, that improved upon prior art methods; and (5) the claims do not merely limit an abstract idea to a specific technological environment, *e.g.*, DNA and nucleic acids.

150. Skilled artisans would further understand that the inventions claimed in the ’137 patent provide numerous improvements and benefits over prior art methods. In addition to addressing the aforementioned drawbacks and limitations of the prior art, the inventions of the ’137 patent also:

- Confer a separate, determinable identity to occurrences of targets that may otherwise be indistinguishable as a result of the diverse labels or label-tags in the newly-generated molecule;
- Allow simultaneous quantitation of multiple target sequences;
- Take quantitative measurements of copies of identical target molecules in a solution by transformation of the information into a digital process for detecting the presence of different or diverse labels or label-tags that are attached to the identical target molecules in a manner that is extremely sensitive and can be multiplexed to high levels;
- Allow newly-generated molecules comprising targets and diverse labels or label-tags to be amplified freely without impacting quantitation of the targets; and
- Convert an analog readout of hybridization signal intensities on arrays into a measurable process that can be scored digitally on the arrays by leveraging the diverse label-tags found in each newly-generated molecule, providing a clear cost-advantage over existing techniques.

See, e.g., ’137 patent at 3:41-43; 3:53-67; 4:7-9; 4:14-18; 14:44-48; 21:52-54; 23:13-20; 23:23-26; 23:32-36; 23:39-46; 24:18-22; 25:52-55; 32:14-15; 32:62-65; 33:33-43. Skilled artisans would understand that these benefits inure from the claimed inventions and inventive concepts (alone or in combination with the other limitations), including the plurality of primers comprising a different variable label region being attached to a plurality of nucleic acids to generate a plurality of newly-generated labeled nucleic acids comprising a variable label region and a complementary copy of a nucleic acid that was attached to a primer, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, the attaching of a plurality of second primers to the plurality of labeled nucleic acids and extending the plurality of second primers to produce a plurality of double-stranded labeled nucleic acids, and the other limitations (alone or in combination) of the independent and dependent claims, including as described above and below.

151. Skilled artisans would further understand that quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, was not well-understood, routine, or conventional at the time of the invention. They would further understand that the steps recited in the claims of the ’137 patent, either alone or in combination and including those recited above and below, were not well-understood, routine, or conventional at the time of the invention and are integral to addressing the problems in the prior art remedied by the improved functionality of the claimed inventions and inventive concepts. They would further understand that the specific structures and manipulations recited in the claims of the ’137 patent, including a plurality of primers, a plurality of nucleic acids, a plurality

of second primers, a plurality of double-stranded labeled nucleic acids, a plurality of newly-generated labeled nucleic acids, including through stochastic attachment of primers with variable label regions and/or by multiplexing to allow simultaneous quantitation of multiple nucleic acids, wherein each one of the plurality of labeled nucleic acids comprises a variable label region and a complementary copy of a nucleic acid that was attached to a primer, are essential to addressing the problems remedied by the improved functionality of the claimed inventions. *See also supra* ¶ 150.

152. They would further understand that the additional limitations (alone or in combination) of at least dependent claims 2-14, 18-24, 26-36, and 38-41 are not directed to an abstract idea and recite inventive concepts for additional reasons, including that they recite additional structure; are not routine, conventional, or well-known; improve upon prior art methods by providing increased functionality; and do not risk preemption as a result of the additional limitations in those claims.

153. They would further understand that claim 6 of the ’358 patent is not substantially similar to nor linked to any abstract idea, much less the same abstract idea as all claims of the ’137 patent, including because the claims of the ’137 patent recite additional, tangible structures and manipulations, provide further improvements and innovations, address additional technological problems, add one or more inventive concepts, and involve different facts relating to issues of preemption and patentability that are not reflected in claim 6 of the ’358 patent. *See also supra* at ¶¶ 150-52.

154. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the ’137 patent, including at least claim 1 of the ’137 patent

directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

155. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the '137 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '137 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

156. In the **Single Cell 3' Workflow** Accused Product "analyzing a sample comprising a plurality of nucleic acids" occurs because "[t]he 10x™ GemCode™ Technology samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome . . . by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs)"[61] and because cells contain a plurality of poly A-tailed mRNA transcripts,[62] which is a "sample." The "Cell Ranger™" analysis software performs "demultiplexing, alignment, and gene counting"[63] and the information generated with the Cell Ranger software is used for "cell clustering, cell type classification, and differential gene expression at a scale of hundreds to millions of cells."[64] "Cell Ranger is a set of analysis pipelines [that perform gene expression analysis by] alignment,

[61] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[62] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf
[63] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf);
[64] *Id.*

filtering, barcode counting, and UMI counting,"[65] which is "analyzing a sample comprising a plurality of nucleic acids."

157. In the **Single Cell 5' Workflow** Accused Products "analyzing a sample comprising a plurality of nucleic acids" occurs because "[t]he contents of the GEM (oligos, lysed cell components and Master Mix that contains the Poly-dT RT primer) are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA [plurality of nucleic acids] from poly-adenylated mRNA"[66] which is a "sample" and because "Cell Ranger™" analysis software performs "demultiplexing, alignment, and gene counting"[67] and because the information generated with the Cell Ranger software is used for "cell clustering, cell type classification, and differential gene expression at a scale of hundreds to millions of cells." [68] "Cell Ranger is a set of analysis pipelines [that perform gene expression analysis by] alignment, filtering, barcode counting, and UMI counting,"[69] which is "analyzing a sample comprising a plurality of nucleic acids."

158. In the **Single Cell 3' Workflow** Accused Products, the "attaching a plurality of primers to the plurality of nucleic acids from the sample, wherein each primer of the plurality of primers comprises a different variable label region, and the plurality of nucleic acids comprises multiple occurrences of a target nucleic acid" of step (a) in claim 1 occurs when "[t]he contents of the GEM (oligos, lysed cell components and Master Mix) are incubated in an RT

[65] https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger
[66] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[67] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[68] *Id.*
[69] https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger

reaction to generate full-length, barcoded cDNA from the poly A-tailed mRNA transcripts."[70] As illustrated below,[71] "each primer of the plurality of primers comprises a different variable label region." Further, "the plurality of nucleic acids comprises multiple occurrences of a target nucleic acid" because cells contain a plurality of "poly A-tailed mRNA transcripts."[72]

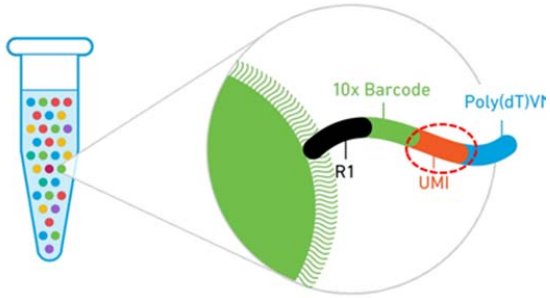
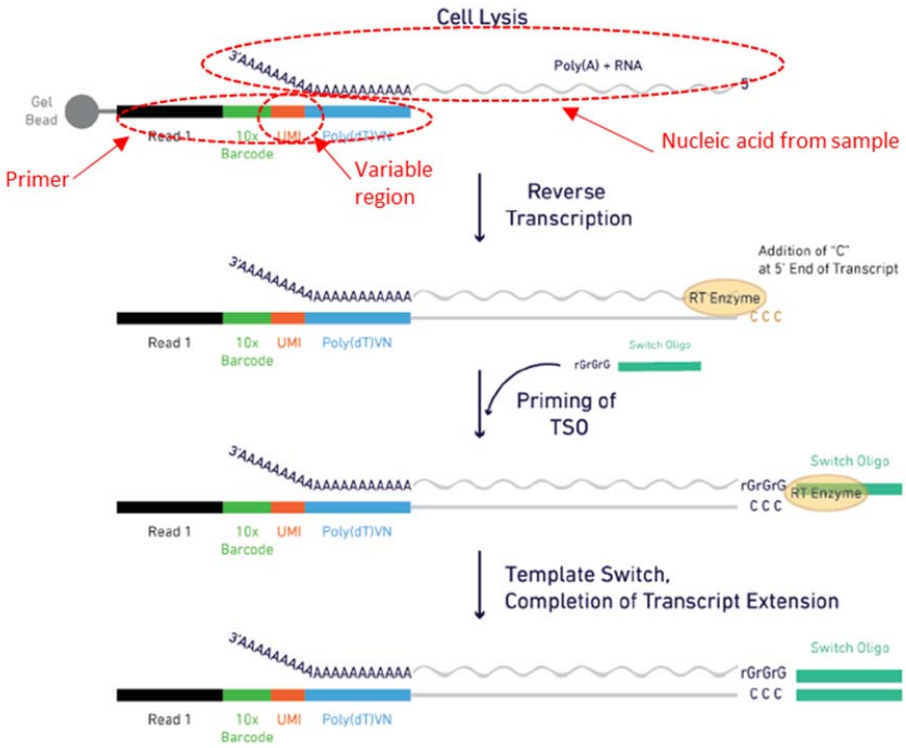


Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

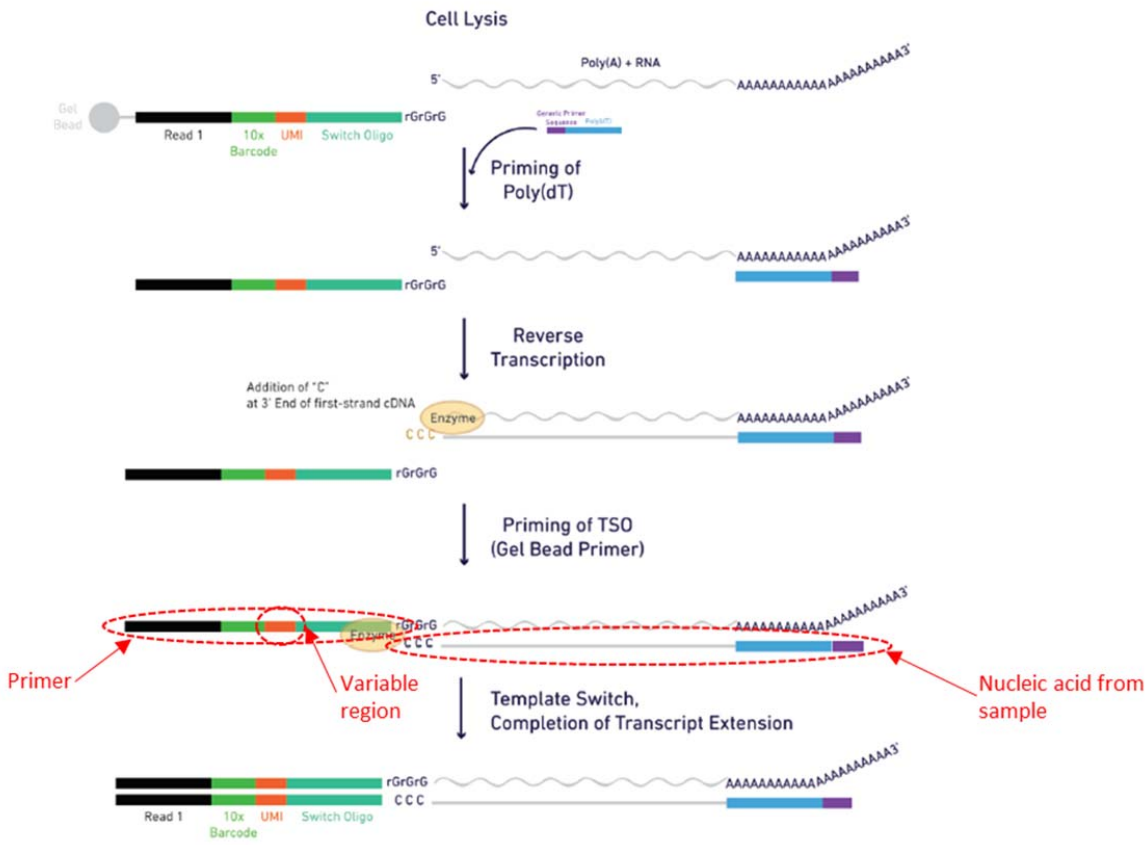
i. Partial Illumina Read 1 sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 30 nt Poly(dT) primer sequence

[70] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[71] *Id.* at Figure 1, Figure 3 (cropped, markings added)
[72] *Id.*



159. In the **Single Cell 5' Workflow** Accused Products, the "attaching a plurality of primers to the plurality of nucleic acids from the sample, wherein each primer of the plurality of primers comprises a different variable label region, and the plurality of nucleic acids comprises multiple occurrences of a target nucleic acid" of step (a) in claim 1 occurs when "[t]he contents of the GEM […] are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA from poly-adenylated mRNA."[73]

[73] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)



160. As illustrated below,[74] "each primer of the plurality of primers comprises a different variable label region" in form of the 10 nucleotide Unique Molecular Identifier (UMI). Further, "the plurality of nucleic acids comprises multiple occurrences of a target nucleic acid" because the reverse transcription products are generated from a plurality of "poly-adenylated mRNA" from the cell[75]

[74] *Id.* at Figure 1, Figure 3 (cropped, markings added)
[75] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

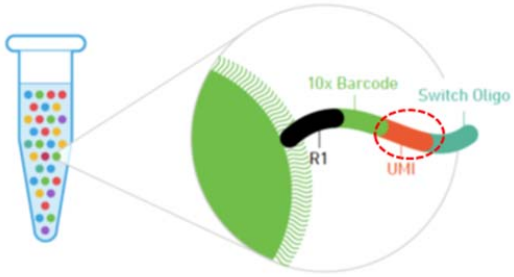
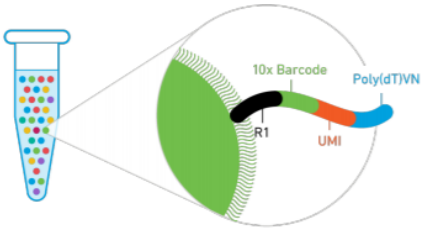


Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

i. Partial Illumina Read 1 Sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 13 nt Switch Oligo

161. As illustrated below,[76] "each primer of the plurality of primers comprises a different variable label region" because each of the beads in both workflows "contain millions of oligo primers"[77] that comprise different "Unique Molecular Identifiers" that make up "a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[78] As shown below[79], these barcodes in the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are a "10nt Unique Molecular Identifier."

Each Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1):



i. Partial Illumina Read 1 sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 30 nt Poly(dT) primer sequence

Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

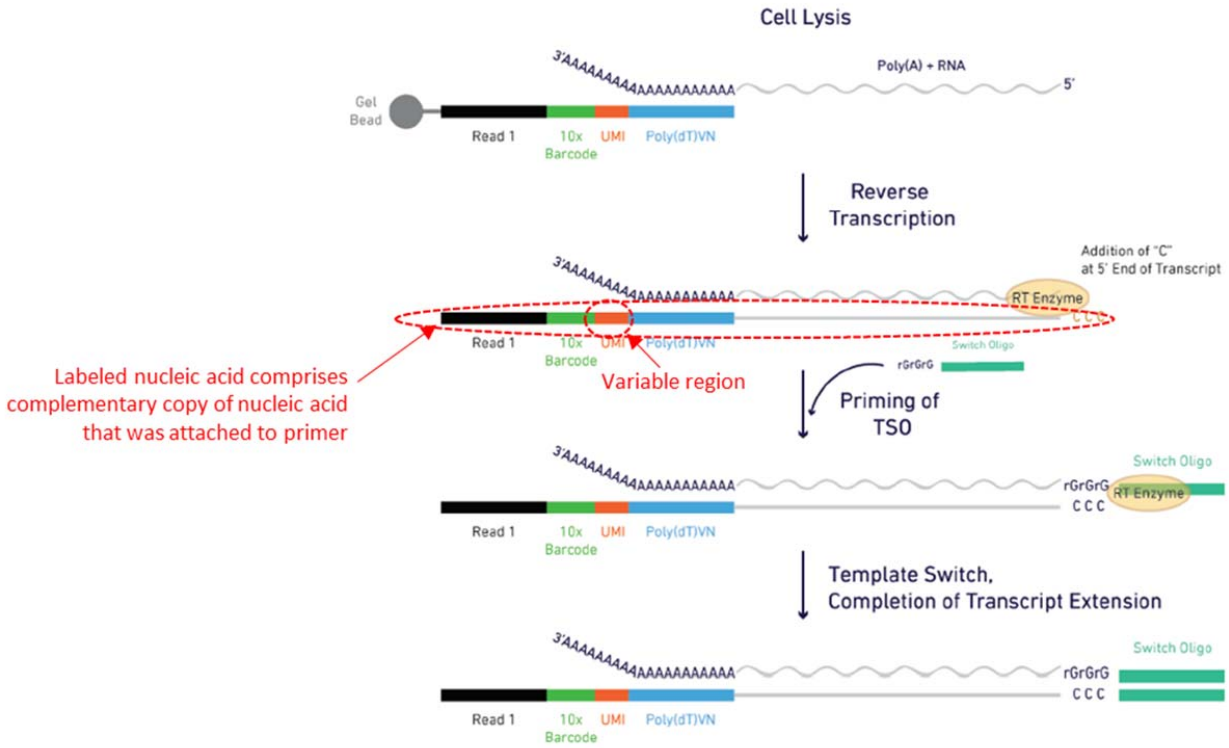
[76] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[77] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[78] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[79] *Id,*

Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

162. Further, in the **Single Cell 3' Workflow** and **Single Cell 5' Workflows,** "the plurality of nucleic acids comprises multiple occurrences of a target nucleic acid" because cells contain a plurality of poly A-tailed mRNA transcripts.[80]

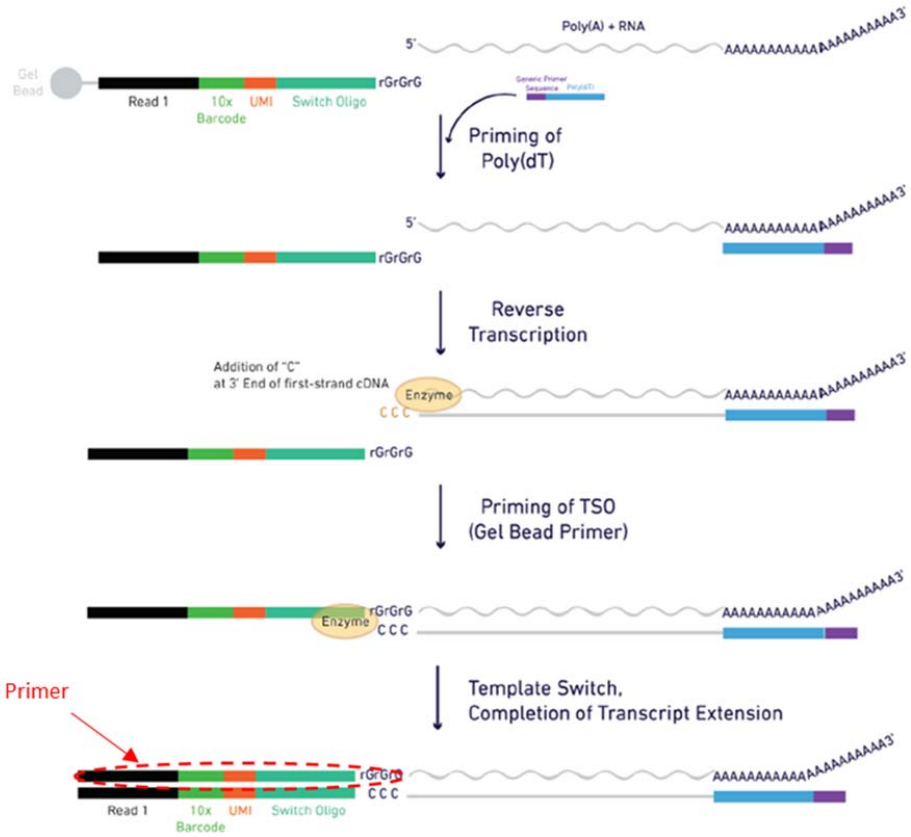
163. In the **Single Cell 3' Workflow** Accused Products, the "extending the plurality of primers attached to the plurality of nucleic acids to produce a plurality of labeled nucleic acids" occurs because a "reverse transcription reaction is primed by the barcoded Gel Bead oligo."[81] As illustrated below[82], the "primers" hybridize to "the plurality of nucleic acids from the sample" and thereby generate the "a plurality of labeled nucleic acids" by an extension reaction wherein "each one of the plurality of labeled nucleic acids comprises (i) a variable label region; and (ii) a complementary copy of a nucleic acid that was attached to a primer."

[80] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[81] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[82] *Id.* at Figure 3 (cropped, markings added)



164. In the **Single Cell 5' Workflow** Accused Products, the "extending the plurality of primers attached to the plurality of nucleic acids to produce a plurality of labeled nucleic acids wherein each one of the plurality of labeled nucleic acids comprises (i) a variable label region; and (ii) a complementary copy of a nucleic acid that was attached to a primer" occurs because the "Post GEM-RT Cleanup" step uses "DynaBeads MyOne Silane" beads to binds DNA in the sample.[83] On information and belief, "DynaBeads MyOne Silane" bind to DNA fragments at least 50 base pairs in length or larger [84] and therefore will also bind the primer indicated below.

[83] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[84] ThermoFisher Scientific "A complete Workflow for Circulating DNA Isolation and Analysis"

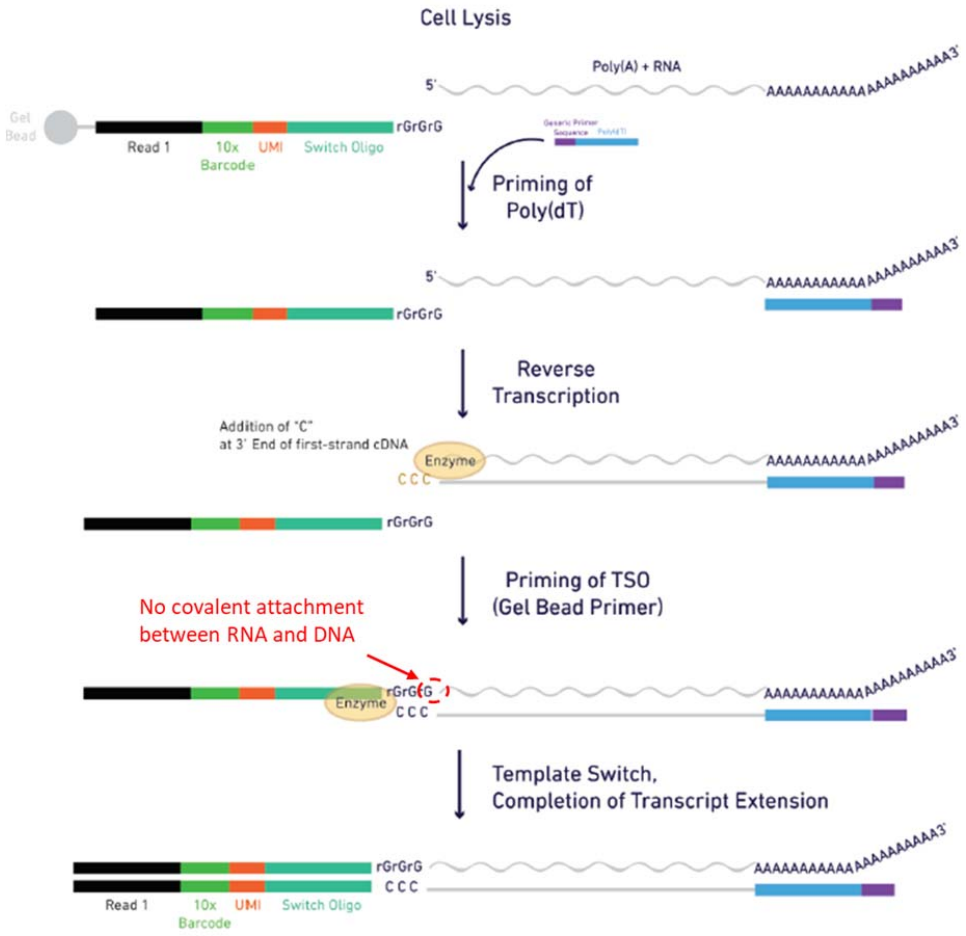


165. The "Post GEM-RT Cleanup" step uses nuclease free water, but does not use ***ribo***nuclease-free water. [85] On information and belief, the presence of ribonucleases in the "Post GEM-RT Cleanup Step" will result in degradation of the RNA in the duplex highlighted above to yield the below structure.[86]

166. In the alternative, the **Single Cell 5' Workflow** Accused Products, the "extending the plurality of primers attached to the plurality of nucleic acids to produce a plurality of labeled nucleic acids wherein each one of the plurality of labeled nucleic acids comprises (i) a

[85] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[86] This is illustration is a modification of the figure in the 10x materials adapted to demonstrate the hybrid arising due to the presence of RNAses in the sample.

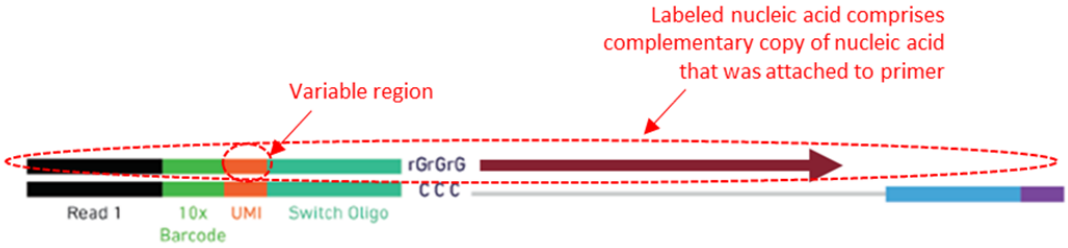
variable label region; and (ii) a complementary copy of a nucleic acid that was attached to a primer" occurs because the RNA molecule in the below illustration is not covalently attached to a DNA molecule.



167. On information and belief, the RNA molecule will dissociate from DNA prior to the PCR amplification step to form the structure illustrated below:[87]

[87] This is illustration is a modification of the figure in the 10x materials adapted to demonstrate the hybrid arising due to dissociation of RNA form the hybrid in the last step of the figure in the preceding paragraph.

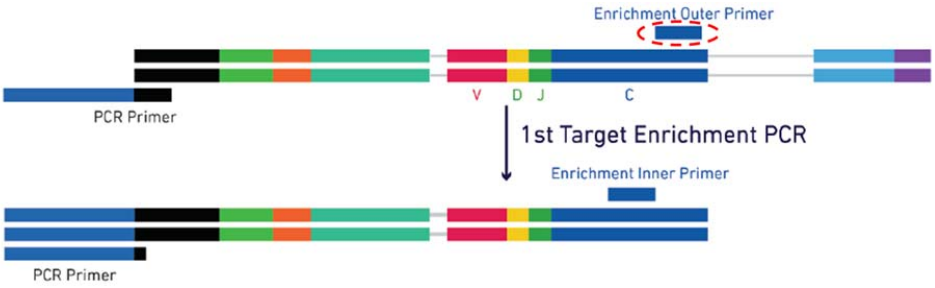
168. In the next step of the **Single Cell 5' Workflow** Accused Products, PCR amplification is performed by "Direct Target Enrichment" or "cDNA Amplification followed by Target Enrichment."[88] On information and belief, as illustrated with the arrow below, performing either of the PCR extension step will result in "extending the plurality of primers attached to the plurality of nucleic acids to produce a plurality of labeled nucleic acids." As is illustrated below, the extension products generated in this step are a "plurality of labeled nucleic acids [comprising] (i) a variable label region; and (ii) a complementary copy of a nucleic acid that was attached to a primer."



169. In the **Single Cell 3' Workflow** Accused Products, the "attaching a plurality of second primers to the plurality of labeled nucleic acids and extending the plurality of second primers to produce a plurality of double-stranded labeled nucleic acids" occurs because "[t]he GEMs are then 'broken', pooling single-stranded, barcoded cDNA molecules from every cell" and "[a] bulk PCR-amplification and Enzymatic Fragmentation" follows.[89] As illustrated below[90], in the first step of the reaction, a plurality of PCR primers which are a "plurality of second primers" attach to the plurality of labeled nucleic acids and extend "to produce a plurality of double-stranded labeled nucleic acids."

[88] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[89] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[90] *Id.* at Figure 3 (cropped, markings added)

170. The **Single Cell 5' Workflow** Accused Products "offers the option to generate" by PCR amplification, "Direct Target Enrichment" or "cDNA Amplification followed by Target Enrichment."[91] As illustrated below[92], in the Direct Target Enrichment option of the **Single Cell 5' Workflow** Accused Products, the "attaching a plurality of second primers to the plurality of labeled nucleic acids and extending the plurality of second primers to produce a plurality of double-stranded labeled nucleic acids" occurs because "[a]fter incubation, the GEMs are broken and the pooled post GEM-RT reaction mixtures are recovered," followed by "PCR amplification with primers."[93] As illustrated below[94] a plurality of PCR "enrichment outer" primers which are a "plurality of second primers" attach to the plurality of labeled nucleic acids and extend "to produce a plurality of double-stranded labeled nucleic acids."



[91] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[92] *Id.* at Figure 3 (cropped, markings added)
[93] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[94] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Figure 3 (cropped, markings added)

171. As demonstrated in **Exhibit 18**, the **Single Cell 3' Workflow** Accused Products satisfy the claim limitations of at least claims 1-14, 18-23, 26-36, and 38-41 of the '137 patent. As demonstrated in **Exhibit 19**, the **Single Cell 5' Workflow** Accused Products satisfy the claim limitations of at least claims 1-14, 18-24, 28, 29, 31-36, and 38-41 of the '137 patent. As demonstrated in **Exhibit 20**, the **Spatial Transcriptomics** Accused Products satisfy the claim limitations of at least claims 1-4, 26-36, and 38-40 of the '137 patent. The demonstration of infringement illustrated **in Exhibits 18, 19, and** 20 is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '137 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

172. 10X has also induced and currently induces infringement of at least claim 1 of the '137 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, 10X knows infringes at least claim 1 of the '137 patent.[95] 10X has known of the '137 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the '137 patent.

173. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the '137 patent. 10X has designed the Accused Products specifically to be used in a manner as claimed at least claim 1 of the '137 patent.[96] As such, the Accused Products are a material component of the patented combination, specifically

[95] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[96] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

designed to be used according at least claim 1 of the ’137 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the ’137 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the ’137 patent. 10X has knowledge of the ’137 patent and is aware that the Accused Products are especially made to be used in a system that infringes the ’137 patent.

174. Defendant’s infringement has been willful and deliberate because Defendant has known of the ’137 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the ’137 patent.

175. As the direct and proximate result of Defendant’s conduct, Plaintiffs have suffered and, if Defendant’s conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs’ remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive relief. Plaintiffs’ business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 4
(INFRINGEMENT OF THE ’809 PATENT)

176. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

177. U.S. Patent No. 9,290,809 (the “’809 patent”), entitled “Digital Counting of Individual Molecules by Stochastic Attachment of Diverse Labels,” was duly and legally issued on March 22, 2016 to inventors Stephen P. A. Fodor and Glenn K. Fu. A true and accurate copy of the ’809 patent is attached as **Exhibit 4**.

178. Skilled artisans would understand that, prior to the inventions of the ’809 patent, numerous problems existed in the prior art relating to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample. Analytical methods for measuring the abundance of different molecules in a sample (*e.g.*, nucleic acids) existed, but were generally comparative techniques and were limited by signal to noise issues. Prior art techniques offered limited utility in cases where samples comprised a large number of different molecules or where the number of molecules of interest was low in comparison to the number of background molecules. *See, e.g.*, ’809 patent at 2:57-61; 3:5-7; 3:15-24; 3:29-33. Other drawbacks and limitations in prior art methods included, for example:

- A requirement for one-to-one correspondence between probe sequences and oligonucleotide tag sequences in techniques where oligonucleotide tags are hybridized to their complements;
- A requirement for customizing dilutions for each type of molecule in digital methods, which generally limited the practice to analysis of a small number of different molecules and required physical separation of molecules;
- An inability to ensure that all sequences are captured in microarray and sequencing based technologies;
- A limited ability to correlate intensity of hybridization signal (or signal intensity) to the concentration of target molecules in hybridization-based methods;
- Variability relating to probe hybridization differences and cross-reactivity;
- Limitations on the ability to stochastically attach labels to known targets, in a known location, in the context of sequencing and amplification-based methodologies; and
- Dynamic range limitations in array-based methods.

See, e.g., *id.* at 2:5-13; 2:43-3:20; 3:29-33; 14:36-40; 19:49-58; 22:50-53; 23:4-11; 23:22-26; 24:7-11; 24:35-48; 32:51-61; 33:20-38.

179. Skilled artisans would understand that the inventions as recited in the common specifications of the Fodor patents are generally directed to quantitation of the

abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules. *See, e.g.*, '809 patent at 3:37-4:4 ("High-sensitivity single molecule digital counting by the stochastic labeling of a collection of identical molecules is disclosed. Each copy of a molecule randomly chooses from a non-depleting reservoir of diverse labels. . . . The labeled fragments for a target molecule of choice are detected with high specificity using a microarray readout system, and with DNA sequencing. The results are consistent with a stochastic process, and yield highly precise relative and absolute counting statistics of selected molecules within a vast background of other molecules. . . . The attachment of the label confers a separate, determinable identity to each occurrence of targets that may otherwise be indistinguishable."). The claimed inventions of the '809 patent are directed in general to compositions and kits comprising a plurality of oligonucleotide labels, each label comprising an oligo dT sequence, sequencing primer binding site, as well as, a common sequence and a unique label tag. More specifically, skilled artisans would understand that the asserted independent claims of the '809 patent are directed to specific implementations of the inventions of the Fodor patents, reciting "[a] composition" and "[a] kit" "comprising a plurality of oligonucleotide labels, wherein each oligonucleotide label of the plurality of oligonucleotide labels comprises an oligo dT sequence, a sequencing primer binding site, a common sequence that is the same for all oligonucleotide labels of the plurality of oligonucleotide labels, and a unique label tag sequence, wherein the unique label tag sequence is selected from a set of . . . different label tag sequences" ('809 patent, cls. 1, 14).

180. Skilled artisans would further understand that (1) quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules

by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, is not an abstract idea but rather a concrete and tangible method for manipulating molecules and generating new molecules that provide an improved method of quantitation; (2) the specific implementations of the inventions of the Fodor patents recited in the claims of the '809 patent are not directed to an abstract idea, nor are the claims directed merely to labeling different molecules or objects with different labels or all implementations thereof; (3) labeling nucleic acids with different labels is not an abstract idea; (4) the claims do not describe concepts long-practiced in society but rather claim novel and innovative compositions and kits used for quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, that improved upon prior art compositions and kits; and (5) the claims do not merely limit an abstract idea to a specific technological environment, *e.g.*, DNA and nucleic acids.

181. Skilled artisans would further understand that the inventions claimed in the '809 patent provide numerous improvements and benefits over prior art methods. In addition to addressing the aforementioned drawbacks and limitations of the prior art, the inventions of the '809 patent also:

- Confer a separate, determinable identity to occurrences of targets that may otherwise be indistinguishable as a result of the diverse labels or label-tags in the newly-generated molecule;
- Allow simultaneous quantitation of multiple target sequences;
- Take quantitative measurements of copies of identical target molecules in a solution by transformation of the information into a digital process for detecting the presence of different or diverse labels or label-tags that are attached to the identical target

molecules in a manner that is extremely sensitive and can be multiplexed to high levels;

- Allow newly-generated molecules comprising targets and diverse labels or label-tags to be amplified freely without impacting quantitation of the targets; and
- Convert an analog readout of hybridization signal intensities on arrays into a measurable process that can be scored digitally on the arrays by leveraging the diverse label-tags found in each newly-generated molecule, providing a clear cost-advantage over existing techniques.

See, e.g., '809 patent at 3:37-39; 3:39-62; 4:1-4; 4:8-12; 14:36-40; 21:29-31; 23:4-11; 23:14-17; 23:22-26; 23:30-37; 24:7-11; 25:39-42; 31:59-60; 32:40-43; 33:9-19. Skilled artisans would understand that these benefits inure from the claimed inventions and inventive concepts (alone or in combination with the other limitations), including the plurality of oligonucleotide labels with an oligo dT sequence, the sequencing primer binding site, the common sequence, and the unique label tag sequence, which can be used for, *e.g.*, stochastic attachment of diverse labels and/or multiplexing to allow simultaneous quantitation of multiple molecules, and the other limitations (alone or in combination) of the independent and dependent claims, including as described above and below.

182. Skilled artisans would further understand that quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, was not well-understood, routine, or conventional at the time of the invention. They would further understand that the claimed compositions and kits recited in the '809 patent, including the limitations recited above and below, comprising oligonucleotide labels with an oligo dT sequence, a sequencing primer binding site, a common sequence, and a unique label tag sequence, were not well-understood, routine, or conventional at the time of the invention and are

integral to addressing the problems in the prior art remedied by the improved functionality of the claimed inventions and inventive concepts. They would further understand that the claims of the ’809 patent recite concrete and tangible compositions of matter and kits that amount to significantly more than mere labels, as they are designed for quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules. They would further understand that the specific structures recited in the claims of the ’809 patent, including a plurality of oligonucleotide labels, an oligo dT sequence, a sequencing primer binding site, a common sequence, and a unique label tag sequence, are essential to addressing the problems remedied by the improved functionality of the claimed inventions. *See also supra* ¶ 181.

183. They would further understand that the additional limitations (alone or in combination) of at least dependent claims 2-4, 7-10, 13, and 17 are not directed to an abstract idea and recite inventive concepts for additional reasons, including that they recite additional structure; are not routine, conventional, or well-known; improve upon prior art methods by providing increased functionality; and do not risk preemption as a result of the additional limitations in those claims.

184. They would further understand that claim 6 of the ’358 patent is not substantially similar to nor linked to any abstract idea, much less the same abstract idea as all claims of the ’809 patent, including because the claims of the ’809 patent recite additional, tangible structures, provide further improvements and innovations, address additional technological problems, add one or more inventive concepts, and involve different facts relating to issues of preemption and patentability that are not reflected in claim 6 of the ’358 patent, and

because claim 6 of the ’358 patent recites a method, while the claims of the ’809 patent recite compositions and kits. *See also supra* at ¶¶ 181-83.

185. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the ’809 patent, including at least claim 1 of the ’809 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

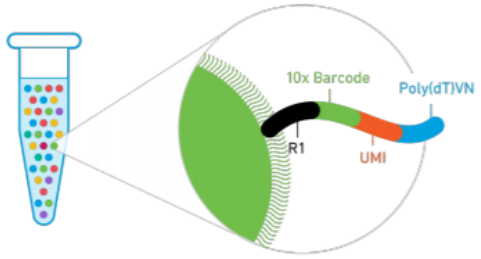
186. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the ‘809 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD’s ability to demonstrate Defendant’s direct, indirect, literal, or equivalent infringement of additional ’809 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

187. Each Gel Bead of the **Single Cell 3’ Workflow** Accused Products contains “a plurality of oligonucleotide labels” since the Gel Beads comprise “millions of oligo primers that comprise different Unique Molecular Identifiers”[97] that make up “a pool of ~ 750000 barcodes to separately index each cell’s transcriptome”[98] As shown below[99], “each oligonucleotide label of the plurality of oligonucleotide labels” in the **Single Cell 3’ Workflow** Accused Products comprise (i) “an oligo dT sequence” (“30nt Poly(dT) primer sequence”), (ii)

[97] “TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3’ v2 Libraries” (CG000108_AssayConfiguration_SC3v2.pdf)
[98] “Chromium™ Single Cell 3’ Reagent Kits v2 User Guide” (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf)
[99] *Id.*

"a sequencing primer binding site" ("an Illumina® R1 sequence (read 1 sequencing primer)"),[100] (iii) "a common sequence that is the same for all oligonucleotide labels of the plurality of oligonucleotide labels" ("16 nt 10x Barcode")[101], and (iv) "a unique label tag sequence, wherein the unique label tag sequence is selected from a set of at least m different label tag sequences" ("10 nt Unique Molecular Identifier").[102]

Each Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1):



i. Partial Illumina Read 1 sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 30 nt Poly(dT) primer sequence

Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

188. As demonstrated in **Exhibit 21**, the **Single Cell 3' Workflow** Accused Products satisfy the claim limitations of at least claims 1-4, 7-10, and 14 of the '809 patent. As demonstrated in **Exhibit 22**, the **Spatial Transcriptomics** Accused Products satisfy the claim limitations of at least claims 1-4, 7-10, 13, 14, and 17 of the '809 patent. The demonstration of infringement illustrated in **Exhibits 21 and 22** is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '809 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

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[100] "During library preparation, sequence components essential for Illumina sequencing and downstream data analysis are incorporated into the final library construct." *See* "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)

[101] All of the oligonucleotides of a gel bead "share a common 10x Barcode." *See* "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)

[102] "The 10x™ GemCode™ Technology samples a pool of ~ 750000 barcodes." *See* "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)

189. 10X has also induced and currently induces infringement of at least claim 1 of the '809 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, induces customers to use a composition that infringes at least claim 1 of the '809 patent.[103] 10X has known of the '809 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the '809 patent.

190. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the '809 patent. 10X has designed the Accused Products specifically to be used with the composition as claimed at least claim 1 of the '809 patent.[104] As such, the Accused Products are a material component of the patented combination, specifically designed for use with the composition of at least claim 1 of the '809 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the '809 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the '809 patent. 10X has knowledge of the '809 patent and is aware that the Accused Products are especially made to be used in a system that infringes the '809 patent.

191. 10X also has induced and currently induces infringement of at least claim 2 of the '809 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products,

[103] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

[104] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

along with directions for use that, when followed in an intended manner and in a normal mode of operation, 10X knows infringes at least claim 2 of the '809 patent.[105]

192. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 2 of the '809 patent. 10X has designed the Accused Products specifically to be used in a manner that generates the composition as claimed in at least claim 2 of the '809 patent.[106] As such, the Accused Products are a material component of the patented combination, specifically designed to make a composition according to at least claim 2 of the '809 patent, and especially made and adapted for use in a manner that infringes at least claim 2 of the '809 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 2 of the '809 patent. 10X has knowledge of the '809 patent and is aware that the Accused Products are especially made to be used in a system that makes a composition that infringes the '809 patent.

193. Defendant's infringement has been willful and deliberate because Defendant has known of the '809 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the '809 patent.

194. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive

[105] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[106] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 5
(INFRINGEMENT OF THE '808 PATENT)

195. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

196. U.S. Patent No. 9,290,808 (the "'808 patent"), entitled "Digital Counting of Individual Molecules by Stochastic Attachment of Diverse Labels," was duly and legally issued on March 22, 2016 to inventors Stephen P. A. Fodor and Glenn K. Fu. A true and accurate copy of the '808 patent is attached as **Exhibit 5**.

197. Skilled artisans would understand that, prior to the inventions of the '808 patent, numerous problems existed in the prior art relating to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample. Analytical methods for measuring the abundance of different molecules in a sample (*e.g.*, nucleic acids) existed, but were generally comparative techniques and were limited by signal to noise issues. Prior art techniques offered limited utility in cases where samples comprised a large number of different molecules or where the number of molecules of interest was low in comparison to the number of background molecules. *See, e.g.*, '808 patent at 2:57-61; 3:5-7; 3:15-24; 3:29-33. Other drawbacks and limitations in prior art methods included, for example:

- A requirement for one-to-one correspondence between probe sequences and oligonucleotide tag sequences in techniques where oligonucleotide tags are hybridized to their complements;
- A requirement for customizing dilutions for each type of molecule in digital methods, which generally limited the practice to analysis of a small number of different molecules and required physical separation of molecules;
- An inability to ensure that all sequences are captured in microarray and sequencing based technologies;

- A limited ability to correlate intensity of hybridization signal (or signal intensity) to the concentration of target molecules in hybridization-based methods;
- Variability relating to probe hybridization differences and cross-reactivity;
- Limitations on the ability to stochastically attach labels to known targets, in a known location, in the context of sequencing and amplification-based methodologies; and
- Dynamic range limitations in array-based methods.

See, e.g., *id.* at 2:5-13; 2:43-3:20; 3:29-33; 14:36-40; 19:28-37; 22:31-34; 22:52-59; 23:3-7; 23:55-59; 24:16-29; 32:32-42; 33:1-20.

198. Skilled artisans would understand that the inventions as recited in the common specifications of the Fodor patents are generally directed to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules. *See, e.g.*, '808 patent at 3:37-4:4 ("High-sensitivity single molecule digital counting by the stochastic labeling of a collection of identical molecules is disclosed. Each copy of a molecule randomly chooses from a non-depleting reservoir of diverse labels. . . . The labeled fragments for a target molecule of choice are detected with high specificity using a microarray readout system, and with DNA sequencing. The results are consistent with a stochastic process, and yield highly precise relative and absolute counting statistics of selected molecules within a vast background of other molecules. . . . The attachment of the label confers a separate, determinable identity to each occurrence of targets that may otherwise be indistinguishable."). The claimed inventions of the '808 patent are directed in general to a method for determining a number of occurrences of a target molecule from a single cell comprising steps of generating an indexed library by performing a labeling step that combines target molecules with diverse label-tag sequences, wherein the ratio of the number of diverse label-tag sequences to the number of occurrences of a

target molecule is greater than 5, to thereby generate target-label-tag molecules via hybridization and an extension reaction, amplifying the target-label-tag molecules, and sequencing at least a portion of the target-label-tag molecules. More specifically, skilled artisans would understand that the asserted independent claims of the '808 patent are directed to specific implementations of the inventions of the Fodor patents, reciting "generating an indexed library by performing a labeling step, the labeling step comprising" "combining in a specified container a sample comprising a plurality of target molecules from the single cell with a plurality of diverse label-tag, wherein the ratio of the number of diverse label-tag sequences to the number of occurrences of a target molecule is greater than 5" and "generating a plurality of target-label-tag molecules by hybridizing label-tags of the plurality of diverse label-tag to target molecules of the plurality of target molecules and performing an extension reaction, wherein a target-label-tag molecule comprises a label-tag and a portion of a complementary sequence of a target molecule," "amplifying the target-label-tag molecules from the indexed library," and "sequencing at least a portion of the amplified product . . . to determine a number of different label-tag sequences associated with the portion of the complementary sequence of a target molecule from the single cell" ('808 patent, cl. 1). They would further understand that asserted dependent claims are directed to further specific implementations of the methods recited in the independent claims, including "wherein the method is multiplexed" ('808 patent, cl. 3) and "wherein the attaching is stochastic" ('808 patent, cl. 23).

199. Skilled artisans would further understand that (1) quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules,

is not an abstract idea but rather a concrete and tangible method for manipulating molecules and generating new molecules that provide an improved method of quantitation; (2) the specific implementations of the inventions of the Fodor patents recited in the claims of the ’808 patent are not directed to an abstract idea, nor are the claims directed merely to labeling different molecules or objects with different labels or all implementations thereof; (3) labeling nucleic acids with different labels is not an abstract idea; (4) the claims do not describe concepts long-practiced in society but rather claim novel and innovative methods used for quantitation of the abundance of genetic material in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, that improved upon prior art methods; and (5) the claims do not merely limit an abstract idea to a specific technological environment, *e.g.*, DNA and nucleic acids.

200. Skilled artisans would further understand that the inventions claimed in the ’808 patent provide numerous improvements and benefits over prior art methods. In addition to addressing the aforementioned drawbacks and limitations of the prior art, the inventions of the ’808 patent also:

- Confer a separate, determinable identity to occurrences of targets that may otherwise be indistinguishable as a result of the diverse labels or label-tags in the newly-generated molecule;
- Allow simultaneous quantitation of multiple target sequences;
- Take quantitative measurements of copies of identical target molecules in a solution by transformation of the information into a digital process for detecting the presence of different or diverse labels or label-tags that are attached to the identical target molecules in a manner that is extremely sensitive and can be multiplexed to high levels;
- Allow newly-generated molecules comprising targets and diverse labels or label-tags to be amplified freely without impacting quantitation of the targets; and

- Convert an analog readout of hybridization signal intensities on arrays into a measurable process that can be scored digitally on the arrays by leveraging the diverse label-tags found in each newly-generated molecule, providing a clear cost-advantage over existing techniques.

See, e.g., '808 patent at 3:37-39; 3:49-62; 4:1-4; 4:8-12; 14:36-40; 21:10-12; 22:52-59; 22:62-65; 23:3-7; 23:11-18; 23:55-59; 25:21-24; 31:40-41; 32:21-24; 32:57-67. Skilled artisans would understand that these benefits inure from the claimed inventions and inventive concepts (alone or in combination with the other limitations), including the diverse label-tag sequences being attached to target molecules from a single cell, wherein the ratio of the number of diverse label-tag sequences to the number of occurrences of a target molecule is greater than 5, to generate new target-label-tag molecules comprising a label-tag and a portion of a complementary sequence of a target molecule, including through stochastic attachment of diverse label-tags and/or by multiplexing to allow simultaneous quantitation of multiple molecules, the amplification of the target-label-tag molecules, and the other limitations (alone or in combination) of the independent and dependent claims, including as described above and below.

201. Skilled artisans would further understand that quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, was not well-understood, routine, or conventional at the time of the invention. They would further understand that the steps recited in the claims of the '808 patent, either alone or in combination, were not well-understood, routine, or conventional at the time of the invention and are integral to addressing the problems in the prior art remedied by the improved functionality of the claimed inventions and inventive concepts. They would further understand that the specific structures and manipulations recited in the claims of the '808 patent, including a single cell, an

indexed library, a specified container, a plurality of target molecules from the single cell, a plurality of diverse label-tags, diverse label-tag sequences, wherein the ratio of the number of diverse label-tag sequences to the number of occurrences of a target molecule is greater than 5, a complementary sequence of a target molecule, amplified product, sequencing at least a portion of the amplified product, and a plurality of newly-generated target-label-tag molecules, including through stochastic hybridization of diverse label-tags and/or by multiplexing to allow simultaneous quantitation of multiple molecules, are essential to addressing the problems remedied by the improved functionality of the claimed inventions. *See also supra* ¶ 200.

202. They would further understand that additional limitations (alone or in combination) of at least dependent claims 2-4, 6-11, 13-17, 20, 21, 23-27, and 29 are not directed to an abstract idea and recite inventive concepts for additional reasons, including that they recite additional structure; are not routine, conventional, or well-known; improve upon prior art methods by providing increased functionality; and do not risk preemption as a result of the additional limitations in those claims.

203. They would further understand that claim 6 of the ’358 patent is not substantially similar to nor linked to any abstract idea, much less the same abstract idea as all claims of the ’808 patent, including because the claims of the ’808 patent recite additional, tangible structures and manipulations, provide further improvements and innovations, address additional technological problems, add one or more inventive concepts, and involve different facts relating to issues of preemption and patentability that are not reflected in claim 6 of the ’358 patent. *See also supra* at ¶¶ 200-02.

204. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues

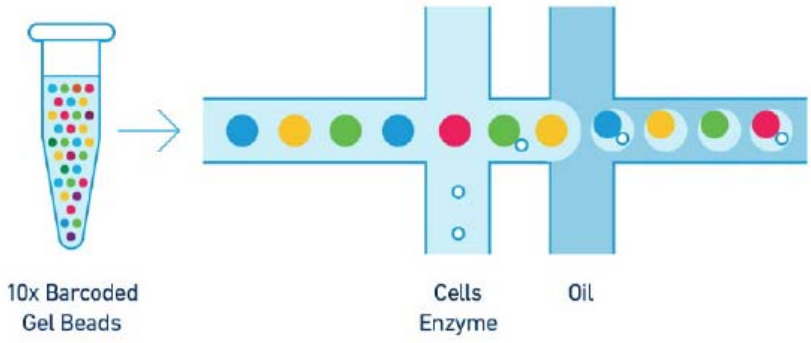
to infringe one or more claims of the ’808 patent, including at least claim 1 of the ’808 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

205. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the ‘808 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD’s ability to demonstrate Defendant’s direct, indirect, literal, or equivalent infringement of additional ’808 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

206. As shown below the **Single Cell 3’ Workflow** and **Single Cell 5’ Workflow** Accused Products are “a method for determining a number of occurrences of a target molecule from a single cell” because the “Cell Ranger™” analysis software performs “demultiplexing, alignment, and gene counting”[107] and because the information generated with the Cell Ranger software is used for “cell clustering, cell type classification, and differential gene expression at a scale of hundreds to millions of cells.” [108] “Cell Ranger is a set of analysis pipelines [that perform gene expression analysis by] alignment, filtering, barcode counting, and UMI counting,”[109] which is “determining a number of occurrences of a target molecule from a single cell.” “The 10x™ GemCode™ Technology partition[s] thousands of cells” with the 10x

[107] “Chromium™ Single Cell 3’ Reagent Kits v2 User Guide” (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); “Chromium™ Single Cell V(D)J Reagent Kits User Guide” (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[108] *Id.*
[109] https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger

Barcoded Gel Beads "into nanoliter-scale Gel Bead-In-EMulsions (GEMs)."[110] As illustrated below[111], "the cells are delivered at a limiting dilution, such that the majority (~90-99%) of generated GEMs contains no cell, while the remainder largely contain a single cell."[112]



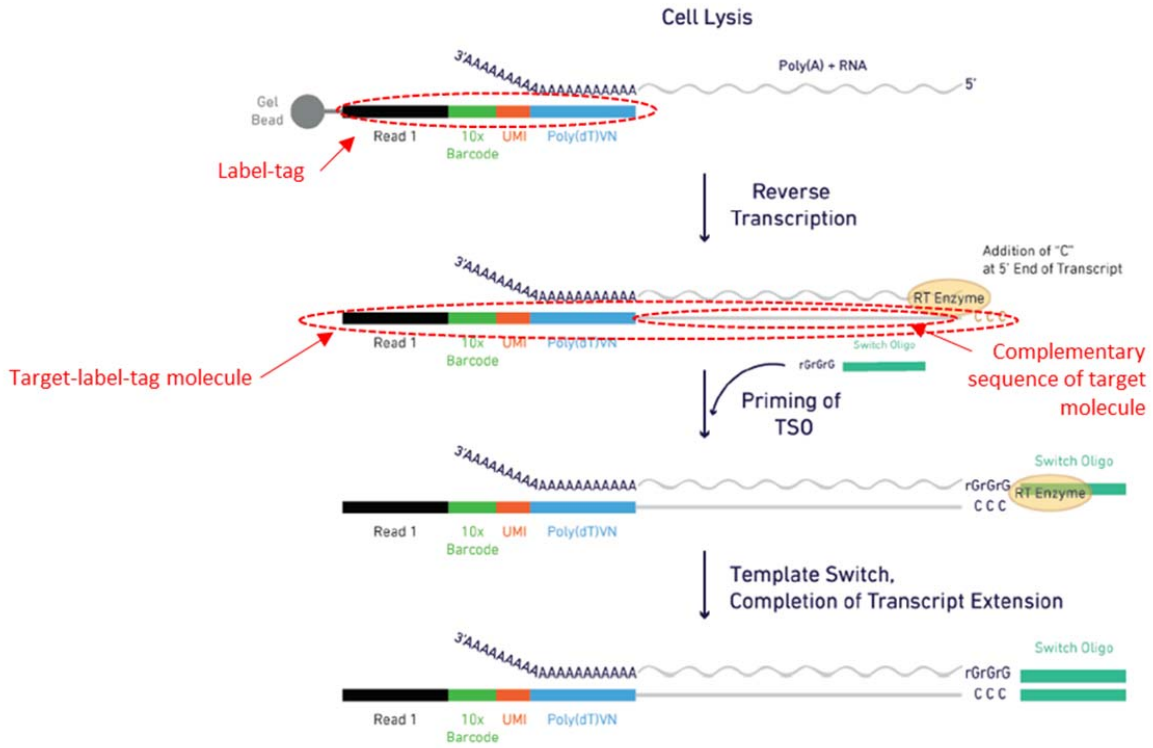
207. In the **Single Cell 3' Workflow** Accused Products, "generating an indexed library by performing a labeling step comprising: (i) combining in a specified container a sample comprising a plurality of target molecules from the single cell with a plurality of diverse label-tag" as recited in step (a) and substep (a)(i) of claim 1 occurs because "[t]he contents of the GEM (oligos, lysed cell components and Master Mix) are incubated in an RT reaction to generate full-length, barcoded cDNA from the poly A-tailed mRNA transcripts."[113] In the **Single Cell 3' Workflow** Accused Products, "the ratio of the number of diverse label-tag sequences to the number of occurrences of a target molecule is greater than 5" as recited in step (a) and substep (a)(i) of claim 1 because "[t]he 10x™ GemCode™ Technology samples a pool of

[110] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[111] *Id.*
[112] *Id.*
[113] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); *see also* "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

~ 750000 barcodes to separately index each cell's transcriptome,"[114] and because the "number of each of the plurality of target molecules" is less than 150000. For example, single cell analysis shows "~4,500 genes and 27,000 transcripts […] detected" in human and mouse cells.[115]

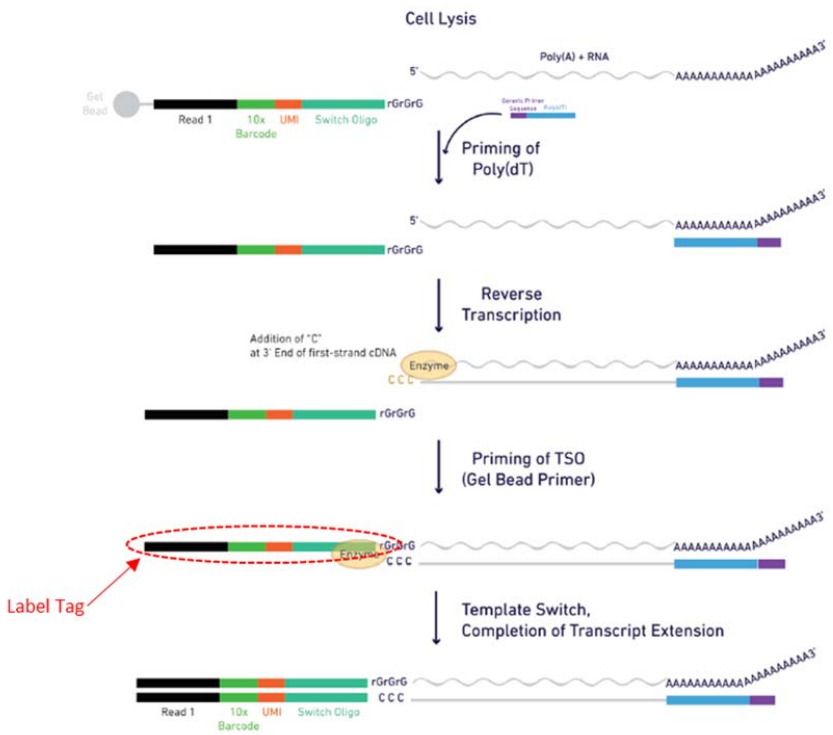
208. In the **Single Cell 3' Workflow** Accused Products, "generating a plurality of target-label-tag molecules by hybridizing label-tags of the plurality of diverse label-tag to target molecules of the plurality of target molecules and performing an extension reaction, wherein a target-label-tag molecule comprises a label-tag and a portion of a complementary sequence of a target molecule" as recited in substep (ii) of step (a) occurs because a "reverse transcription reaction is primed by the barcoded Gel Bead oligo."[116] As illustrated below[117], the "label-tags of the plurality of diverse label-tag " hybridize to "target molecules of the plurality of target molecules " and thereby generate the "a plurality of target-label-tag molecules " by an extension reaction. Further, as illustrated below[118], the resulting "target-label-tags molecules" comprise "a label-tag and a portion of a complementary sequence of a target molecule" as recited in substep (ii) of step (a).

[114] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[115] Chromium™ Single Cell Solutions 10x Single Cell App Note (10x_Single_Cell_App_Note.pdf)
[116] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[117] *Id.* at Figure 3 (cropped, markings added)
[118] *Id.*



209. In the **Single Cell 5' Workflow** Accused Products, "generating a plurality of target-label-tag molecules by hybridizing label-tags of the plurality of diverse label-tag to target molecules of the plurality of target molecules and performing an extension reaction" as recited in claim 1 step (a) substep (ii) occurs because "[t]he contents of the GEM […] are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA from poly-adenylated mRNA."[119] As illustrated below[120], the "label-tags of the plurality of diverse label tags" hybridize to a reverse transcription product which is the "target molecule."

[119] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[120] *Id.* at Figure 3 (cropped, markings added)

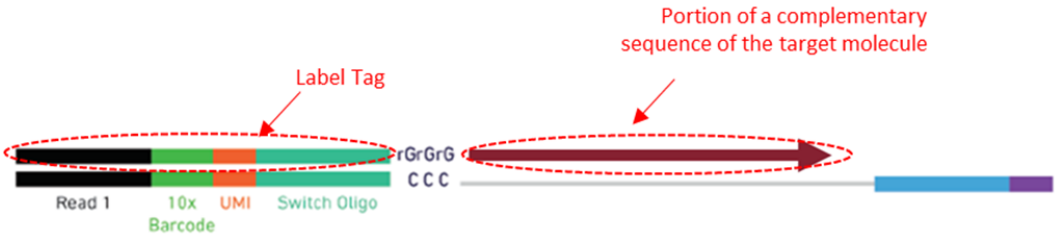


210. On information and belief, the RNA molecule will dissociate from DNA prior to the PCR amplification step to form the structure illustrated below:[121]

211. In the next step of the **Single Cell 5' Workflow** Accused Products, PCR amplification is performed by "Direct Target Enrichment" or "cDNA Amplification followed by Target Enrichment."[122] On information and belief, as illustrated with the arrow below, performing either of the PCR extension step will result in "performing an extension reaction, wherein a target-label-tag molecule comprises the label-tag and a portion of a complementary

[121] This illustration is a modification of the figure in the 10x materials adapted to demonstrate the hybrid arising due to dissociation of RNA from the hybrid in the last step of the figure in the preceding paragraph.
[122] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

sequence of a target molecule." As is illustrated below, the extension products generated in this step are "a target-label-tag molecule [comprising] the label-tag and a portion of a complementary sequence of the target molecule."

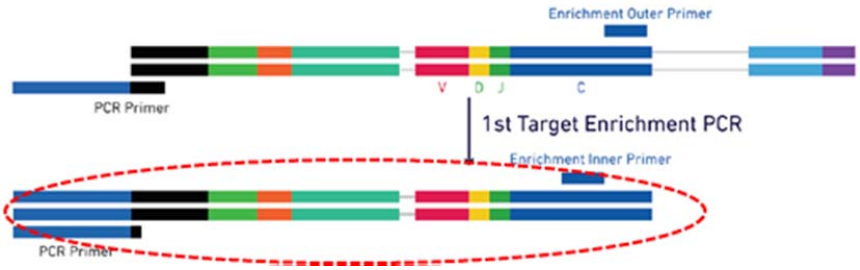


212. In the **Single Cell 3' Workflow** Accused Products, the "amplifying the target-label-tag molecules from the indexed library" recited in step (b) of claim 1 occurs because "[t]he GEMs are then 'broken', pooling single-stranded, barcoded cDNA molecules from every cell" and "[a] bulk PCR-amplification and Enzymatic Fragmentation" follows.[123] As illustrated below[124], this PCR step results in amplification of the target-label-tag molecules.

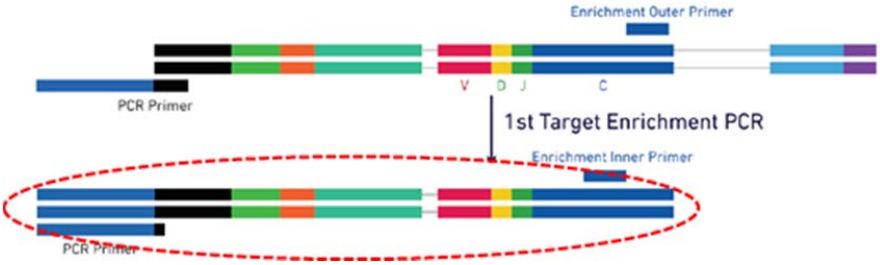
213. In the **Single Cell 5' Workflow** Accused Products, the "amplifying the target-label-tag molecules from the indexed library" recited in step (b) of claim 1 occurs because "[t]he Single Cell V(D)J Solution offers the option to generate" by PCR amplification, "Direct Target Enrichment" or "cDNA Amplification followed by Target Enrichment."[125] As illustrated

[123] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[124] *Id.* at Figure 3 (cropped, markings added)
[125] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

below[126], the PCR step in "Direct Target Enrichment" option results in amplification of the target-label-tag molecules.



214. As illustrated below[127], the PCR step in "cDNA Amplification followed by Target Enrichment" option also results in amplification of the target-label-tag molecules.



215. In the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products, the "sequencing at least a portion of the amplified product of step (b) to determine a number of different label-tag sequences associated with the portion of the complementary sequence of a target molecule from the single cell" as recited in step (c) of claim 1 occurs because "[d]uring library preparation, sequence components essential for Illumina sequencing

[126] *Id.* at Figure 3 (cropped)
[127] *Id.* at Figure 4 (cropped)

and downstream data analysis are incorporated into the final library construct,"[128] and because the Single Cell 3' and Single Cell 5' Workflows produce "Illumina-ready sequencing libraries" and the libraries "generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions."[129]

216. Further, sequencing in the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products produces a result wherein "the number of different label-tag sequences indicates the number of occurrences of the target molecule from the single cell" because once these libraries are "generated and sequenced," "the 10x Barcodes are used to associate individual reads back to the individual partitions."[130] Correlation between "the number of different label-tag sequences" and "the number of occurrences of the target molecule from the single cell" as recited in step (c) occurs because the amplified products of step (b) of claim 1 are processed with "Cell Ranger™" analysis software to perform "demultiplexing, alignment, and gene counting."[131] The information generated with the Cell Ranger™ software can be used for "cell clustering, cell type classification, and differential gene expression at a scale of hundreds to millions of cells."[132] "Cell Ranger™ is a set of analysis pipelines [that perform gene expression analysis by] alignment, filtering, barcode counting, and UMI counting,"[133] which is a sub-element wherein "the number of different label-tag sequences indicates the number of occurrences of the target molecule from the single cell."

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[128] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[129] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[130] *Id.*
[131] *Id.*
[132] *Id.*
[133] https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger

217. As demonstrated in **Exhibit 23**, the **Single Cell 3' Workflow** Accused Products satisfy the claim limitations of at least claims 1-4, 7-11, 13-17, 20, 21, 23-27, and 29 of the '808 patent. As demonstrated in **Exhibit 24**, the **Single Cell 5' Workflow** Accused Products satisfy the claim limitations of at least claims 1-4, 6, 9-11, 13-16, 20, 21, 23-27, and 29 of the '808 patent. As demonstrated in **Exhibit 25**, the **Spatial Transcriptomics** Accused Products satisfy the claim limitations of at least claims 1-4, 6-11, 13-17, 20, 21, 23-27, and 29 of the '808 patent. The demonstration of infringement illustrated in **Exhibits 23, 24, and 25** is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '808 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

218. 10X has also induced and currently induces infringement of at least claim 1 of the '808 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, 10X knows infringes at least claim 1 of the '808 patent.[134] 10X has known of the '808 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the '808 patent.

219. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the '808 patent. 10X has designed the Accused

[134] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

Products specifically to be used in a manner as claimed at least claim 1 of the '808 patent.[135] As such, the accused products are a material component of the patented combination, specifically designed to be used according to at least claim 1 of the '808 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the '808 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the '808 patent. 10X has knowledge of the '808 patent and is aware that the Accused Products are especially made to be used in a system that infringes the '808 patent.

220. Defendant's infringement has been willful and deliberate because Defendant has known of the '808 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the '808 patent.

221. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 6
(INFRINGEMENT OF THE '659 PATENT)

222. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

[135] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

223. U.S. Patent No. 9,708,659 (the "'659 patent"), entitled "Digital Counting of Individual Molecules by Stochastic Attachment of Diverse Labels," was duly and legally issued on July 18, 2017 to inventors Stephen P. A. Fodor and Glenn K. Fu. A true and accurate copy of the '659 patent is attached as **Exhibit 6**.

224. Skilled artisans would understand that, prior to the inventions of the '659 patent, numerous problems existed in the prior art relating to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample. Analytical methods for measuring the abundance of different molecules in a sample (*e.g.*, nucleic acids) existed, but were generally comparative techniques and were limited by signal to noise issues. Prior art techniques offered limited utility in cases where samples comprised a large number of different molecules or where the number of molecules of interest was low in comparison to the number of background molecules. *See, e.g.*, '659 patent at 2:59-63; 3:7-10; 3:18-28; 3:33-37. Other drawbacks and limitations in prior art methods included, for example:

- A requirement for one-to-one correspondence between probe sequences and oligonucleotide tag sequences in techniques where oligonucleotide tags are hybridized to their complements;
- A requirement for customizing dilutions for each type of molecule in digital methods, which generally limited the practice to analysis of a small number of different molecules and required physical separation of molecules;
- An inability to ensure that all sequences are captured in microarray and sequencing based technologies;
- A limited ability to correlate intensity of hybridization signal (or signal intensity) to the concentration of target molecules in hybridization-based methods;
- Variability relating to probe hybridization differences and cross-reactivity;
- Limitations on the ability to stochastically attach labels to known targets, in a known location, in the context of sequencing and amplification-based methodologies; and
- Dynamic range limitations in array-based methods.

See, e.g., *id.* at 2:7-15; 2:45-3:24; 3:33-37; 14:51-55; 19:55-64; 22:64-67; 23:19-26; 23:38-42; 24:23-27; 24:51-65; 33:14-24; 33:51-34:2.

225. Skilled artisans would understand that the inventions as recited in the common specifications of the Fodor patents are generally directed to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules. *See, e.g.*, '659 patent at 3:41-4:9 ("High-sensitivity single molecule digital counting by the stochastic labeling of a collection of identical molecules is disclosed. Each copy of a molecule randomly chooses from a non-depleting reservoir of diverse labels. . . . The labeled fragments for a target molecule of choice are detected with high specificity using a microarray readout system, and with DNA sequencing. The results are consistent with a stochastic process, and yield highly precise relative and absolute counting statistics of selected molecules within a vast background of other molecules. . . . The attachment of the label confers a separate, determinable identity to each occurrence of targets that may otherwise be indistinguishable."). The claimed inventions of the '659 patent are directed in general to a system for counting a number of nucleic acid target molecules that are present in a single cell. The system comprises at least more different labels (from a set of diverse labels) than the number of nucleic acid target molecules. The system further comprises reaction vessels for attaching the different labels to the nucleic acid target molecules and processing software for counting the number of nucleic acid target molecules from a number of labeled nucleic acid target molecules detected. More specifically, skilled artisans would understand that the asserted independent claims of the '659 patent are directed to specific implementations of the inventions of the Fodor patents, reciting "[a] system for counting

n, wherein n is a number of nucleic acid target molecules that are present in a single cell" comprising "a diverse set of labels, wherein the set comprises m different labels, wherein the ratio of m to n is greater than 5," "a plurality of reaction vessels for attaching a label from the diverse set of labels to each occurrence of the nucleic acid target molecules from each single cell from said sample comprising cells to generate a set of labeled nucleic acid target molecules, wherein the individual labeled nucleic acid target molecules comprise all or a portion of the complementary sequence of a nucleic acid target molecule and a label from the diverse set of labels," and "processing software for counting [a number of nucleic acid target molecules present in a single cell]" ('659 patent, cl. 1) and "[a] system for counting n, wherein n is a number of nucleic acid target molecules that are present in a single cell" comprising "a diverse set of labels comprising a plurality of oligonucleotides attached to each bead of a plurality of beads, wherein the set of labels comprises m different labels, wherein m>n, and wherein each oligonucleotide of the plurality of oligonucleotides comprises a common sequence, a variable target label sequence, and a target-specific recognition sequence capable of attaching to or hybridizing to the target molecule," "a plurality of reaction vessels comprising a single cell from said sample comprising cells and a single bead from said plurality of beads, wherein each reaction vessel is used for attaching a label from the diverse set of labels attached to the bead contained therein to each occurrence of the nucleic acid target molecules from the single cell contained therein to generate a set of labeled nucleic acid target molecules, wherein the individual labeled nucleic acid target molecules comprise all or a portion of the complementary sequence of a nucleic acid target molecule and a label from the diverse set of labels," and "processing software for counting [a number of nucleic acid target molecules present in a single cell]" ('659 patent, cl. 13).

226. Skilled artisans would further understand that (1) quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, is not an abstract idea but rather a concrete and tangible method for manipulating molecules and generating new molecules that provide an improved method of quantitation; (2) the specific implementations of the inventions of the Fodor patents recited in the claims of the ’659 patent are not directed to an abstract idea, nor are the claims directed merely to labeling different molecules or objects with different labels or all implementations thereof; (3) labeling nucleic acids with different labels is not an abstract idea; (4) the claims do not describe concepts long-practiced in society but rather claim novel and innovative systems used for quantitation of the abundance of genetic material in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, that improved upon prior art methods; and (5) the claims do not merely limit an abstract idea to a specific technological environment, *e.g.*, DNA and nucleic acids.

227. Skilled artisans would further understand that the inventions claimed in the ’659 patent provide numerous improvements and benefits over prior art methods. In addition to addressing the aforementioned drawbacks and limitations of the prior art, the inventions of the ’659 patent also:

- Confer a separate, determinable identity to occurrences of targets that may otherwise be indistinguishable as a result of the diverse labels or label-tags in the newly-generated molecule;
- Allow simultaneous quantitation of multiple target sequences;

- Take quantitative measurements of copies of identical target molecules in a solution by transformation of the information into a digital process for detecting the presence of different or diverse labels or label-tags that are attached to the identical target molecules in a manner that is extremely sensitive and can be multiplexed to high levels;
- Allow newly-generated molecules comprising targets and diverse labels or label-tags to be amplified freely without impacting quantitation of the targets; and
- Convert an analog readout of hybridization signal intensities on arrays into a measurable process that can be scored digitally on the arrays by leveraging the diverse label-tags found in each newly-generated molecule, providing a clear cost-advantage over existing techniques.

See, e.g., '659 patent at 3:41-43; 3:53-67; 4:7-9; 4:14-18; 14:51-55; 21:39-41; 23:19-26; 23:29-32; 23:38-42; 23:45-52; 24:23-27; 25:58-61; 32:20-21; 33:1-4; 33:40-50. Skilled artisans would understand that these benefits inure from the claimed inventions and inventive concepts (alone or in combination with the other limitations), including the label from the diverse set of labels being attached to each occurrence of the nucleic acid target molecules from each single cell to generate a set of labeled nucleic acid target molecules comprising all or a portion of the complementary sequence of a nucleic acid target molecule and a diverse label, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, and the other limitations (alone or in combination) of the independent and dependent claims, including as described above and below.

228. Skilled artisans would further understand that quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, was not well-understood, routine, or conventional at the time of the invention. They would further understand that the systems recited in the claims of the '659 patent, including the limitations recited above and below, comprising reaction vessels for attaching diverse labels to

nucleic acid target molecules from a single cell, were not well-understood, routine, or conventional at the time of the invention and are integral to addressing the problems in the prior art remedied by the improved functionality of the claimed inventions and inventive concepts. They would further understand that the claims of the ’659 patent recite concrete and tangible systems that amount to significantly more than a mere label, as they are designed for quantitation of the abundance of genetic material in a sample through the generation of a set of labeled nucleic acid target molecules by attaching diverse labels to nucleic acid target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple nucleic acid target molecules. They would further understand that the specific structures recited in the claims of the ’659 patent, including a number of nucleic acid target molecules, a single cell, a diverse set of labels, wherein the number of diverse labels is at least greater than the number of nucleic acid target molecules, a plurality of reaction vessels for attaching a label from the diverse set of labels to each occurrence of the nucleic acid target molecules from each single cell, a newly-generated set of labeled nucleic acid target molecules, wherein the individual labeled nucleic acid target molecules comprise all or a portion of the complementary sequence of a nucleic acid target molecule and a label from the diverse set of labels, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, and processing software are essential to addressing the problems remedied by the improved functionality of the claimed inventions. *See also supra* ¶ 227.

229. They would further understand that the additional limitations (alone or in combination) of at least dependent claims 4-11, 16, 18, and 19 are not directed to an abstract idea and recite inventive concepts for additional reasons, including that they recite additional

structure; are not routine, conventional, or well-known; improve upon prior art methods by providing increased functionality; and do not risk preemption as a result of the additional limitations in those claims.

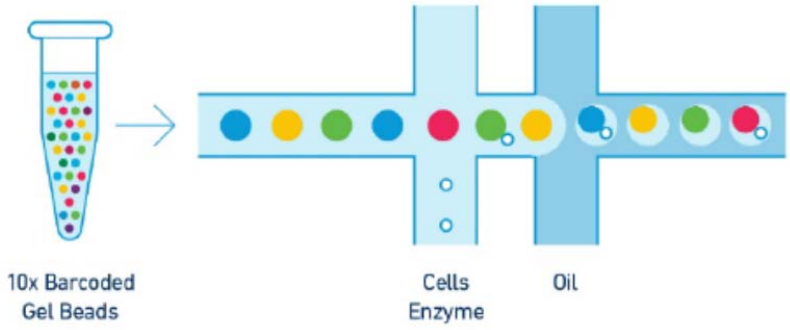
230. They would further understand that claim 6 of the ’358 patent is not substantially similar to nor linked to any abstract idea, much less the same abstract idea as all claims of the ’659 patent, including because the claims of the ’659 patent recite additional, tangible structures and manipulations, provide further improvements and innovations, address additional technological problems, add one or more inventive concepts, and involve different facts relating to issues of preemption and patentability that are not reflected in claim 6 of the ’358 patent, and because claim 6 of the ’358 patent recites a method while the ’659 patent recites systems. *See also supra* at ¶¶ 227-29.

231. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the ’659 patent, including at least claim 1 of the ’659 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

232. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the ‘659 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD’s ability to demonstrate Defendant’s direct, indirect, literal, or equivalent infringement of additional ’659 patent claims,

including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

233. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are "a system for counting n, wherein n is a number of nucleic acid target molecules that are present in a single cell from a sample comprising cells" as recited in claim 1, because "[t]he 10x™ GemCode™ Technology samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome . . . by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs)."[136] As illustrated below,[137] "the cells are delivered at a limiting dilution, such that the majority (~90-99%) of generated GEMs contains no cell, while the remainder largely contain a single cell."



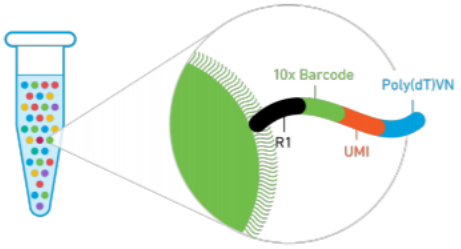
234. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are for "counting n, wherein n is a number of nucleic acid target molecules" because the "Cell Ranger™" analysis software performs "demultiplexing, alignment, and gene counting"[138] and because the information generated with the Cell Ranger software is used for "cell clustering, cell type classification, and differential gene expression at a scale of hundreds to

[136] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[137] *Id.*
[138] *Id.*

millions of cells."[139] "Cell Ranger is a set of analysis pipelines [that perform gene expression analysis by] alignment, filtering, barcode counting, and UMI counting,"[140] which is "counting n, wherein n is a number of nucleic acid target molecules system produces."

235. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products comprise "a diverse set of labels, wherein the set comprises m different labels" because "Gel Beads are… functionalized with millions of copies of a 10x Barcoded primer."[141] As illustrated below[142], the system comprises "~ 750000 barcodes to separately index each cell's transcriptome."[143] As shown below[144], the "diverse set of labels, wherein the set comprises m different labels" in the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products is the "10nt Unique Molecular Identifier."

Each Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1):



i. Partial Illumina Read 1 sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 30 nt Poly(dT) primer sequence

Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

[139] *Id.*
[140] https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger
[141] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[142] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[143] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[144] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

236. In the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products, "the ratio of m to n is greater than 5" as recited in step (a) because "[t]he 10x™ GemCode™ Technology… samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[145] and because the "number of nucleic acid target molecules that are present in a single cell" is less than 150000. For example, single cell analysis shows "~4,500 genes and 27,000 transcripts […] detected" in human and mouse cells.[146]

237. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products comprise "a plurality of reaction vessels for attaching a label from the diverse set of labels to each occurrence of the nucleic acid target molecules from each single cell from said sample comprising cells" as recited in step (b) of claim 1 because "[t]he 10x™ GemCode™ Technology… partition[s] thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs),"[147] and because "[o]nce partitioned, the Gel Bead dissolves and its oligo primers are

[145] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide": CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf

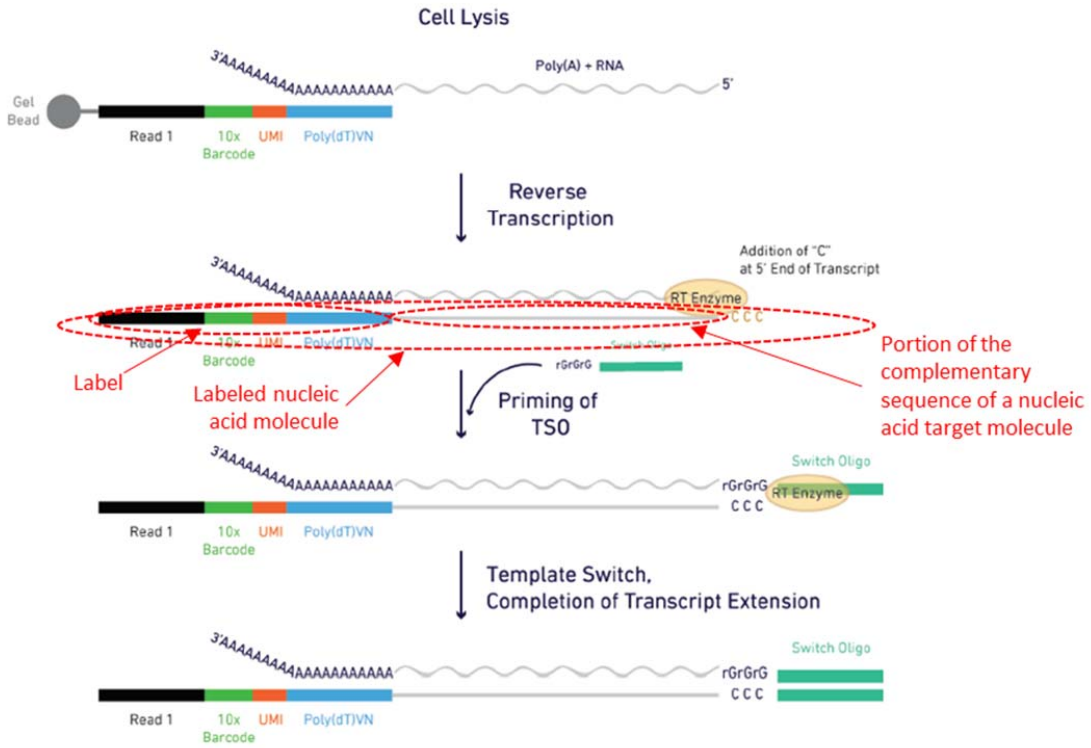
[146] "Chromium™ Single Cell Solutions 10x Single Cell App Note" (10x_Single_Cell_App_Note.pdf)

[147] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

released into the aqueous environment of the GEM" [148] and because "[t]he contents of the GEM […] are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA from poly-adenylated mRNA."[149]

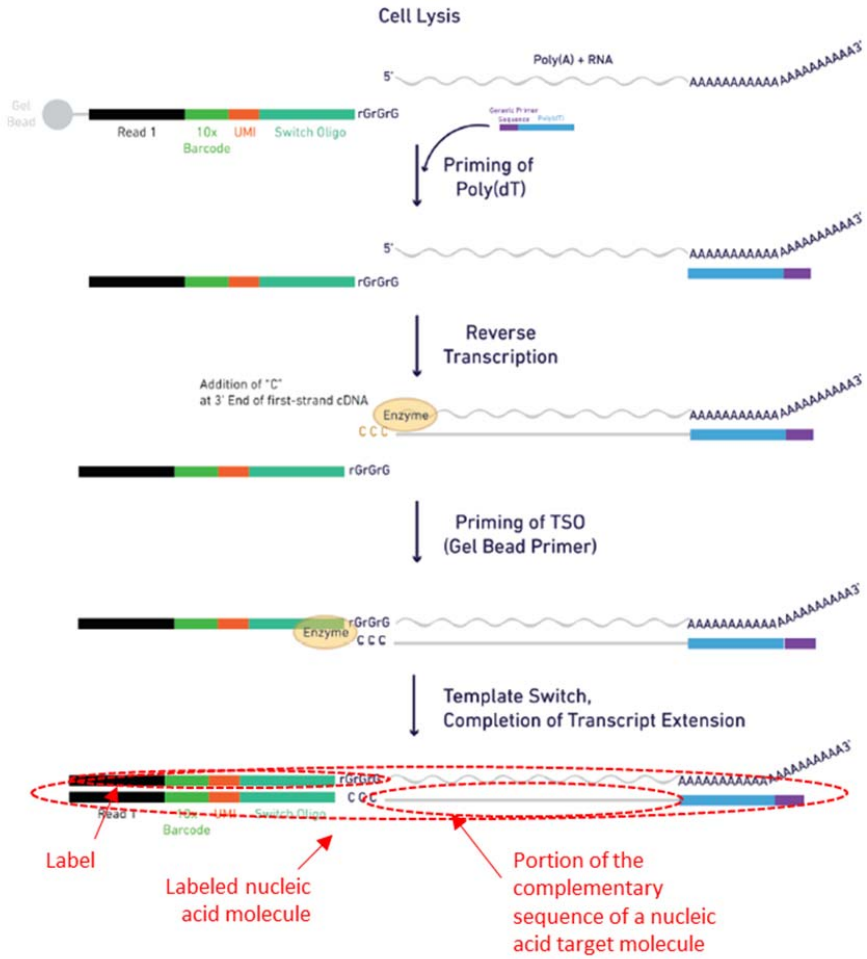
238. The **Single Cell 3' Workflow** Accused Products comprise "a plurality of reaction vessels for attaching a label from the diverse set of labels to each occurrence of the nucleic acid target molecules from each single cell from said sample comprising cells to generate a set of labeled nucleic acid target molecules" as recited in step (b) of claim 1 because a "reverse transcription reaction is primed by the barcoded Gel Bead oligo."[150] As illustrated below[151], the "labels" are attached to "nucleic acid target molecules from each single cell" and thereby generate the "set of labeled nucleic acid target molecules" by an extension reaction, which "comprise all or a portion of the complementary sequence of a nucleic acid target molecule and a label from the diverse set of labels" as recited in step (b) of claim 1.

[148] TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[149] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); *see also* "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.docx)
[150] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[151] *Id.* at Figure 3 (cropped, markings added)



239. The **Single Cell 5' Workflow** Accused Products comprise "a plurality of reaction vessels for attaching a label from the diverse set of labels to each occurrence of the nucleic acid target molecules from each single cell from said sample comprising cells to generate a set of labeled nucleic acid target molecules" as recited in step (a) of claim 1 because "[t]he contents of the GEM […] are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA from poly-adenylated mRNA."[152] As illustrated below[153], the "labels" hybridize to a reverse transcription product of the "nucleic acid target molecules." The "set of labeled nucleic acid target molecules" are generated upon a "template switch" step, each of which "comprise all or a portion of the complementary sequence of a nucleic acid target molecule and a label from the diverse set of labels" as recited in step (b) of claim 1.

[152] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[153] *Id.* at Figure 3 (cropped, markings added)



240. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products comprise "processing software for counting n from a number of labeled nucleic acid target molecules detected" as recited in step (c) of claim 1 because "the 10x Barcodes are used to associate individual reads back to the individual partitions[154] using "Cell Ranger™" analysis software to perform "demultiplexing, alignment, and gene counting."[155] The information

[154] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[155] *Id.*

generated with the Cell Ranger software is used for "cell clustering, cell type classification, and differential gene expression at a scale of hundreds to millions of cells."[156]

241. As demonstrated in **Exhibit 26**, the **Single Cell 3' Workflow** Accused Products satisfy the claim limitations of at least claims 1, 4, 6-11, 13, 16, 18, and 19 of the '659 patent. As demonstrated in **Exhibit 27**, the **Single Cell 5' Workflow** Accused Products satisfy the claim limitations of at least claims 1, 4, 6-11, 13, 16, 18, and 19 of the '659 patent. As demonstrated in **Exhibit 28**, the **Spatial Transcriptomics** Accused Products satisfy the claim limitations of at least claims 1 and 4-6 of the '659 patent. The demonstration of infringement illustrated in **Exhibits 26, 27, and 28** is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '659 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

242. 10X has also induced and currently induces infringement of at least claim 1 of the '659 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, 10X knows infringes at least claim 1 of the '659 patent.[157] 10X has known of the '659 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the '659 patent.

243. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the '659 patent. 10X has designed the Accused

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[156] *Id.*
[157] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

Products specifically to be used in a manner as claimed at least claim 1 of the '659 patent.[158] As such, the Accused Products are a material component of the patented combination, specifically designed to be used according to at least claim 1 of the '659 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the '659 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the '659 patent. 10X has knowledge of the '659 patent and is aware that the Accused Products are especially made to be used in a system that infringes the '659 patent.

244. Defendant's infringement has been willful and deliberate because Defendant has known of the '659 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the '659 patent.

245. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 7
(INFRINGEMENT OF THE '502 PATENT)

246. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

[158] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

247. U.S. Patent No. 9,845,502 (the "'502 patent"), entitled "Digital Counting of Individual Molecules by Stochastic Attachment of Diverse Labels," was duly and legally issued on December 19, 2017 to inventors Stephen P. A. Fodor and Glenn K. Fu. A true and accurate copy of the '502 patent is attached as **Exhibit 7**.

248. Skilled artisans would understand that, prior to the inventions of the '502 patent, numerous problems existed in the prior art relating to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample. Analytical methods for measuring the abundance of different molecules in a sample (*e.g.*, nucleic acids) existed, but were generally comparative techniques and were limited by signal to noise issues. Prior art techniques offered limited utility in cases where samples comprised a large number of different molecules or where the number of molecules of interest was low in comparison to the number of background molecules. *See, e.g.*, '502 patent at 3:57-61; 4:5-8; 4:15-25; 4:30-34. Other drawbacks and limitations in prior art methods included, for example:

- A requirement for one-to-one correspondence between probe sequences and oligonucleotide tag sequences in techniques where oligonucleotide tags are hybridized to their complements;
- A requirement for customizing dilutions for each type of molecule in digital methods, which generally limited the practice to analysis of a small number of different molecules and required physical separation of molecules;
- An inability to ensure that all sequences are captured in microarray and sequencing based technologies;
- A limited ability to correlate intensity of hybridization signal (or signal intensity) to the concentration of target molecules in hybridization-based methods;
- Variability relating to probe hybridization differences and cross-reactivity;
- Limitations on the ability to stochastically attach labels to known targets, in a known location, in the context of sequencing and amplification-based methodologies; and
- Dynamic range limitations in array-based methods.

See, e.g., *id.* at 3:5-13; 3:43-4:21; 4:30-34; 14:35-39; 19:38-47; 22:28-31; 22:50-57; 23:2-6; 23:54-58; 24:15-29; 32:45-55; 33:15-33.

249. Skilled artisans would understand that the inventions as recited in the common specifications of the Fodor patents are generally directed to quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules. *See, e.g.*, '502 patent at 4:38-5:6 ("High-sensitivity single molecule digital counting by the stochastic labeling of a collection of identical molecules is disclosed. Each copy of a molecule randomly chooses from a non-depleting reservoir of diverse labels. . . . The labeled fragments for a target molecule of choice are detected with high specificity using a microarray readout system, and with DNA sequencing. The results are consistent with a stochastic process, and yield highly precise relative and absolute counting statistics of selected molecules within a vast background of other molecules. . . . The attachment of the label confers a separate, determinable identity to each occurrence of targets that may otherwise be indistinguishable."). The claimed inventions of the '502 patent are directed in general to a method for determining a number of occurrences of a target molecule from a single cell, the method comprising steps of generating an indexed library comprising a plurality of target-label-tag molecules by performing a labeling step that combines target molecules with diverse label-tags, wherein the ratio of the number of diverse label-tags to the number of target molecules is greater than 5, to thereby generate target-label-tag molecules via hybridization and an extension reaction, amplifying the plurality of target-label-tag molecules to generate amplified products, and sequencing at least a portion of the plurality of amplified products. More specifically, skilled artisans would understand that the asserted independent

claim of the ’502 patent is directed to specific implementations of the inventions of the Fodor patents, reciting “generating an indexed library by performing a labeling step” comprising “combining each of a target molecule from a plurality of target molecules from a single cell with a label-tag from a plurality of diverse label-tags, wherein the ratio of the number of the plurality of diverse label-tags to the number of each of the plurality of target molecules is greater than 5” and “generating the indexed library comprising a plurality of target-label-tag molecules by hybridizing the label-tag of the plurality of diverse label-tags to the target molecule of the plurality of target molecules and performing an extension reaction, wherein a target-label-tag molecule comprises the label-tag and a portion of a complementary sequence of the target molecule,” “amplifying the plurality of target-label-tag molecules from the indexed library to generate a plurality of amplified products,” and “sequencing at least a portion of the plurality of amplified products . . . to determine a number of different label-tag sequences associated with the portion of the complementary sequence of the target molecule from the single cell” (’502 patent, cl. 1). They would further understand that asserted dependent claims are directed to further specific implementations of the methods recited in the independent claims, including “wherein the method is multiplexed” (’502 patent, cl. 3) and “wherein the attaching is stochastic” (’502 patent, cl. 24).

250. Skilled artisans would further understand that (1) quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, is not an abstract idea but rather a concrete and tangible method for manipulating molecules and generating new molecules that provide an improved method of quantitation; (2) the specific

implementations of the inventions of the Fodor patents recited in the claims of the ’502 patent are not directed to an abstract idea, nor are the claims directed merely to labeling different molecules or objects with different labels or all implementations thereof; (3) labeling nucleic acids with different labels is not an abstract idea; (4) the claims do not describe concepts long-practiced in society but rather claim novel and innovative methods used for quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, that improved upon prior art methods; and (5) the claims do not merely limit an abstract idea to a specific technological environment, *e.g.*, DNA and nucleic acids.

251. Skilled artisans would further understand that the inventions claimed in the ’502 patent provide numerous improvements and benefits over prior art methods. In addition to addressing the aforementioned drawbacks and limitations of the prior art, the inventions of the ’502 patent also:

- Confer a separate, determinable identity to occurrences of targets that may otherwise be indistinguishable as a result of the diverse labels or label-tags in the newly-generated molecule;
- Allow simultaneous quantitation of multiple target sequences;
- Take quantitative measurements of copies of identical target molecules in a solution by transformation of the information into a digital process for detecting the presence of different or diverse labels or label-tags that are attached to the identical target molecules in a manner that is extremely sensitive and can be multiplexed to high levels;
- Allow newly-generated molecules comprising targets and diverse labels or label-tags to be amplified freely without impacting quantitation of the targets; and
- Convert an analog readout of hybridization signal intensities on arrays into a measurable process that can be scored digitally on the arrays by leveraging the diverse label-tags found in each newly-generated molecule, providing a clear cost-advantage over existing techniques.

See, e.g., ’502 patent at 4:38-40; 4:50-64; 5:4-6; 5:10-14; 14:35-39; 21:22-24; 22:50-57; 22:60-63; 23:2-6; 23:9-16; 23:54-58; 25:21-24; 31:50-51; 32:33-36; 33:4-14. Skilled artisans would understand that these benefits inure from the claimed inventions and inventive concepts (alone or in combination with the other limitations), including the diverse label-tags being attached to target molecules from a single cell, wherein the ratio of the number of the plurality of diverse label-tags to the number of each of the plurality of target molecules is greater than 5, to generate new target-label-tag molecules comprising label-tags and a portion of a complementary sequence of the target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, the amplification of the target-label-tag molecules, and the other limitations (alone or in combination) of the independent and dependent claims, including as described above and below.

252. Skilled artisans would further understand that quantitation of the abundance of molecules, *e.g.*, nucleic acids, in a sample through the generation of new molecules by attaching diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, was not well-understood, routine, or conventional at the time of the invention. They would further understand that the steps recited in the claims of the ’502 patent, either alone or in combination and including those recited above and below, were not well-understood, routine, or conventional at the time of the invention and are integral to addressing the problems in the prior art remedied by the improved functionality of the claimed inventions and inventive concepts. They would further understand that the specific structures and manipulations recited in the claims of the ’502 patent, including a plurality of target molecules, a single cell, an indexed library, a plurality of diverse label-tags, wherein the ratio of the number of the plurality of

diverse label-tags to the number of each of the plurality of target molecules is greater than 5, a complementary sequence of the target molecule, a plurality of amplified products, sequencing at least a portion of the plurality of amplified products, and a plurality of new target-label-tag molecules, generated by hybridizing diverse labels to target molecules, including through stochastic attachment of diverse labels and/or by multiplexing to allow simultaneous quantitation of multiple molecules, are essential to addressing the problems remedied by the improved functionality of the claimed inventions. *See also supra* ¶ 251.

253. They would further understand that the additional limitations (alone or in combination) of at least dependent claims 2-4, 6-12, 14-18, 21, 22, 24-28, and 30 are not directed to an abstract idea and recite inventive concepts for additional reasons, including that they recite additional structure; are not routine, conventional, or well-known; improve upon prior art methods by providing increased functionality; and do not risk preemption as a result of the additional limitations in those claims.

254. They would further understand that claim 6 of the ’358 patent is not substantially similar to nor linked to any abstract idea, much less the same abstract idea as all claims of the ’502 patent, including because the claims of the ’502 patent recite additional, tangible structures and manipulations, provide further improvements and innovations, address additional technological problems, add one or more inventive concepts, and involve different facts relating to issues of preemption and patentability that are not reflected in claim 6 of the ’358 patent. *See also supra* at ¶¶ 251-53.

255. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the ’502 patent, including at least claim 1 of the ’502 patent

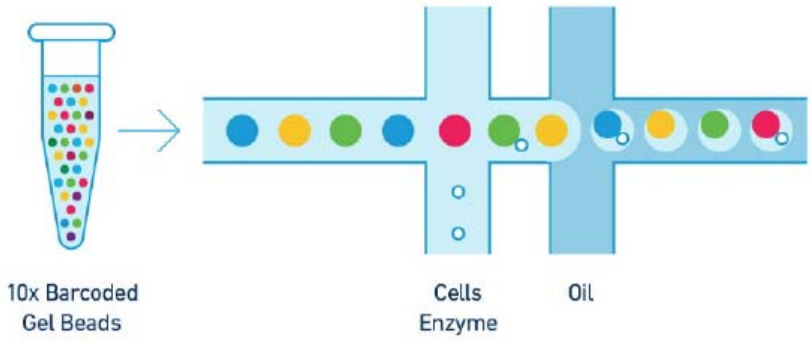
directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

256. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the '502 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '502 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

257. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are "a method for determining a number of occurrences of a target molecule from a single cell" as recited in claim 1, because the "Cell Ranger™" analysis software performs "demultiplexing, alignment, and gene counting"[159] and the information generated with the Cell Ranger™ [160] software is used for "cell clustering, cell type classification, and differential gene expression at a scale of hundreds to millions of cells."[161] Cell Ranger™ is a set of analysis pipelines [that perform gene expression analysis by] alignment, filtering, barcode counting, and UMI counting," which is "determining a number of occurrences of a target molecule from a single cell."[162] "The 10x™ GemCode™ Technology partition[s] thousands of cells" with the

[159] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[160] *Id.*
[161] *Id.*
[162] https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger

10x Barcoded Gel Beads "into nanoliter-scale Gel Bead-In-EMulsions (GEMs)."[163] As illustrated below[164], "the cells are delivered at a limiting dilution, such that the majority (~90-99%) of generated GEMs contains no cell, while the remainder largely contain a single cell."[165]



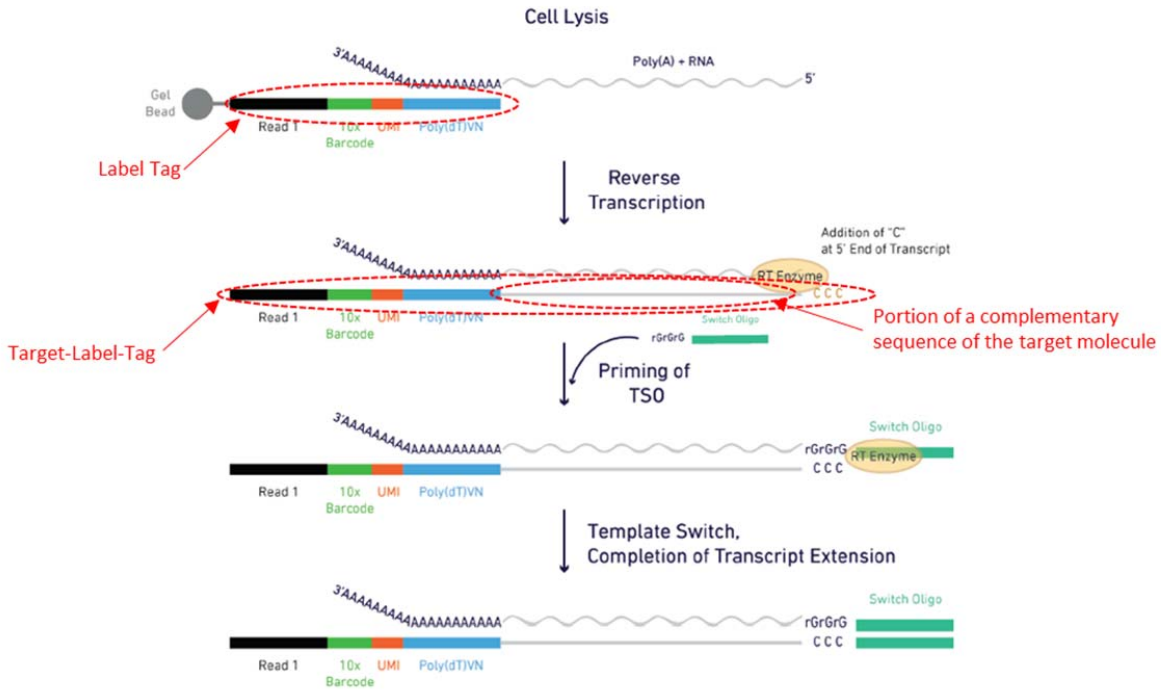
258. In the **Single Cell 3' Workflow** Accused Products "generating an indexed library by performing a labeling step, the label step comprising (i) combining each of a target molecule from a plurality of target molecules from a single cell with a label-tag from a plurality of diverse label-tags" as recited in step (a) and substep (a)(i) of claim 1 occurs because a "[t]he contents of the GEM (oligos, lysed cell components and Master Mix) are incubated in an RT reaction to generate full-length, barcoded cDNA from the poly A-tailed mRNA transcripts."[166] In the **Single Cell 3' Workflow** Accused Products, "the ratio of the number of the plurality of diverse label-tags to the number of each of the plurality of target molecules is greater than 5" as recited in step (a) and substep (a)(i) of claim 1 because "[t]he 10x™ GemCode™ Technology… samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[167] and

[163] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[164] *Id.*
[165] *Id.*
[166] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[167] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

because the "number of each of the plurality of target molecules" is less than 150000. For example, single cell analysis shows "~4,500 genes and 27,000 transcripts […] detected" in human and mouse cells.[168]

259. In the **Single Cell 3' Workflow** Accused Products, "generating the indexed library comprising a plurality of target-label-tag molecules by hybridizing the label-tag of the plurality of diverse label-tags to the target molecule of the plurality of target molecules and performing an extension reaction" as recited in claim 1 step (a) substep (ii) occurs because a "reverse transcription reaction is primed by the barcoded Gel Bead oligo."[169] As illustrated below[170], the "label-tag of the plurality of diverse label tags" hybridize to "the target molecule of the plurality of target molecules" and thereby generate the "target-label-tag molecules" by an extension reaction. Further, as illustrated below[171], the resulting "target-label-tag molecules" comprise "the label-tag and a portion of a complementary sequence of the target molecule" as recited in substep (ii) of step (a).

[168] Chromium™ Single Cell Solutions 10x Single Cell App Note (10x_Single_Cell_App_Note.pdf)
[169] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[170] *Id.* at Figure 3 (cropped, markings added)
[171] *Id.*



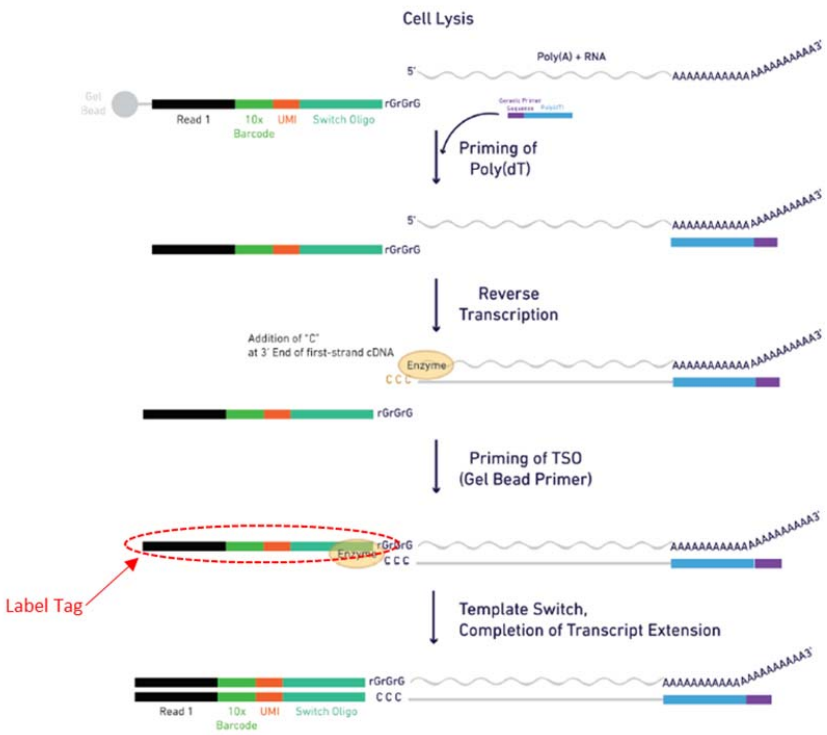
260. In the **Single Cell 5' Workflow** Accused Products, "generating an indexed library by performing a labeling step, the label step comprising combining each of a target molecule from a plurality of target molecules from a single cell with a label-tag from a plurality of diverse label-tags" as recited in step (a) and substep (a)(i) of claim 1 because "[t]he contents of the GEM […] are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA from poly-adenylated mRNA."[172] In the **Single Cell 5' Workflow** Accused Products, "the ratio of the number of the plurality of diverse label-tags to the number of each of the plurality of target molecules is greater than 5" as recited in step (a) and substep (a)(i) of claim 1 because "[t]he 10x™ GemCode™ Technology… samples a pool of ~ 750000

[172] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

barcodes to separately index each cell's transcriptome"[173] and because the "number of each of the plurality of target molecules" is less than 150000. For example, single cell analysis shows "~4,500 genes and 27,000 transcripts […] detected" in human and mouse cells.[174]

261. In the **Single Cell 5' Workflow** Accused Products, "generating the indexed library comprising a plurality of target-label-tag molecules by hybridizing the label-tag of the plurality of diverse label-tags to the target molecule of the plurality of target molecules and performing an extension reaction" as recited in claim 1 step (a) substep (ii) occurs because "[t]he contents of the GEM […] are incubated in a reverse transcription (RT) reaction to generate full-length, barcoded cDNA from poly-adenylated mRNA."[175] As illustrated below[176], the "label-tag of the plurality of diverse label tags" hybridize to a reverse transcription product which is the "target molecule."

[173] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[174] Chromium™ Single Cell Solutions 10x Single Cell App Note (10x_Single_Cell_App_Note.pdf)
[175] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[176] *Id.* at Figure 3 (cropped, markings added)

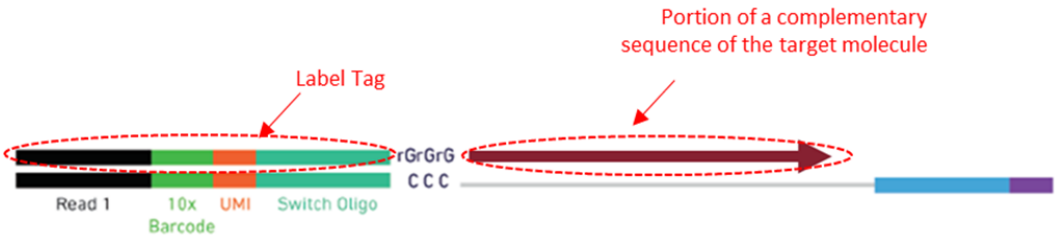


262. On information and belief, the RNA molecule will dissociate from DNA prior to the PCR amplification step to form the structure illustrated below:[177]

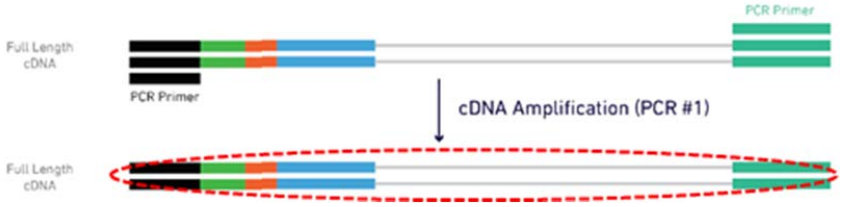
263. In the next step of the **Single Cell 5' Workflow** Accused Products, PCR amplification is performed by "Direct Target Enrichment" or "cDNA Amplification followed by Target Enrichment."[178] On information and belief, as illustrated with the arrow below, performing either of the PCR extension step will result in "performing an extension reaction, wherein a target-label-tag molecule comprises the label-tag and a portion of a complementary

[177] This is illustration is a modification of the figure in the 10x materials adapted to demonstrate the hybrid arising due to dissociation of RNA form the hybrid in the last step of the figure in the preceding paragraph.
[178] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

sequence of the target molecule." As is illustrated below, the extension products generated in this step are a "a target-label-tag molecule [comprising] the label-tag and a portion of a complementary sequence of the target molecule."



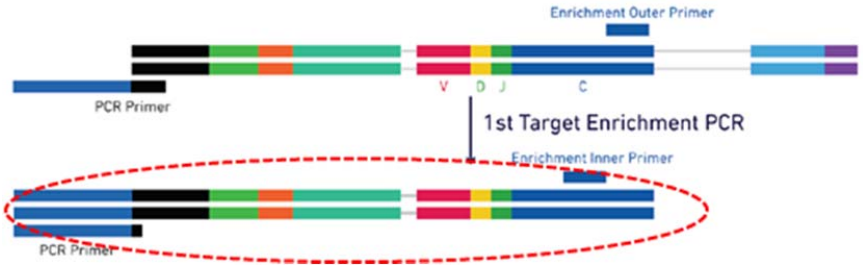
264. The **Single Cell 3' Workflow** Accused Products comprise a step of "amplifying the plurality of target-label-tag molecules from the indexed library to generate a plurality of amplified products" as recited in step (b) of claim 1 because "[t]he GEMs are then 'broken', pooling single-stranded, barcoded cDNA molecules from every cell" and "[a] bulk PCR-amplification and Enzymatic Fragmentation" follows.[179] As illustrated below[180], this PCR step results in amplification of the target-label-tag molecules.



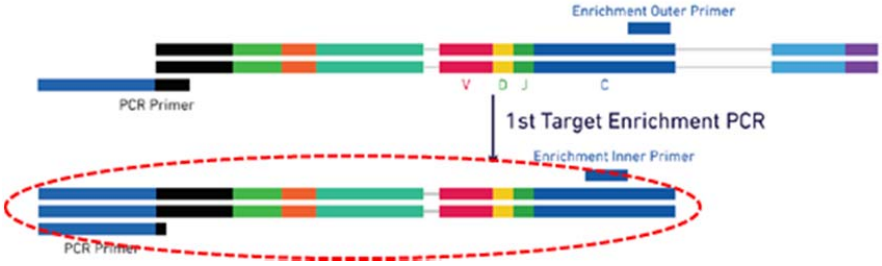
265. In the **Single Cell 5' Workflow** Accused Products, the "amplifying the plurality of target-label-tag molecules from the indexed library to generate a plurality of amplified products" recited in step (b) of claim 1 occurs because "[t]he Single Cell V(D)J Solution offers the option to generate" by PCR amplification, "Direct Target Enrichment" or

[179] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[180] *Id.* at Figure 3 (cropped, markings added)

"cDNA Amplification followed by Target Enrichment."[181] As illustrated below[182], the PCR step in "Direct Target Enrichment" option results in amplification of the target-label-tag molecules.



266. As illustrated below[183], the PCR step in "cDNA Amplification followed by Target Enrichment" option also results in amplification of the target-label-tag molecules.



267. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products comprise a step of "sequencing at least a portion of the plurality of amplified products of step (b) to determine a number of different label-tag sequences associated with the portion of the complementary sequence of the target molecule from the single cell" as recited in step (c) of claim 1 because "[d]uring library preparation, sequence components essential for Illumina

[181] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[182] *Id.* at Figure 3 (cropped, markings added)
[183] *Id.* at Figure 4 (cropped, markings added)

sequencing and downstream data analysis are incorporated into the final library construct,"[184] and because the Single Cell 3' and Single Cell 5' Workflows produce "Illumina-ready sequencing libraries" and the libraries "generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions."[185]

268. Further, sequencing in the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products produces a result "wherein the number of different label-tag sequences indicates the number of occurrences of the target molecule from the single cell" because once these libraries are "generated and sequenced," "the 10x Barcodes are used to associate individual reads back to the individual partitions."[186] Correlation between the "the number of different label-tag sequences" and "the number of occurrences of the target molecule from the single cell" as recited in step (c) occurs because the amplified products of step (b) of claim 1 are processed with "Cell Ranger™" analysis software to perform "demultiplexing, alignment, and gene counting."[187] The information generated with the Cell Ranger software can be used for "cell clustering, cell type classification, and differential gene expression at a scale of hundreds to millions of cells."[188] "Cell Ranger™ is a set of analysis pipelines [that perform gene expression analysis by] alignment, filtering, barcode counting, and UMI counting,"[189] which is a sub-element "wherein the number of different label-tag sequences indicates the number of occurrences of the target molecule from the single cell."

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[184] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[185] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[186] *Id.*
[187] *Id.*
[188] *Id.*
[189] https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger

269. As demonstrated in **Exhibit 29**, the **Single Cell 3' Workflow** Accused Products satisfy the claim limitations of at least claims 1-4, 7-12, 14-18, 21, 22, 24-28, and 30 of the '502 patent. As demonstrated in **Exhibit 30**, the **Single Cell 5' Workflow** Accused Products satisfy the claim limitations of at least claims 1-4, 6, 9-12, 14-17, 21-22, 24-28, and 30 of the '502 patent. As demonstrated in **Exhibit 31**, the **Spatial Transcriptomics** Accused Products satisfy the claim limitations of at least claims 1-4, 7-12, 15-18, 21, 22, 24-28, and 30 of the '502 patent. The demonstration of infringement illustrated in **Exhibits 29, 30 and 31** is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '502 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

270. 10X has also induced and currently induces infringement of at least claim 1 of the '502 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, 10X knows infringes at least claim 1 of the '502 patent.[190] 10X has known of the '502 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the '502 patent.

271. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the '502 patent. 10X has designed the Accused

[190] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

Products specifically to be used in a manner as claimed at least claim 1 of the '502 patent.[191] As such, the Accused Products are a material component of the patented combination, specifically designed to be used according to at least claim 1 of the '502 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the '502 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the '502 patent. 10X has knowledge of the '502 patent and is aware that the Accused Products are especially made to be used in a system that infringes the '502 patent.

272. Defendant's infringement has been willful and deliberate because Defendant has known of the '502 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the '502 patent.

273. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 8
(INFRINGEMENT OF THE '645 PATENT)

274. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

[191] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

275. U.S. Patent No. 9,567,645 (the "'645 patent"), entitled "Massively Parallel Single Cell Analysis," was duly and legally issued on February 14, 2017 to inventors Christina Fan, Stephen P.A. Fodor, Glenn Fu, Geoffrey Richard Facer, and Julie Wilhelmy. A true and accurate copy of the '645 patent is attached as **Exhibit 8**.

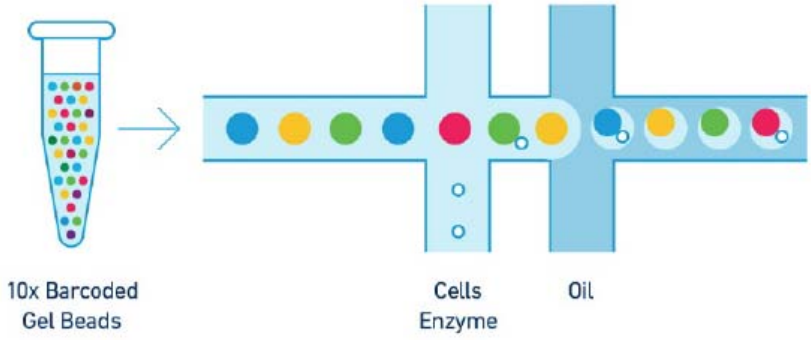
276. The invention of the '645 patent is directed in general to methods for associating a single cell with a single bead, the single bead comprising a plurality of oligonucleotides (*i.e.*, at least 100 oligonucleotides) comprising an identical cellular label sequence, a target-binding region, and different molecular label sequences.

277. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the '645 patent, including at least claim 1 of the '645 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

278. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the '645 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '645 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

279. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "associating a single bead with a single cell" limitation of claim 1 of the '645

patent because "[t]he 10x™ GemCode™ Technology partition[s] thousands of cells" with the 10x Barcoded Gel Beads "into nanoliter-scale Gel Bead-In-EMulsions (GEMs)." [192] As illustrated below, "the cells are delivered at a limiting dilution, such that the majority (~90-99%) of generated GEMs contains no cell, while the remainder largely contain a single cell."[193]



280. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "wherein said single bead comprises a plurality of oligonucleotides," limitation of claim 1 of the '645 patent because the "Gel Beads are . . . functionalized with millions of copies of a 10x Barcoded primer." [194] The "10x Barcoded primer" is an oligonucleotide ("[e]ach Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1)."[195]). The oligonucleotides of the Gel Beads for the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are shown in the Figures below[196]:

[192] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[193] *Id.*
[194] *Id.*
[195] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[196] *Id.*

Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

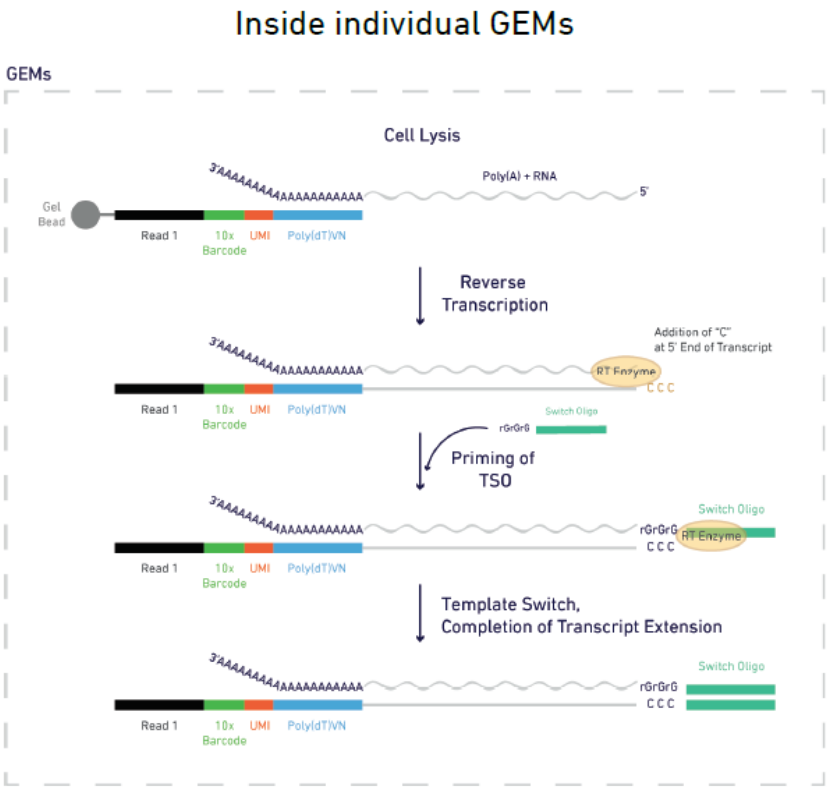
Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

281. The **Single Cell 3' Workflow** Accused Products meet the "wherein each of said plurality of oligonucleotides comprises an identical cellular label sequence, a molecular label sequence, and a target-binding region," limitation of claim 1 of the '645 patent because each oligonucleotide of each bead comprises a "16nt 10x™ Barcode," (shown in green in Fig. 1 and below[197]) which is a cellular label sequence,[198] a "10nt Unique Molecular Identifier (UMI)," (shown in red in Fig. 1 and below) which is a molecular label sequence, and a "30nt Poly(dT) primer sequence," (shown in blue in Fig. 1 and below) which is a target-binding region.[199] The "16nt 10x™ Barcode," is an identical cellular label sequence because "[t]he 10x™ GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning

[197] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 4 (cropped)
[198] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[199] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)

thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[200] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."

282. As shown below[201], the "30nt Poly(dT) primer sequence" is a target-binding region that binds the poly(A) sequence at the 3' ends of RNA molecules.[202]



[200] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[201] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 3 (cropped)
[202] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)

283. The **Single Cell 5' Workflow** Accused Products meet the "wherein each of said plurality of oligonucleotides comprises an identical cellular label sequence, a molecular label sequence, and a target-binding region," limitation of claim 1 of the '645 patent because each oligonucleotide of the bead comprises a "16nt 10x™ Barcode," (shown in bright green in Figure 1 and below[203]) which is a cellular label sequence,[204] a "10nt Unique Molecular Identifier (UMI)," (shown in red in Figure 1 and below) which is a molecular label sequence, and a "13nt Switch Oligo," (shown in dark green in Figure 1 and below) which is a target-binding region.[205] The "16nt 10x™ Barcode," is an identical cellular label sequence because "[t]he 10x™ GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[206] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."

284. As shown below[207], the "13nt Switch Oligo" is a target-binding region that binds the "CCC" sequence at the '3 ends of a cDNA molecule.[208]

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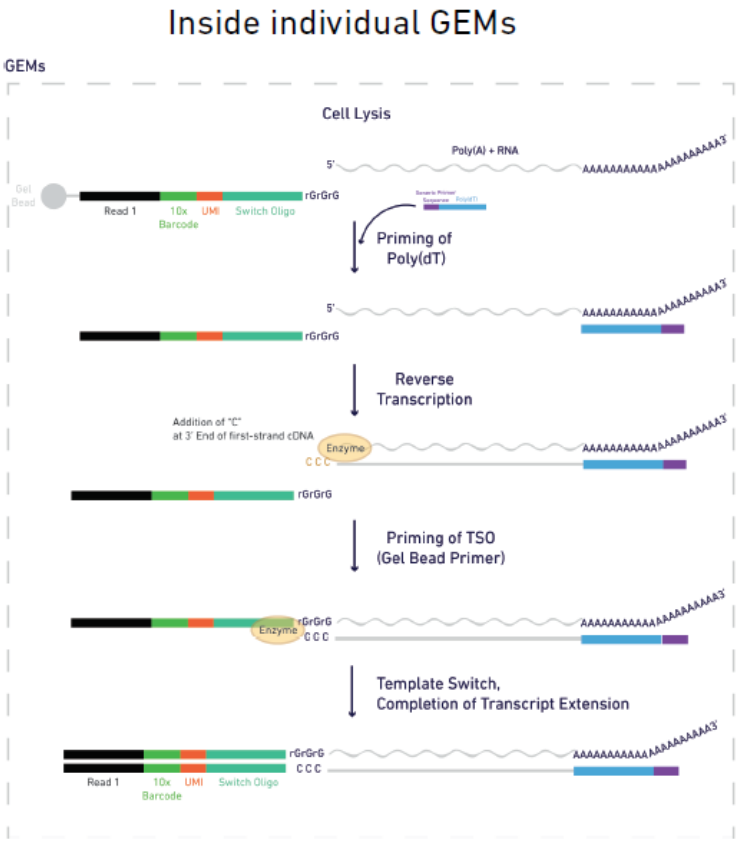
[203] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Table 1 (cropped)
[204] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[205] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[206] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[207] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Figure 3 (cropped)
[208] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)



285. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "wherein at least 100 of said plurality of oligonucleotides comprise different molecular label sequences" limitation of claim 1 of the '645 patent because "[t]he 10x™ GemCode™ Technology samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[209] according to a method wherein "[e]ach Gel Bead contains millions of oligo primers."[210]

[209] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052-SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[210] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

286. 10X has also induced and currently induces infringement of at least claim 1 of the ’645 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, 10X knows infringes at least claim 1 of the ’645 patent.[211] 10X has known of the ’645 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the ’645 patent.

287. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the ’645 patent. 10X has designed the Accused Products specifically to be used in a manner as claimed at least claim 1 of the ’645 patent.[212] As such, the Accused Products are a material component of the patented combination, specifically designed to be used according to at least claim 1 of the ’645 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the ’645 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the ’645 patent. 10X has knowledge of the ’645 patent and is aware that the Accused Products are especially made to be used in a system that infringes the ’645 patent.

288. Defendant’s infringement has been willful and deliberate because Defendant has known of the ’645 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the ’645 patent.

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[211] See, e.g., “Chromium™ Single Cell 3’ Reagent Kits v2 User Guide” (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); “Chromium™ Single Cell V(D)J Reagent Kits User Guide” (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

[212] See, e.g., “Chromium™ Single Cell 3’ Reagent Kits v2 User Guide” (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); “Chromium™ Single Cell V(D)J Reagent Kits User Guide” (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

289. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 9
(INFRINGEMENT OF THE '646 PATENT)

290. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

291. U.S. Patent No. 9,567,646 (the "'646 patent"), entitled "Massively Parallel Single Cell Analysis," was duly and legally issued on February 14, 2017 to inventors Christina Fan, Stephen P.A. Fodor, Glenn Fu, Geoffrey Richard Facer, and Julie Wilhelmy. A true and accurate copy of the '646 patent is attached as **Exhibit 9**.

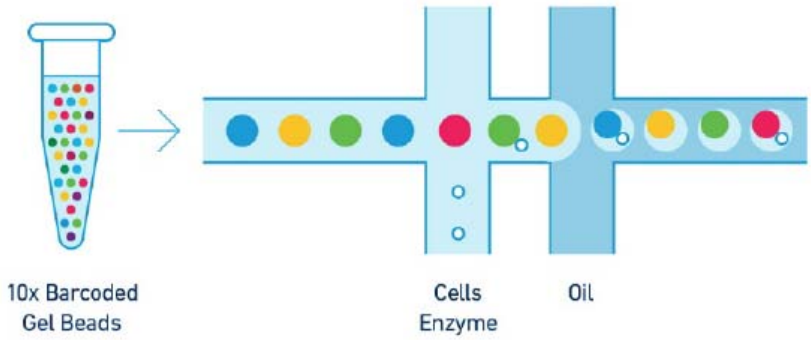
292. The invention of the '646 patent is directed in general to a single cell and a single bead, the single bead comprising a plurality of oligonucleotides (*i.e.*, at least 100 oligonucleotides) comprising an identical cellular label sequence, a target-binding region, and different molecular label sequences.

293. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the '646 patent, including at least claim 1 of the '646 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using,

offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

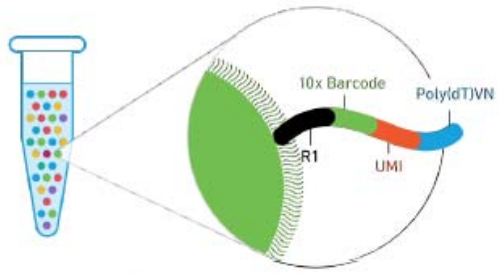
294. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the ’646 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD’s ability to demonstrate Defendant’s direct, indirect, literal, or equivalent infringement of additional ’646 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

295. The **Single Cell 3’ Workflow** and **Single Cell 5’ Workflow** Accused Products meet the “a single cell and a single bead” limitation of claim 1 of the ‘646 patent because “[t]he 10x™ GemCode™ Technology partition[s] thousands of cells” with the 10x Barcoded Gel Beads “into nanoliter-scale Gel Bead-In-EMulsions (GEMs).”[213] As illustrated below, “the cells are delivered at a limiting dilution, such that the majority (~90-99%) of generated GEMs contains no cell, while the remainder largely contain a single cell.”[214]



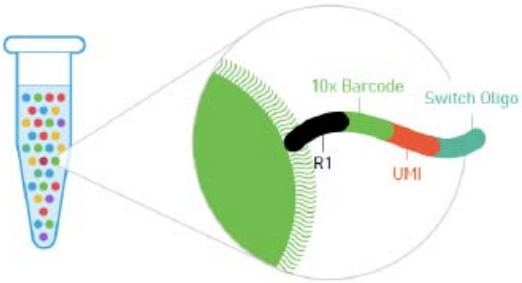
[213] “Chromium™ Single Cell 3’ Reagent Kits v2 User Guide” (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); “Chromium™ Single Cell V(D)J Reagent Kits User Guide” (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[214] *Id.*

296. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "wherein said single bead comprises a plurality of oligonucleotides," limitation of claim 1 of the '646 patent because "Gel Beads are . . . functionalized with millions of copies of a 10x Barcoded primer."[215] The "10x Barcoded primer" is an oligonucleotide ("[e]ach Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1)."[216]). The oligonucleotides of the Gel Beads for the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are shown in the Figures below[217]:



i. Partial Illumina Read 1 sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 30 nt Poly(dT) primer sequence

Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.



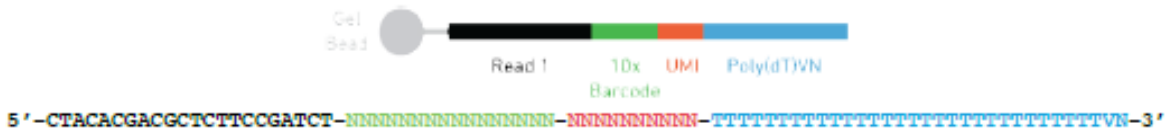
i. Partial Illumina Read 1 Sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 13 nt Switch Oligo

Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

297. The **Single Cell 3' Workflow** Accused Products meet the "wherein each of said plurality of oligonucleotides comprises an identical cellular label sequence, a molecular

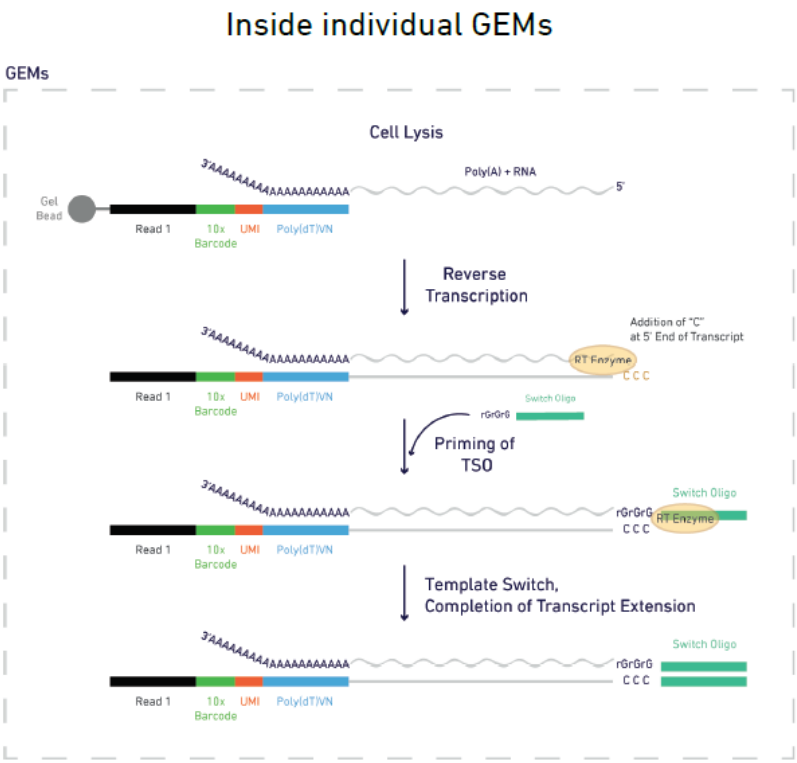
[215] *Id.*
[216] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[217] *Id.*

label sequence, and a target-binding region," limitation of claim 1 of the '646 patent because each oligonucleotide of the bead comprises a "16nt 10x™ Barcode," (shown in green in Fig. 1 and below[218]) which is a cellular label sequence,[219] a "10nt Unique Molecular Identifier (UMI)," (shown in red in Fig. 1 and below) which is a molecular label sequence, and a "30nt Poly(dT) primer sequence," (shown in blue in Fig. 1 and below) which is a target-binding region.[220] The "16nt 10x™ Barcode," is an identical cellular label sequence because "[t]he 10x™ GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[221] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."



298. As shown below[222], the "30nt Poly(dT) primer sequence" is a target-binding region that binds the poly(A) sequence at the 3' ends of RNA molecules.[223]

[218] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 4 (cropped)
[219] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[220] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[221] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[222] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 3 (cropped)
[223] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)



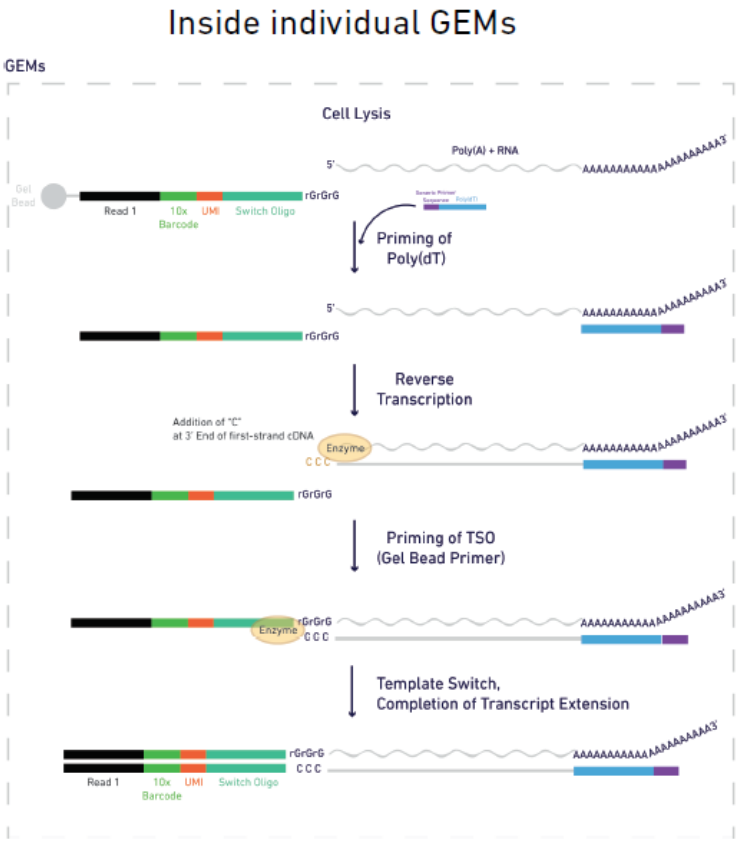
299. The **Single Cell 5' Workflow** Accused Products meet the "wherein each of said plurality of oligonucleotides comprises an identical cellular label sequence, a molecular label sequence, and a target-binding region," limitation of claim 1 of the '646 patent because each oligonucleotide of the bead comprises a "16nt 10x™ Barcode," (shown in bright green in Figure 1 and below[224]) which is a cellular label sequence,[225] a "10nt Unique Molecular Identifier (UMI)," (shown in red in Figure 1 and below) which is a molecular label sequence, and a "13nt Switch Oligo," (shown in dark green in Figure 1 and below) which is a target-binding region.[226] The "16nt 10x™ Barcode," is an identical cellular label sequence because "[t]he 10x™

[224] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Table 1 (cropped)
[225] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[226] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[227] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."

300. As shown below[228], the "13nt Switch Oligo" is a target-binding region that binds the "CCC" sequence at the '3 ends of a cDNA molecule.[229]

[227] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[228] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Figure 3 (cropped)
[229] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pd)



301. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "wherein at least 100 of said plurality of oligonucleotides comprise different molecular label sequences" limitation of claim 1 of the '646 patent because "[t]he 10x™ GemCode™ Technology samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[230] according to a method wherein "[e]ach Gel Bead contains millions of oligo primers."[231]

[230] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[231] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.docx)

302. 10X has also induced and currently induces infringement of at least claim 1 of the ’646 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, induces customers to use a composition that infringes at least claim 1 of the ’646 patent. 10X has known of the ’646 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the ’646 patent.

303. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the ’646 patent. 10X has designed the Accused Products specifically to be used with the composition as claimed at least claim 1 of the ’646 patent. As such, the Accused Products are a material component of the patented combination, specifically designed for use with the composition of at least claim 1 of the ’646 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the ’646 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the ’646 patent. 10X has knowledge of the ’646 patent and is aware that the Accused Products are especially made to be used in a system that infringes the ’646 patent.

304. Defendant’s infringement has been willful and deliberate because Defendant has known of the ’137 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the ’646 patent.

305. As the direct and proximate result of Defendant’s conduct, Plaintiffs have suffered and, if Defendant’s conduct is not stopped, will continue to suffer, severe competitive

harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 10
(INFRINGEMENT OF THE '736 PATENT)

306. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

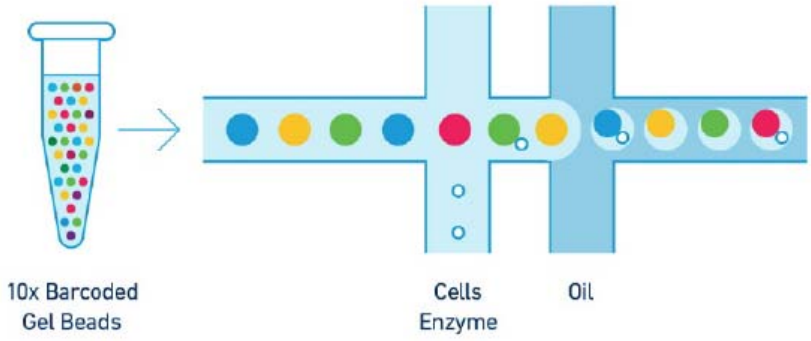
307. U.S. Patent No. 9,598,736 (the "'736 patent"), entitled "Massively Parallel Single Cell Analysis," was duly and legally issued on March 21, 2017 to inventors Christina Fan, Stephen P.A. Fodor, Glenn Fu, Geoffrey Richard Facer, and Julie Wilhelmy. A true and accurate copy of the '736 patent is attached as **Exhibit 10**.

308. The invention of the '736 patent is directed in general to a particle comprising a plurality of oligonucleotides (*i.e.*, at least 100 oligonucleotides) comprising an identical cellular label sequence, a target-binding region, and different molecular label sequences.

309. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the '736 patent, including at least claim 16 of the '736 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

310. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 16 of the '736 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '736 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

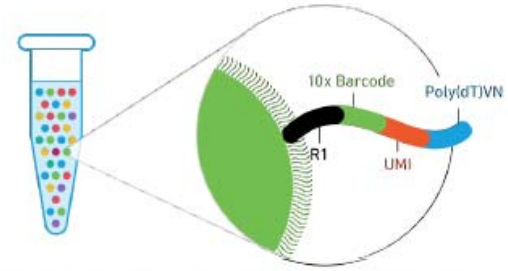
311. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "[a] kit comprising a plurality of particles" limitation of claim 16 of the '736 patent because the "Chromium™ Single Cell 3' Reagent Kits" include "Single Cell 3' Gel Beads,"[232] and the "Chromium™ Single Cell V(D)J Reagent Kits" include "Single Cell 5' Gel Beads."[233] The "Single Cell 3' Gel Beads," and the "Single Cell 5' Gel Beads" are a plurality of particles as shown below[234].



312. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "each [of the plurality of particles] comprising a plurality of oligonucleotides,"

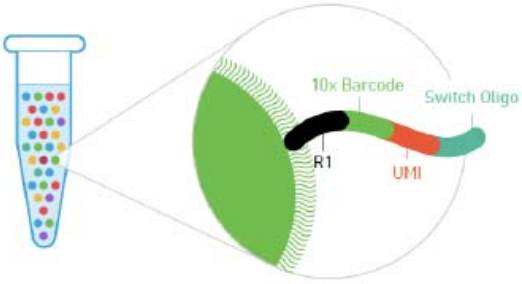
[232] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[233] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[234] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

limitation of claim 16 of the '736 patent because "Gel Beads are . . . functionalized with millions of copies of a 10x Barcoded primer."[235] The "10x Barcoded primer" is an oligonucleotide ("[e]ach Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1)."[236]). The oligonucleotides of the Gel Beads for the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are shown in the Figures below[237]:



i. Partial Illumina Read 1 sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 30 nt Poly(dT) primer sequence

Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.



i. Partial Illumina Read 1 Sequence (22 nucleotides (nt))
ii. 16 nt 10x™ Barcode
iii. 10 nt Unique Molecular Identifier (UMI)
iv. 13 nt Switch Oligo

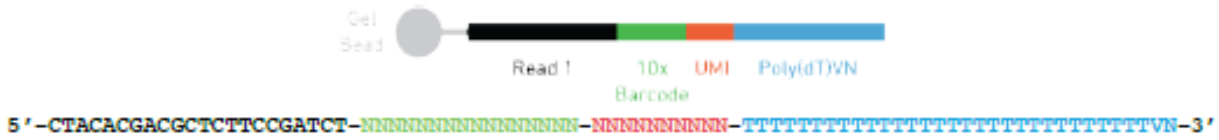
Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

313. The **Single Cell 3' Workflow** Accused Products meet the "wherein each of the plurality of oligonucleotides comprises a cellular label sequence, a molecular label sequence, and a target-binding region, wherein the cellular label sequence of each of the plurality

[235] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[236] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[237] *Id.*

of oligonucleotides is the same," limitation of claim 16 of the '736 patent because each oligonucleotide of the bead comprises a "16nt 10x™ Barcode," (shown in green in Fig. 1 and below[238]) which is a cellular label sequence,[239] a "10nt Unique Molecular Identifier (UMI)," (shown in red in Fig. 1 and below) which is a molecular label sequence, and a "30nt Poly(dT) primer sequence," (shown in blue in Fig. 1 and below) which is a target-binding region.[240]

314. The "16nt 10x™ Barcode," is a cellular label sequence which is the same for each of the plurality of oligonucleotides. "The 10x™ GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[241] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."



315. As shown below[242], the "30nt Poly(dT) primer sequence" is a target-binding region that binds the poly(A) sequence at the 3' ends of RNA molecules.[243]

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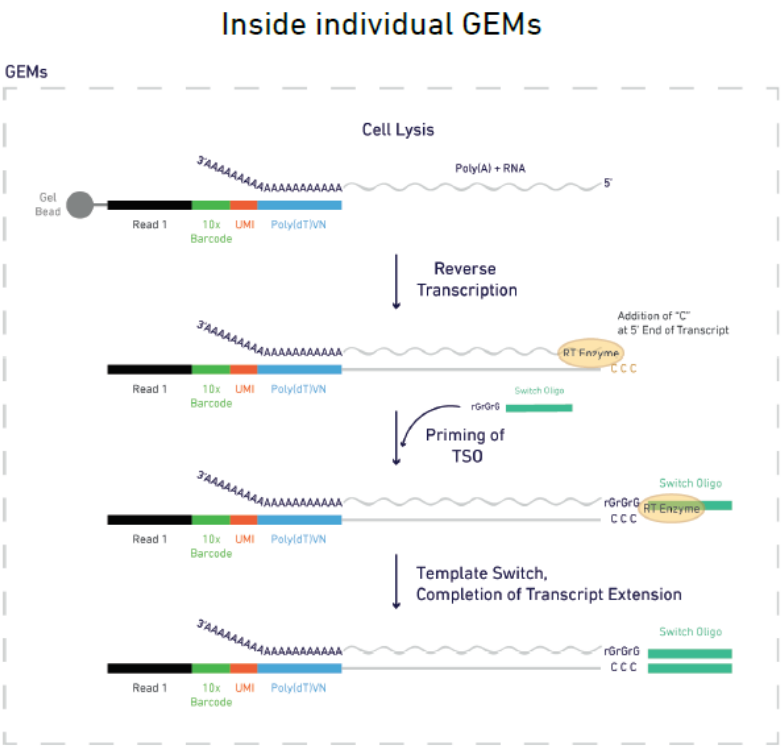
[238] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 4 (cropped)
[239] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[240] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[241] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[242] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 3 (cropped)
[243] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)



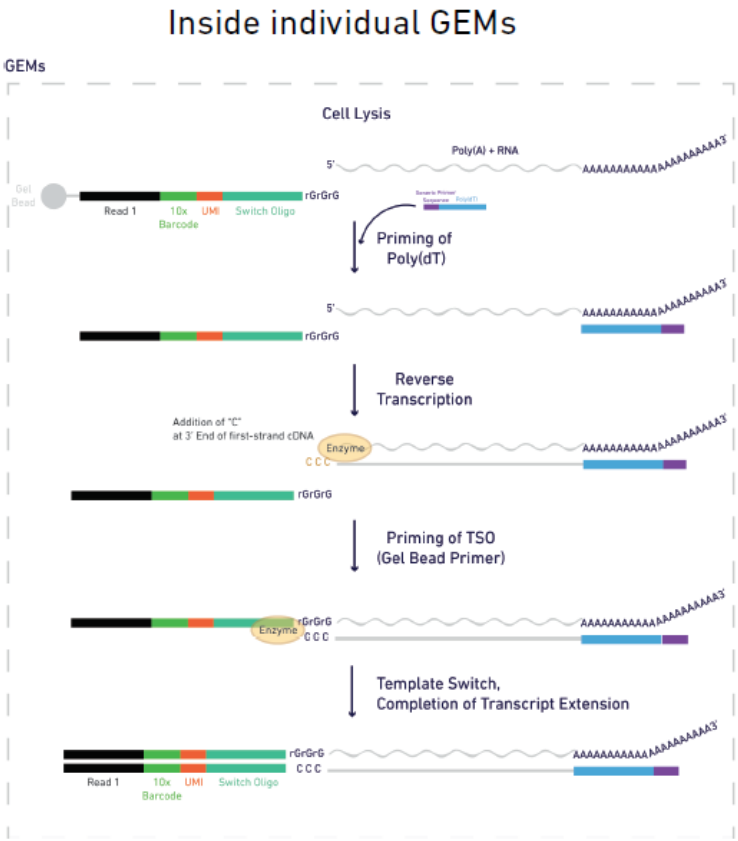
316. The **Single Cell 5' Workflow** Accused Products meet the "wherein each of said plurality of oligonucleotides comprises an identical cellular label sequence, a molecular label sequence, and a target-binding region, wherein the cellular label sequence of each of the plurality of oligonucleotides is the same," limitation of claim 16 of the '736 patent because each oligonucleotide of the bead comprises a "16nt 10x™ barcode," (shown in bright green in Figure 1 and below[244]) which is a cellular label sequence,[245] a "10nt Unique Molecular Identifier (UMI)," (shown in red in Figure 1 and below) which is a molecular label sequence, and a "13nt Switch Oligo," (shown in dark green in Figure 1 and below) which is a target-binding region.[246]

[244] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Table 1 (cropped)
[245] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[246] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

317. The "16nt 10x™ Barcode," is a cellular label sequence which is the same for each of the plurality of oligonucleotides. "The 10x™ GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[247] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."

318. As shown below[248], the "13nt Switch Oligo" is a target-binding region that binds the "CCC" sequence at the '3 ends of a cDNA molecule.[249]

[247] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[248] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Figure 3 (cropped)
[249] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)



319. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "at least 100 of the plurality of oligonucleotides comprise different molecular label sequences" limitation of claim 16 of the '736 patent because "[t]he 10x™ GemCode™ Technology samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[250] according to a method wherein "[e]ach Gel Bead contains millions of oligo primers."[251]

[250] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide": CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf

[251] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

320. 10X has also induced and currently induces infringement of at least claim 16 of the ’736 patent under 35 U.S.C. § 271(b) by providing to customers an instrument the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, induces customers to use a kit that infringes at least claim 16 of the ’736 patent. 10X has known of the ’736 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the ’736 patent.

321. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 16 of the ’736 patent. 10X has designed the Accused Products specifically to be used with the kit as claimed at least claim 16 of the ’736 patent. As such, the Accused Products are a material component of the patented combination, specifically designed for use with the kit of at least claim 16 of the ’736 patent, and especially made and adapted for use in a manner that infringes at least claim 16 of the ’736 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 16 of the ’736 patent. 10X has knowledge of the ’736 patent and is aware that the Accused Products are especially made to be used in a system that infringes the ’736 patent.

322. Defendant’s infringement has been willful and deliberate because Defendant has known of the ’736 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the ’736 patent.

323. As the direct and proximate result of Defendant’s conduct, Plaintiffs have suffered and, if Defendant’s conduct is not stopped, will continue to suffer, severe competitive

harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 11

(INFRINGEMENT OF THE '799 PATENT)

324. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

325. U.S. Patent No. 9,637,799 (the "'799 patent"), entitled "Massively Parallel Single Cell Analysis," was duly and legally issued on May 2, 2017 to inventors Christina Fan, Stephen P.A. Fodor, Glenn Fu, Geoffrey Richard Facer, and Julie Wilhelmy. A true and accurate copy of the '799 patent is attached as **Exhibit 11**.

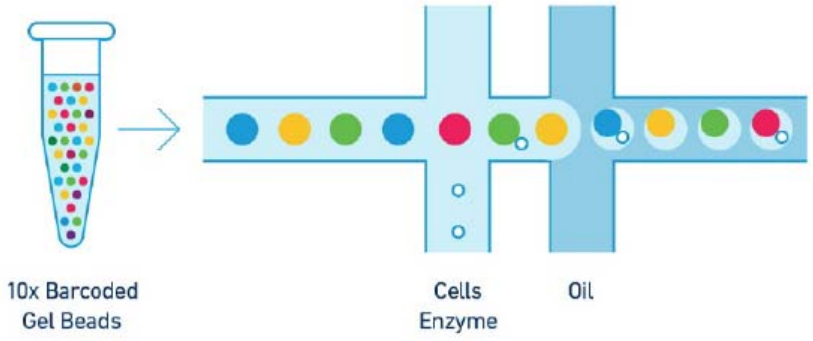
326. The invention of the '799 patent is directed in general to a droplet comprising a single bead and a single cell, the single bead comprising a plurality of oligonucleotides (*i.e.*, at least 100 oligonucleotides) comprising an identical cellular label sequence, an oligo dT sequence, and different molecular label sequences, lysing said single cell to release nucleic acid targets, and attaching the nucleic acid targets to the oligonucleotides.

327. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the '799 patent, including at least claim 1 of the '799 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using,

offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

328. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 1 of the '799 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '799 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

329. The **Single Cell 3' Workflow** Accused Products meet the "droplet comprising: a. a single bead" limitation (a) "a single cell" limitation (b) of claim 1 of the '799 patent because "[t]he 10x™ GemCode™ Technology partition[s] thousands of cells" with the 10x Barcoded Gel Beads "into nanoliter-scale Gel Bead-In-EMulsions (GEMs)." 252 As illustrated below, "the cells are delivered at a limiting dilution, such that the majority (~90-99%) of generated GEMs contains no cell, while the remainder largely contain a single cell."[253] The "nanoliter-scale Gel Bead-In-EMulsions (GEMs) " is a droplet because it is a "single nanoliter reaction volume[] partitioned by oil."[254]



[252] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[253] *Id.*
[254] *Id.*

330. The **Single Cell 3' Workflow** Accused Products meet the "a single bead comprising a plurality of oligonucleotides," limitation (a) of claim 1 of the '799 patent because the "Gel Beads are . . . functionalized with millions of copies of a 10x Barcoded primer."[255] The "10x Barcoded primer" is an oligonucleotide ("[e]ach Gel Bead contains millions of oligo primers that are comprises of the following sequences (Figure 1)."[256]). The oligonucleotides of the Gel Beads for the **Single Cell 3' Workflow** Accused Products are shown in Fig. 1 below[257]:

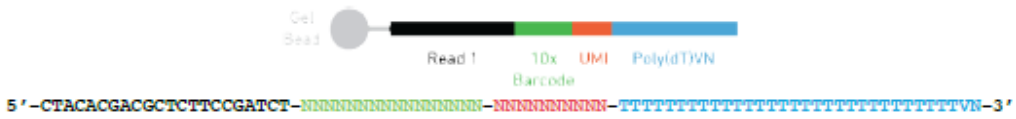
Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

331. The **Single Cell 3' Workflow** Accused Products meet the "wherein each of the plurality of oligonucleotides comprises a molecular label sequence, a cellular label sequence, and an oligo dT sequence, and wherein the cellular label sequence of each of the plurality of oligonucleotides is the same" limitation (a) of claim 1 of the '799 patent because each oligonucleotide of the bead comprises a "16nt 10x™ Barcode," (shown in green in Fig. 1 and below[258]) which is a cellular label sequence,[259] a "10nt Unique Molecular Identifier (UMI),"

[255] *Id.*
[256] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[257] *Id.*
[258] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 4 (cropped)
[259] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)

(shown in red in Fig. 1 and below) which is a molecular label sequence, and a "30nt Poly(dT) primer sequence," (shown in blue in Fig. 1 and below) which is an oligo dT sequence.[260]

332. The "16nt 10x™ Barcode," is a cellular label sequence which is the same for each of the plurality of oligonucleotides. "The 10x™ GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[261] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."



333. The **Single Cell 3' Workflow** Accused Products meet the "at least 100 of the plurality of oligonucleotides comprise different molecular label sequences" limitation (a) of claim 1 of the '799 patent because "[t]he 10x™ GemCode™ Technology samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[262] according to a method wherein "[e]ach Gel Bead contains millions of oligo primers."[263]

334. 10X has also induced and currently induces infringement of at least claim 1 of the '799 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, induces customers to use a composition that infringes at least claim 1 of the '799

[260] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[261] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[262] *Id.*
[263] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)

patent.[264] 10X has known of the '799 patent and of its infringement of that patent since at least May 2017. By providing its customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the '799 patent.

335. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 1 of the '799 patent. 10X has designed the Accused Products specifically to be used with the composition as claimed at least claim 1 of the '799 patent. As such, the Accused Products are a material component of the patented combination, specifically designed for use with the composition of at least claim 1 of the '799 patent, and especially made and adapted for use in a manner that infringes at least claim 1 of the '799 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 1 of the '799 patent. 10X has knowledge of the '799 patent and is aware that the Accused Products are especially made to be used in a system that infringes the '799 patent.

336. Defendant's infringement has been willful and deliberate because Defendant has known of the '799 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the '799 patent.

337. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive

[264] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

COUNT 12

(INFRINGEMENT OF THE '799 PATENT)

338. Plaintiffs incorporate all of the above paragraphs as though fully set forth herein.

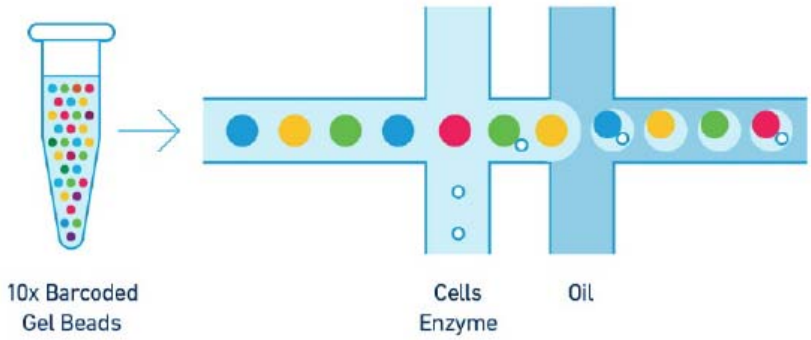
339. The '799 patent, entitled "Massively Parallel Single Cell Analysis," was duly and legally issued on May 2, 2017 to inventors Christina Fan, Stephen P.A. Fodor, Glenn Fu, Geoffrey Richard Facer, and Julie Wilhelmy. A true and accurate copy of the '799 patent is attached as **Exhibit 11**.

340. The invention of the '799 patent is directed in general to methods for introducing a single cell and a single bead into a droplet, the single bead comprising a plurality of oligonucleotides (*i.e.,* at least 100 oligonucleotides) comprising an identical cellular label sequence, a target-binding region, and different molecular label sequences, lysing said single cell to release nucleic acid targets, and attaching the nucleic acid targets to the oligonucleotides.

341. On information and belief, as set forth below, Defendant, directly or through the actions of its employees, divisions, and/or subsidiaries, has infringed and continues to infringe one or more claims of the '799 patent, including at least claim 17 of the '799 patent directly, indirectly, literally, and/or by equivalents under 35 U.S.C. *et seq*, including, but not limited to § 271 by, among other things, importing the Accused Products and/or making, using, offering for sale, and selling the Accused Products in the United States or inducing or contributing to such acts.

342. As demonstrated below, the Accused Products satisfy the claim limitations of at least claim 17 of the '799 patent. The demonstration of infringement illustrated below is offered by way of example only and without limitation to BD's ability to demonstrate Defendant's direct, indirect, literal, or equivalent infringement of additional '799 patent claims, including by making, using, selling, offering for sale, or importing additional products or inducing or contributing to such acts.

343. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "introducing a single cell and a single bead into a droplet" limitation (a) of claim 17 of the '799 patent because "[t]he 10x™ GemCode™ Technology partition[s] thousands of cells" with the 10x Barcoded Gel Beads "into nanoliter-scale Gel Bead-In-EMulsions (GEMs)."[265] As illustrated below, "the cells are delivered at a limiting dilution, such that the majority (~90-99%) of generated GEMs contains no cell, while the remainder largely contain a single cell."[266] The "nanoliter-scale Gel Bead-In-EMulsions (GEMs) " is a droplet because it is a "single nanoliter reaction volume[] partitioned by oil."[267]



[265] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[266] *Id.*
[267] *Id.*

344. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "wherein said single bead comprises a plurality of oligonucleotides," limitation (a) of claim 17 of the '799 patent because the "Gel Beads are . . . functionalized with millions of copies of a 10x Barcoded primer."[268] The "10x Barcoded primer" is an oligonucleotide ("[e]ach Gel Bead contains millions of oligo primers that are comprised of the following sequences (Figure 1)."[269]). The oligonucleotides of the Gel Beads for the **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products are shown in the Figures below[270]:

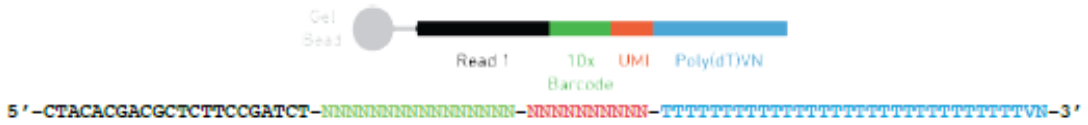
Fig. 1. Schematic of a SC3' v2 Gel Bead oligo primer.

Figure 1. Schematic of a Single Cell 5' Gel Bead oligo primer.

[268] *Id.*
[269] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[270] *Id.*

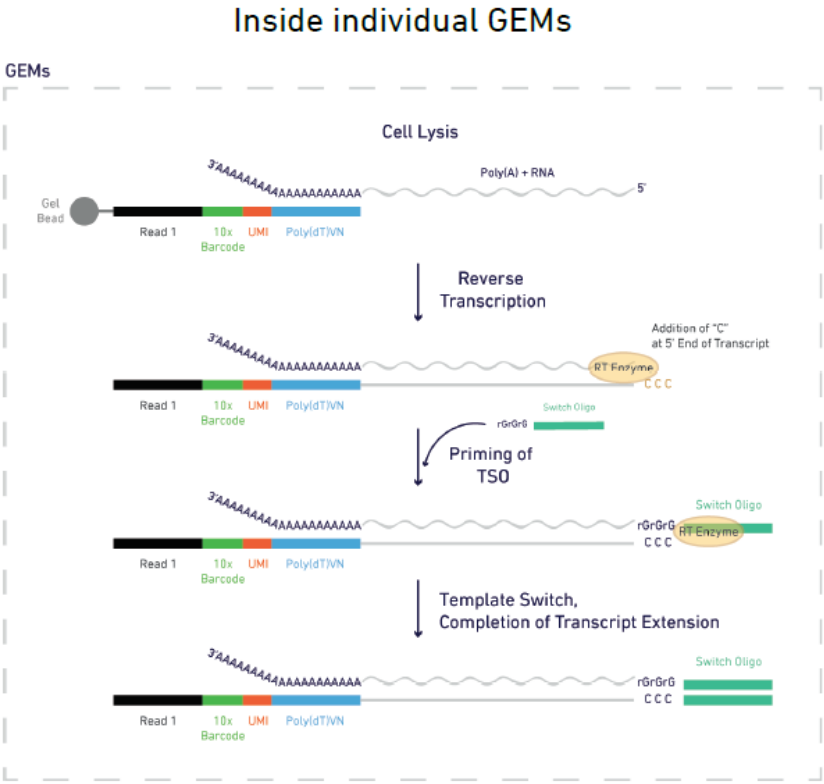
345. The **Single Cell 3' Workflow** Accused Products meet the "wherein each of the plurality of oligonucleotides comprises a cellular label sequence, a target-binding region, and a molecular label sequence , and wherein the cellular label sequence of each of the plurality of oligonucleotides is the same" limitation (a) of claim 17 of the '799 patent because each oligonucleotide of the bead comprises a "16nt 10x™ Barcode," (shown in green in Fig. 1 and below[271]) which is a cellular label sequence,[272] a "10nt Unique Molecular Identifier (UMI)," (shown in red in Fig. 1 and below) which is a molecular label sequence, and a "30nt Poly(dT) primer sequence," (shown in blue in Fig. 1 and below) which is a target-binding region.[273]

346. The "16nt 10x™ Barcode," is a cellular label sequence which is the same for each of the plurality of oligonucleotides. "The 10x™ GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[274] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."



[271] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 4 (cropped)
[272] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell 3' Reagent Kits v2 User Guide": CG00052 SingleCell3'ReagentKitv2UserGuide_RevD.pdf
[273] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[274] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)

347. As shown below[275], the "30nt Poly(dT) primer sequence" is a target-binding region that binds the poly(A) sequence at the 3' ends of RNA molecules.[276]



348. The **Single Cell 5' Workflow** Accused Products meet the "wherein each of said plurality of oligonucleotides comprises a cellular label sequence, a target-binding region, and a molecular label sequence, and wherein the cellular label sequence of each of the plurality of oligonucleotides is the same," limitation (a) of claim 17 of the '799 patent because each oligonucleotide of the bead comprises a "16nt 10x barcode," (shown in bright green in Figure 1 and below[277]) which is a cellular label sequence,[278] a "10nt Unique Molecular Identifier (UMI),"

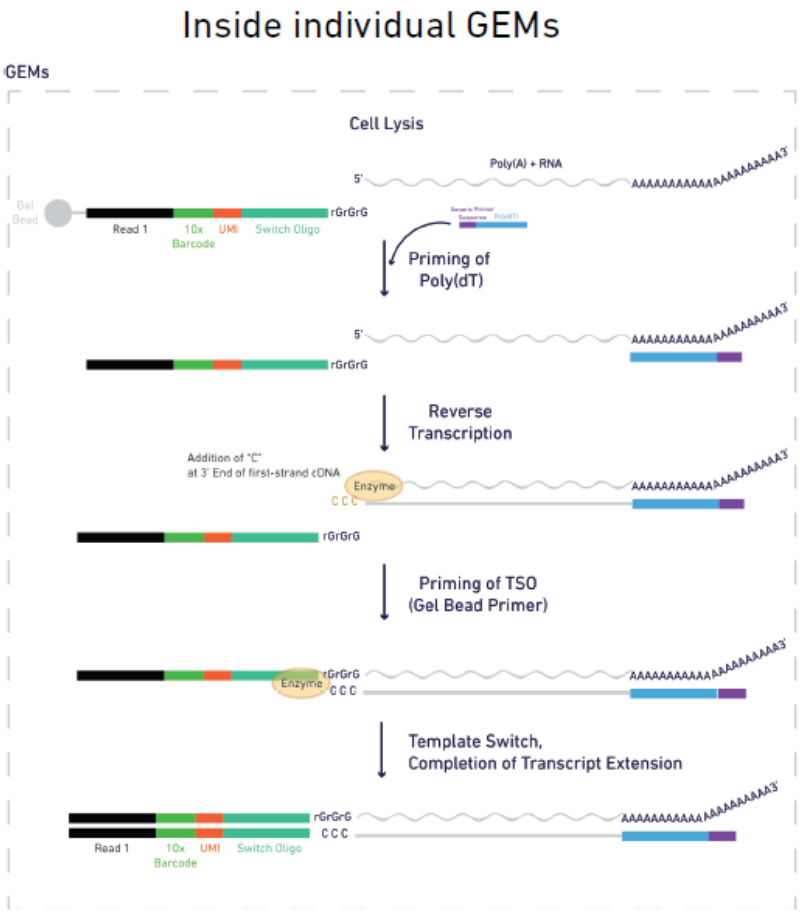
[275] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 3 (cropped)
[276] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf)
[277] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Table 1 (cropped)

(shown in red in Figure 1 and below) which is a molecular label sequence, and a "13nt Switch Oligo," (shown in dark green in Figure 1 and below) which is a target-binding region.[279]

349. The "16nt 10x™ Barcode," is a cellular label sequence which is the same for each of the plurality of oligonucleotides. "The 10x™ GemCode™ Technology . . . separately index[es] each cell's transcriptome. It does so by partitioning thousands of cells into nanoliter-scale Gel Bead-In-EMulsions (GEMs), where all generated cDNA share a common 10x Barcode."[280] Thus, each oligonucleotide on a particular bead has the same "16nt 10x™ Barcode."

350. As shown below[281], the "13nt Switch Oligo" is a target-binding region that binds the "CCC" sequence at the '3 ends of a cDNA molecule.[282]

[278] "[A]ll generated cDNA share a common 10x Barcode. Libraries are generated and sequenced from the cDNA and the 10x Barcodes are used to associate individual reads back to the individual partitions." *See* "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[279] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[280] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[281] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Figure 3 (cropped)
[282] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)



351. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "at least 100 of said plurality of oligonucleotides comprise different molecular label sequences" limitation (a) of claim 17 of the '799 patent because "[t]he 10x™ GemCode™ Technology samples a pool of ~ 750000 barcodes to separately index each cell's transcriptome"[283] according to a method wherein "[e]ach Gel Bead contains millions of oligo primers."[284]

[283] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[284] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)

352. The **Single Cell 3' Workflow** and **Single Cell 5' Workflow** Accused Products meet the "lysing said single cell, thereby releasing nucleic acid targets from said cell" limitation (b) of claim 17 of the '799 patent because "[o]nce partitioned, the Gel Bead dissolves and its oligo primers are released into the aqueous environment of the GEM. The cell captured in the GEM is also lysed. The contents of the GEM (oligos, lysed cell components and Master Mix) are incubated in an RT reaction to generate full-length, barcoded cDNA from the poly A-tailed mRNA transcripts."[285] The poly A-tailed mRNA transcripts are nucleic acid targets release from the cell.

353. The **Single Cell 3' Workflow** Accused Products meet the "attaching said nucleic acid targets to said plurality of oligonucleotides" limitation (c) of claim 17 of the '799 patent because "[u]pon dissolution of the Single Cell 3' Gel Bead in a GEM, primers . . . are released and mixed with cell lysate and Master Mix. Incubation of the GEMs then produces barcoded, full-length cDNA from poly-adenylated mRNA."[286] As shown below,[287] the poly A-tailed mRNA transcripts released from lysing the cell hybridize to the "30nt Poly(dT) primer sequence" and are thus attached to said plurality of oligonucleotides. The subsequent reverse transcriptase reaction "generate[s] full-length, barcoded cDNA from the poly A-tailed mRNA transcripts."[288]

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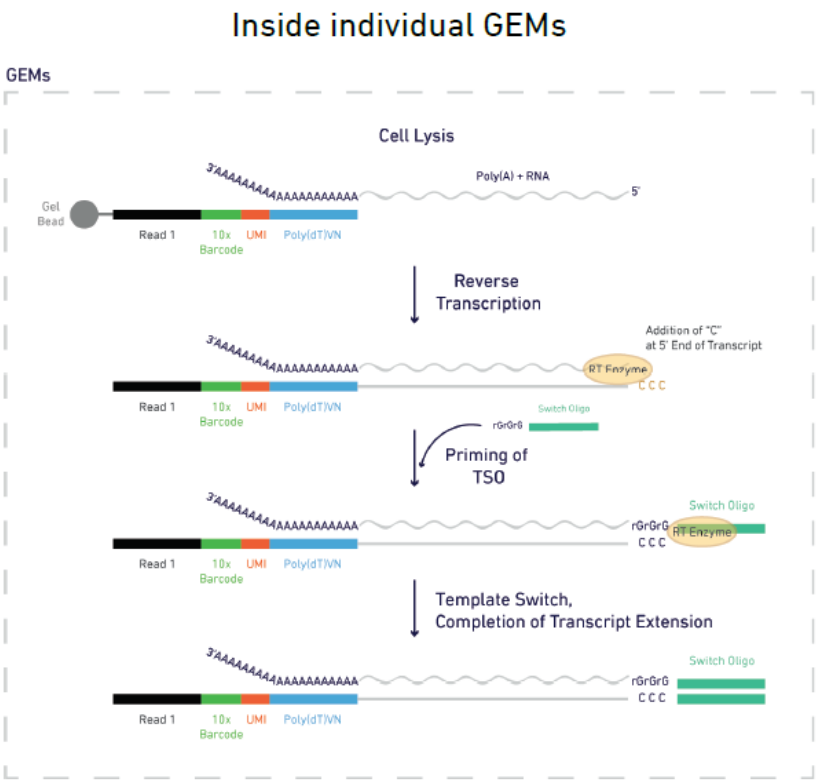
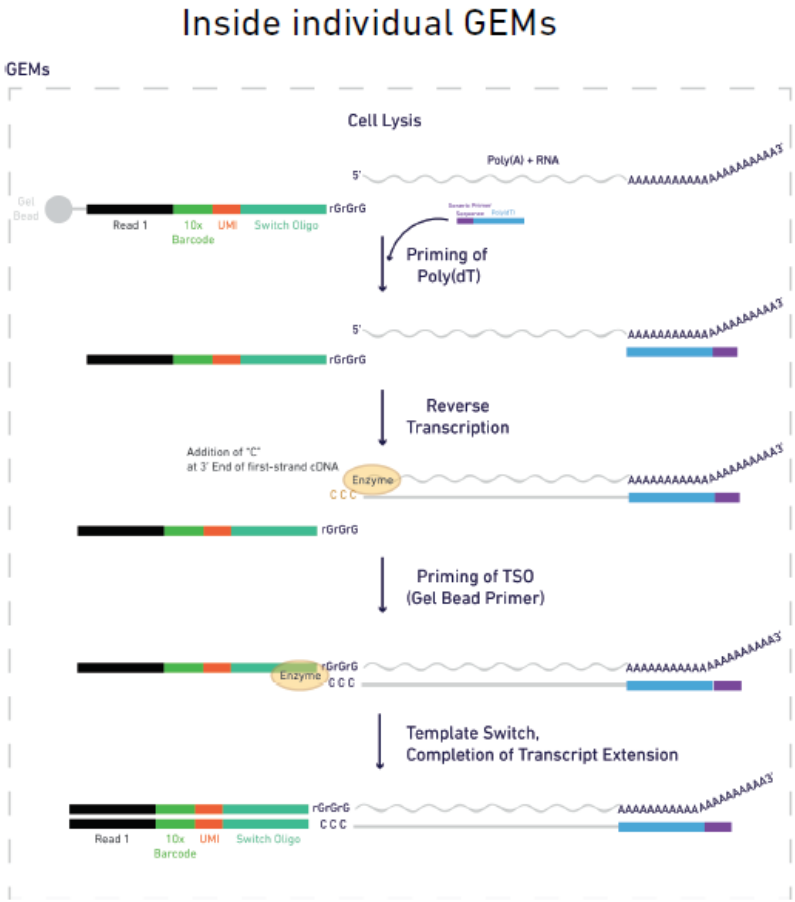
[285] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf); "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf)
[286] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)
[287] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell 3' v2 Libraries" (CG000108_AssayConfiguration_SC3v2.pdf) at Figure 3 (cropped)
[288] "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3_ReagentKitv2UserGuide_RevD.pdf)



354. The **Single Cell 5' Workflow** Accused Products meet the "attaching said nucleic acid targets to said plurality of oligonucleotides" limitation (c) of claim 17 of the '799 patent because "[u]pon dissolution of the Single Cell 5' Gel Bead in a GEM, oligonucleotides . . . are released and mixed with cell lysate and Master Mix that contains reverse transcription (RT) reagents and poly(dT) primers. Incubation of the GEMs then produces barcoded, full-length cDNA from poly-adenylated mRNA."[289] As shown below,[290] the poly A-tailed mRNA transcripts released from lysing the cell are reverse transcribed into cDNA, the 3' end of which hybridizes to the "13nt Switch Oligo." Thus, the poly A-tailed mRNA transcripts released from

[289] "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)
[290] "TECHNICAL NOTE Assay Scheme and Configuration of Chromium™ Single Cell V(D)J Libraries" (CG000109_AssayConfiguration_VDJ_RevD.pdf) at Figure 3 (cropped)

lysing the cell are attached to said plurality of oligonucleotides via hybridization with the cDNA which is hybridized to the "13nt Switch Oligo" of the plurality of oligonucleotides.



355. 10X has also induced and currently induces infringement of at least claim 17 of the '799 patent under 35 U.S.C. § 271(b) by providing to customers the Accused Products, along with directions for use that, when followed in an intended manner and in a normal mode of operation, 10X knows infringes at least claim 17 of the '799 patent.[291] 10X has known of the '799 patent and of its infringement of that patent since at least May 2017. By providing its

[291] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

customers with the Accused Products and those directions for use, 10X specifically intends that its customers infringe the '799 patent.

356. 10X has contributorily infringed and currently contributorily infringes under 35 U.S.C. § 271(c) at least claim 17 of the '799 patent. 10X has designed the Accused Products specifically to be used in a manner as claimed at least claim 17 of the '799 patent.[292] As such, the Accused Products are a material component of the patented combination, specifically designed to be used according to at least claim 17 of the '799 patent, and especially made and adapted for use in a manner that infringes at least claim 17 of the '799 patent. The Accused Products are not staple articles of commerce and they do not have substantial uses that do not infringe at least claim 17 of the '799 patent. 10X has knowledge of the '799 patent and is aware that the Accused Products are especially made to be used in a system that infringes the '799 patent.

357. Defendant's infringement has been willful and deliberate because Defendant has known of the '799 patent since at least May 2017 and knew or should have known of its infringement but acted despite an objectively high likelihood that such acts would infringe the '799 patent.

358. As the direct and proximate result of Defendant's conduct, Plaintiffs have suffered and, if Defendant's conduct is not stopped, will continue to suffer, severe competitive harm, irreparable injury, and significant damages, in an amount to be proven at trial. Because Plaintiffs' remedy at law is inadequate, Plaintiffs seek, in addition to damages and injunctive relief. Plaintiffs' business operates in a competitive market and will continue suffering irreparable harm absent injunctive relief.

[292] See, e.g., "Chromium™ Single Cell 3' Reagent Kits v2 User Guide" (CG00052_SingleCell3'ReagentKitv2UserGuide_RevD.pdf); "Chromium™ Single Cell V(D)J Reagent Kits User Guide" (CG000086_SingleCellVDJReagentKitsUserGuide_RevD.pdf)

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs BD and Cellular Research pray for relief and judgment that:

a. 10X has infringed the Asserted Patents;

b. Plaintiffs are entitled to preliminary and permanent injunctive relief enjoining 10X, its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from manufacturing, using, offering for sale, selling in the United States, or importing into the United States, the Accused Products, and any other product that infringes or induces or contributes to the infringement of the Asserted Patents, prior to the expiration date of the last to expire of those patents;

c. Plaintiffs are entitled to an award of damages pursuant to 35 U.S.C. § 284, including pre-judgment and post-judgment interest;

d. 10X's infringement of the Asserted Patents has been willful and Plaintiffs are entitled to enhanced damages up to and including trebling of the damages awarded to them;

e. Plaintiffs are entitled to their costs and reasonable expenses to the fullest extent permitted by law;

f. This case is exceptional pursuant to 35 U.S.C. § 285, and plaintiffs are entitled to an award of attorneys' fees; and

g. Plaintiffs are entitled to other and further relief as the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Federal Rule of Civil Procedure 38(b), BD and Cellular Research hereby demand a trial by jury on all issues so triable.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Michael J. Flynn

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February 8, 2019

CERTIFICATE OF SERVICE

I hereby certify that on February 8, 2019, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on February 8, 2019, upon the following in the manner indicated:

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