IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

COMPLETE GENOMICS, INC., Plaintiff, v. ILLUMINA, INC., Defendant.	C.A. No. _____ **JURY TRIAL DEMANDED**

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Complete Genomics, Inc., by and through its undersigned counsel, for their complaint against Defendant Illumina, Inc., alleges as follows:

THE PARTIES

1. Plaintiff Complete Genomics, Inc. ("CGI") is a privately held research company with its principal place of business at 2904 Orchard Way, San Jose, California 95134.

2. CGI is incorporated under the laws of the State of Delaware.

3. Defendant Illumina, Inc. ("Illumina") is a Delaware corporation with its principal place of business at 5200 Illumina Way, San Diego, California 92122.

JURISDICTION AND VENUE

4. This Court has personal jurisdiction over Illumina because Illumina is incorporated in the State of Delaware. Upon information and belief, Illumina has systematic and continuous contacts in this judicial district, regularly transacts business within this district, and regularly avails itself of the benefits of this district. Upon information and belief, Illumina also sells, distributes, and supports accused products (and products for practicing accused methods) as

well as practices the accused methods in this district and derives substantial revenues from sales in this district.

5. This action arises under the patent laws of the United States of America, 35 U.S.C. § 1, et seq. This Court has federal question jurisdiction under 28 U.S.C. § 1331 and 28 U.S.C. § 1338(a) because this is a civil action arising under the patent laws of the United States.

6. Venue is proper in this District under 28 U.S.C. § 1400(b) because Illumina is incorporated in the State of Delaware and therefore resides within this district.

THE ’132 PATENT

7. On December 29, 2015, the United States Patent and Trademark Office duly and legally issued U.S. Patent No. 9,222,132 (hereinafter the “’132 patent”), titled “Methods and Compositions for Efficient Base Calling in Sequencing Reactions.” The named inventor of the ’132 patent is Radoje Drmanac. The ’132 patent is attached hereto as Ex. A (ex. U.S. Patent No. 9,222,132).

8. By assignment, CGI obtained the entire right, title, and interest to and in the ’132 patent.

INFRINGEMENT OF THE ’132 PATENT

A. Direct Infringement of the ’132 Patent

9. Illumina sells DNA sequencing systems that it describes as “two-channel” sequencing systems. *See* Ex. B (2-Channel SBS Technology, https://www.illumina.com/science/technology/next-generation-sequencing/sequencing-technology/2-channel-sbs.html).

10. In combination with Illumina's "two-channel" sequencing systems, Illumina sells "Library Preparation Kits" to prepare DNA fragments for sequencing and "Cluster Generation and Sequencing Kits" to immobilize, amplify, and sequence the fragments.

11. As described below, use of Illumina's "two-channel" sequencing systems in combination with Illumina's "Library Preparation Kits" and "Cluster Generation and Sequencing Kits" in the United States by Illumina and its customers constitutes direct infringement of at least claims 1-4 of the '132 patent.

1. Illumina's "Two-Channel" Sequencing Systems

12. Illumina's "two-channel" sequencing systems include at least the NovaSeq 6000 system, the NextSeq series systems, and the MiniSeq system, as shown below:

See Ex. B.

2. Illumina's "Library Preparation Kits"

13. Illumina uses and sells Library Preparation Kits that are specifically compatible and marketed for use with one or more of its "two-channel" sequencing systems (*e.g.*, the

NovaSeq 6000, NextSeq Series, and MiSeq systems). *See, e.g.*, Ex. C (Products for the NovaSeq 6000 System, https://www.illumina.com/products/by-system/novaseq-products.html); Ex. D (Products for the NextSeq Series, https://www.illumina.com/products/by-system/nextseq-products.html); Ex. E (Products for the MiSeq System, https://www.illumina.com/products/by-system/miseq-products.html).

14. According to Illumina's website, at least the following Library Preparation Kits are designed for sequencing genomic DNA and are compatible with the NovaSeq 6000 system: Nextera DNA Exome, Nextera DNA Flex Library Prep Kit, Nextera Flex for Enrichment, TruSeq DNA Exome, TruSeq DNA Nano, and TruSeq DNA PCR-Free (hereinafter "NovaSeq DNA Prep Kits"). *See* Ex. F (Library Preparation Kits for NovaSeq 6000 System).

15. At least the following Library Preparation Kits are designed for sequencing RNA and are compatible with the NovaSeq 6000: TruSeq RNA Exome, TruSeq Stranded Total RNA, TruSeq Stranded Total RNA with Ribo-Zero Globin, TruSeq Stranded Total RNA with Ribo-Zero Plant, TruSeq Stranded mRNA (hereinafter "NovaSeq RNA Prep Kits"). *See* Ex. F.

16. At least the following Library Preparation Kits are designed for sequencing genomic DNA and are compatible with the NextSeq 500/550 series systems: AmpliSeq for Illumina On-Demand, Nextera DNA Exome, Nextera Rapid Capture Custom Enrichment Kit, Nextera XT DNA Library Preparation Kit, TruSeq Custom Amplicon Low Input Kit, TruSeq Custom Amplicon v1.5, TruSeq DNA Exome, TruSeq DNA Nano, TruSeq DNA PCR-Free, TruSeq Methyl Capture EPIC Library Prep Kit, and TruSight Oncology 500 (hereinafter "NextSeq DNA Prep Kits"). *See* Ex. G (Library Preparation Kits for NextSeq 500/550 System).

17. At least the following Library Preparation Kits are designed for sequencing RNA and are compatible with the NextSeq 500/550 series systems: AmpliSeq for Illumina Custom RNA Panel, TruSeq RNA Exome, TruSeq RNA Library Prep Kit v2, TruSeq Stranded Total RNA, TruSeq Stranded Total RNA with RiboZero Globin, TruSeq Stranded Total RNA with Ribo-Zero Plant, TruSeq Stranded mRNA, TruSeq Targeted RNA Expression Library Prep Kits, and TruSight RNA Fusion Panel (hereinafter NextSeq RNA Prep Kits"). *See* Ex. G.

18. At least the following Library Preparation Kits are designed for sequencing genomic DNA and are compatible with the MiSeq system: AmpliSeq for Illumina BRCA Panel, AmpliSeq for Illumina Cancer Hotspot Panel v2, AmpliSeq for Illumina Childhood Cancer Panel, AmpliSeq for Illumina Custom DNA Panel, AmpliSeq for Illumina Focus Panel, AmpliSeq for Illumina Library Prep Indexes and Accessories, AmpliSeq for Illumina Myeloid Panel, Nextera DNA Flex Library Prep Kit, Nextera Flex for Enrichment, Nextera Mate Pair Library Prep Kit, Nextera Rapid Capture Custom Enrichment Kit, TruSeq ChIP Library Preparation Kit, TruSeq Custom Amplicon Low Input Kit, TruSeq Custom Amplicon v1.5, TruSeq DNA Nano, and TruSeq DNA PCR-Free (hereinafter "MiSeq DNA Prep Kits"). Ex. H (Library Preparation Kits for MiSeq System).

19. At least the following Library Preparation Kits are designed for sequencing RNA and are compatible with the MiSeq: AmpliSeq for Illumina Custom RNA Panel, AmpliSeq for Illumina Immune Response Panel, TruSeq RNA Library Prep Kit v2, TruSeq Small RNA Library Preparation Kits, TruSeq Targeted RNA Expression Library Prep Kits, and TruSight RNA Fusion Panel (hereinafter "MiSeq RNA Prep Kits"). *See* Ex. H.

3. Illumina's Cluster Generation and Sequencing Kits

20. Illumina uses and sells for use "Cluster Generation and Sequencing Kits" that are specifically compatible and marketed for use with one or more "two-channel" sequencing systems (*e.g.*, the NovaSeq 6000, NextSeq Series, and MiSeq systems). *See, e.g.*, Ex. I (Reagent Kits for NovaSeq 6000 System); Ex. J (Reagent Kits for NextSeq 500/550 System); and Ex. K (Reagent Kits for MiSeq Ssytem).

21. According to Illumina's website, at least the following Cluster Generation and Sequencing Kits are specifically designed for use with the NovaSeq 6000 system: the NovaSeq Reagent Kits (including SP Reagent Kits, S1 Reagent Kits, S2 Reagent Kits, and S4 Reagent Kits), the NovaSeq Xp Workflow, and the PhiX Control v3 (hereinafter the "NovaSeq Sequencing Kits"). *See* Ex. I.

22. According to Illumina's website, at least the following Cluster Generation and Sequencing Kits are specifically designed for use with the NextSeq 500 Series systems: the NextSeq 500/550 TG Kits (including v1.2, v2, and v2.1), the NextSeq 500/500 v2.5 Kits, and the PhiX control v3 (hereinafter "NextSeq Reagent Kits"). *See* Ex. J.

23. According to Illumina's website, at least the following Cluster Generation and Sequencing Kits are specifically designed for use with the MiSeq system: the MiSeq Reagent Kits v2 (including MiSeq Reagent Kit v2, MiSeq Reagent Micro Kit v2, MiSeq Reagent Nano Kit v2, and TG MiSeq Reagent Kit v2), the MiSeq Reagent Kit v3, and the PhiX Control v3 (hereinafter "MiSeq Reagent Kits"). *See* Ex. K.

4. Infringement Analysis for Claims 1-4 of the ’132 Patent

24. Illumina’s and its customers’ prior and continued use in the United States of Illumina’s “two channel” sequencing systems (*i.e.*, the NovaSeq 6000, NextSeq Series, and MiSeq systems) in combination with Illumina’s “Library Preparation Kits” and “Cluster Generation and Sequencing Kits” constitutes direct infringement pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, of at least claims 1-4 of the ’132 Patent.

25. By way of example only, direct infringement of claims 1-4 by Illumina and its customers’ use of the NovaSeq 6000 in combination with Illumina’s “TruSeq™ DNA PCR-Free” or “TruSeq™ DNA Nano” library preparation kits and the NovaSeq 6000 Reagent Kits is detailed in Paragraphs 31 to 85 below.

26. Illumina’s “TruSeq™ DNA PCR-Free” and “TruSeq™ DNA Nano” kits are also marketed by Illumina for use with the NextSeq Series and MiniSeq systems, and function in the same manner as described below when used with these systems.

27. Moreover, the following infringement analysis of the use of the NovaSeq 6000 system with the “TruSeq™ DNA PCR-Free” or “TruSeq™ DNA Nano” and the NovaSeq Sequencing Kits is also representative of the use of the NovaSeq 6000 system, the NextSeq Series systems, and the MiniSeq system, in conjunction with all of their respective “Library Preparation Kits” and “Cluster Generation and Sequencing Kits,” as described below in paragraphs 28 to 30.

28. Use of the NovaSeq Sequencing Kits by Illumina, or its customers, when used in their normal and intended manner in conjunction with the NovaSeq 6000 system and the NovaSeq DNA Prep Kits constitutes infringement of at least claims 1-4 of the ’132 patent. Use

of the NovaSeq Sequencing Kits by Illumina, or its customers, when used in their normal and intended manner in conjunction with the NovaSeq 6000 system and the NovaSeq RNA Prep Kits constitutes infringement of at least claims 1-2 of the ’132 patent.

29. Use of the NextSeq Reagent Kits by Illumina, or its customers, when used in their normal and intended manner in conjunction with the NextSeq Series systems and the NextSeq DNA Prep Kits constitutes infringement of at least claims 1-4 of the ’132 patent. Use of the NextSeq Reagent Kits by Illumina, or its customers, when used in their normal and intended manner in conjunction with the NextSeq Series system and the NextSeq RNA Prep Kits constitutes infringement of at least claims 1-2 of the ’132 patent.

30. Use of the MiSeq Reagent Kits by Illumina or its customers, when used in their normal and intended manner in conjunction with the MiSeq system and the MiSeq DNA Prep Kits constitutes infringement of at least claims 1-4 of the ’132 patent. Use of the MiSeq Reagent Kits by Illumina, or its customers, when used in their normal and intended manner in conjunction with the MiSeq system and the MiSeq RNA Prep Kits constitutes infringement of at least claims 1-2 of the ’132 patent.

a. Infringement of Claim 1 of the ’132 Patent

31. Claim 1 of the ’132 patent recites:

> A method for determining identities of nucleotides at detection positions of a plurality of different nucleic acid templates by performing sequencing-by-extension reactions, the method comprising:
>
> (a) providing an array comprising single-stranded nucleic acid templates disposed at positions on a surface;
>
> (b) for each of a plurality of said single-stranded nucleic acid templates, determining the identity of nucleotides at detection positions in the nucleic acid template in multiple cycles of a sequencing-by-extension reaction, comprising:

> i) binding a complementary nucleotide to a nucleotide at a detection position,
> ii) detecting, at the position on the surface occupied by the nucleic acid template, the presence or absence of fluorescent signal(s) associated with the complementary nucleotide; wherein
> 1) detecting a first fluorescent signal and not a second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C;
> 2) detecting the second fluorescent signal and not the first fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from the nucleotide selected in (1);
> 3) detecting both the first fluorescent signal and the second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from nucleotides selected in (1) and (2); and
> 4) detecting neither the first fluorescent signal nor the second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from the nucleotides selected in (1), (2) and (3);
> iii) deducing the identity of the nucleotide at the detection position in the nucleic acid template based on the identity of the complementary nucleotide.

i. "A method for determining identities of nucleotides at detection positions of a plurality of different nucleic acid templates by performing sequencing-by-extension reactions, the method comprising:"

32. "Sequencing-by-extension" is also known in the art as "sequencing-by-synthesis" or "SBS." *See* Ex. A at 26:44-45.

33. According to Illumina's website, "[a]ll Illumina sequencing systems use our proven sequencing by synthesis (SBS) technology." Ex. B at 1. The NovaSeq™ 6000 Sequencing System brochure confirms that the NovaSeq 6000 relies on SBS:

> The NovaSeq 6000 System represents the most powerful, simple, scalable, and reliable high-throughput Illumina sequencing platform to date, producing outstanding data quality. ***The***

> ***instrument relies on proven Illumina sequencing by synthesis (SBS) chemistry***. This proprietary reversible terminator–based method enables the massively parallel sequencing of billions of DNA fragments, ***detecting single bases as they are incorporated into growing DNA strands***.

Ex. L (NovaSeq™ 6000 Sequencing System Brochure, https://www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/novaseq-6000-system-specification-sheet-770-2016-025.pdf) at 2. The NovaSeq 6000 is designed to sequence nucleotides using sequencing-by-synthesis, during which nucleotides are detected one-by-one after each nucleotide is incorporated into a growing nucleic acid strand. This process occurs on a plurality of growing nucleic acid strands, each of which is bound to a nucleic acid template. The NovaSeq 6000 performs SBS when used in conjunction with Illumina's Library Preparation Kits and Sequencing Kits (for example, the "TruSeq™ DNA PCR-Free" and the "TruSeq™ DNA Nano" library preparation kits and the "NovaSeq 6000 Reagent Kits"). Therefore, use of the NovaSeq 6000 determines the identities of nucleotides at detection positions of a plurality of different nucleic acid templates.

ii. "(a) providing an array comprising single-stranded nucleic acid templates disposed at positions on a surface"

34. Use of the NovaSeq 6000 system requires a flow cell (*i.e.*, the SP, S1, S2, and S4 flow cells that are part of the NovaSeq Sequencing Kits) that comprises a surface upon which single-stranded nucleic acid templates are disposed at positions on the surface.

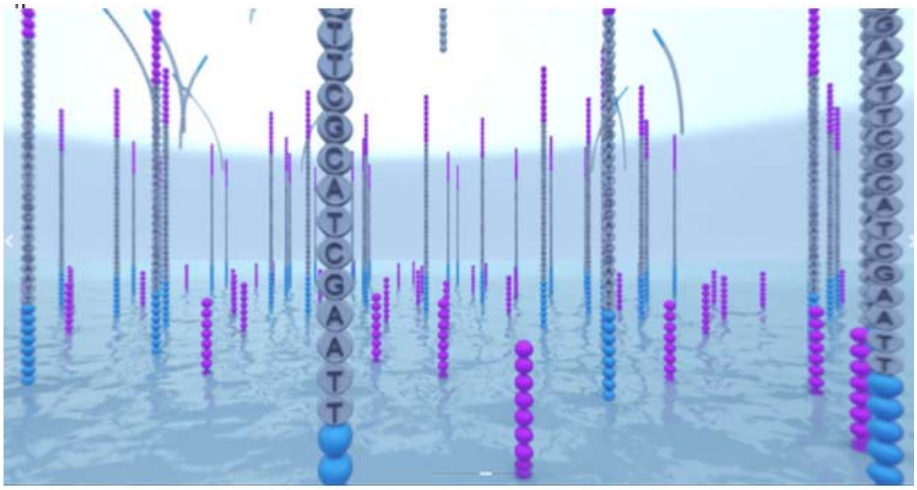
35. Illumina's NovaSeq System Guide describes the arrays formed on the NovaSeq flow cells:

> The NovaSeq 6000 flow cell is a patterned flow cell encased in a cartridge. ***The flow cell is a glass-based substrate containing billions of nanowells*** in an ordered arrangement, which increases

> the number of output reads and sequencing data. ***Clusters are generated in the nanowells from which sequencing is then performed.***

Ex. M (NovaSeq 6000 System Guide, http://jp.support.illumina.com/content/dam/illumina-support/documents/documentation/system_documentation/novaseq/novaseq-6000-system-guide-1000000019358-09.pdf) at 12 (emphasis added). A flow cell that has been prepared using Illumina sample preparation and sequencing kits comprises single stranded nucleic acid templates disposed on a surface. The single-stranded nucleic acid templates are replicated in "clusters," which are localized areas in which multiple copies of the same nucleic acid template are fixed to the surface of the flow cell. *See* Ex. N (Introduction to Next Generation Sequencing Technology, https://www.illumina.com/documents/products/illumina_sequencing_introduction.pdf) (defining "clusters as "[a] clonal grouping of template DNA bound to the surface of a flow cell") at 14.

36. The NovaSeq System Explorer Video, available on Illumina's website, depicts a cluster located inside a nanowell, in which many identical single-stranded nucleic acid molecules are bound to the surface of the nanowell:



Ex. O (Excerpts of NovaSeq System Explorer Video, https://www.illumina.com/systems/sequencing-platforms/novaseq/system-explorer.html); *see also* Ex. P (NovaSeq VR| Experience a Leap Forward in Technology Video, https://www.illumina.com/company/video-hub/68oY5APcfJM.html) at 1:54-1:58.

37. The NovaSeq System Explorer video also depicts the process by which the clusters are generated. Ex. O; *see also* Ex. P at 1:30-2:00.

38. After the single-stranded DNA derived from the sample anneals to the surface-bound oligonucleotide, a polymerase generates the surface-bound template strand. Ex. O; *see also* Ex. P at 1:35-1:40. The sample strand is then dissociated from the template and washed away. *Id.*

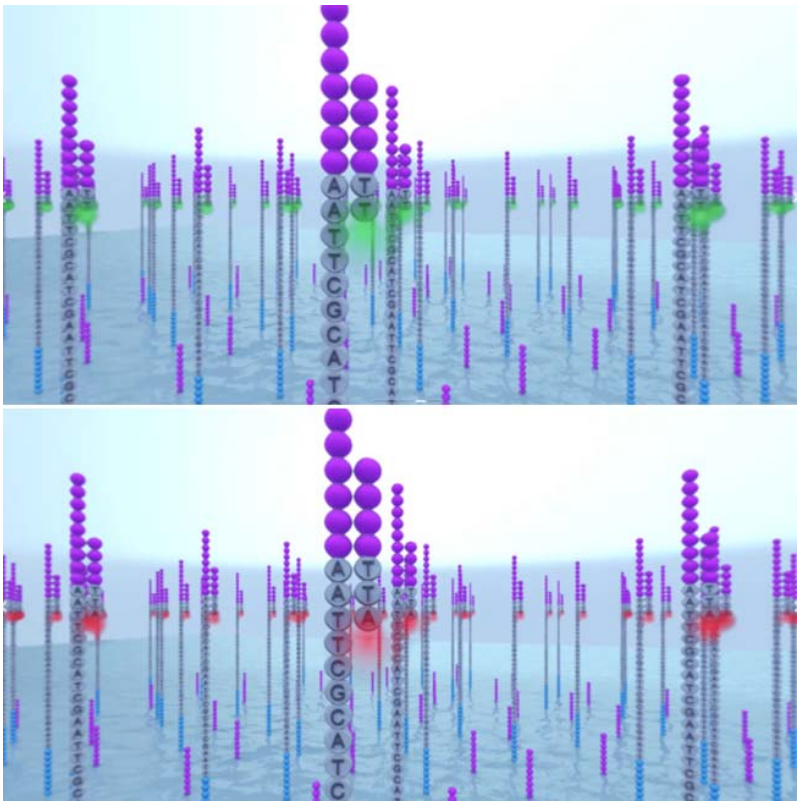
39. Next, a bridge amplification PCR step generates a second surface-bound strand that is the reverse-complement of the original template strand. Ex. O; *see also* Ex. P at 1:40-1:55. This bridge amplification process is repeated over several cycles, thereby generating two sets of surface-bound single-stranded DNA molecules (one forward set and one reverse-complement set). *Id.* Finally, one of the sets is cleaved and washed away, leaving only the other set of surface-bound single-stranded DNA (*e.g.*, the forward set), as depicted in the image above.

40. Thus, use of the NovaSeq 6000 for SBS involves providing an array comprising single-stranded nucleic acid templates disposed on a surface.

iii. "(b) for each of a plurality of said single-stranded nucleic acid templates, determining the identity of nucleotides at detection positions in the nucleic acid template in multiple cycles of a sequencing-by-extension reaction, comprising:"

41. Illumina has described how the NovaSeq 6000 "relies on proven Illumina sequencing by synthesis (SBS) chemistry" and sequences "billions of DNA fragments [by] detecting single bases as they are incorporated into growing DNA strands." Ex. L at 2.

42. Illumina's NovaSeq System Explorer Video depicts multiple cycles of SBS reactions being used to determine the identity of nucleotides on a plurality of single-stranded nucleotide templates:



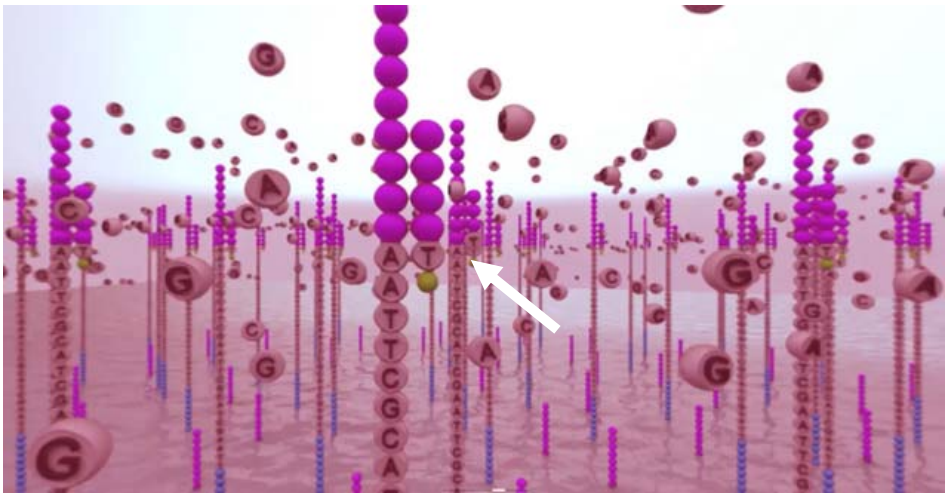
Ex. O; *see also* Ex. P at 2:05-2:08.

43. Thus, the NovaSeq 6000 System sequences a plurality of single-stranded nucleic acid templates by determining the identity of nucleotides at each detection position during multiple cycles of an SBS reaction.

iv. "i) binding a complementary nucleotide to a nucleotide at a detection position,"

44. Each SBS reaction cycle on the NovaSeq 6000 comprises a step of binding a complementary nucleotide to a nucleotide at a detection position.

45. Illumina's NovaSeq System Explorer Video depicts the SBS reaction cycle, and shows a labeled Thymine (T) bound to its complementary Adenine (A) nucleotide at a detection position:

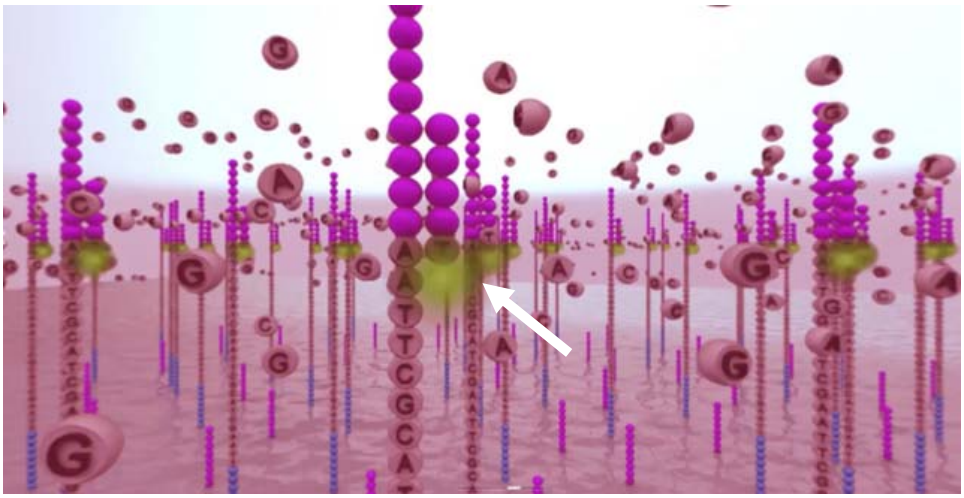


Ex. O (annotated with arrow); *see also* Ex. P at 2:00-2:05.

46. The NovaSeq 6000 Sequencing System brochure describes the NovaSeq's sequencing method as "detecting single bases as they are incorporated into growing DNA strands." Ex. L at 2.

47. The NovaSeq 6000 detects incorporation of single bases by detecting the presence or absence of fluorescent signal(s) that are associated with the identity of the complementary nucleotide that was incorporated. Ex. M at 68 ("Intensities for each cluster are extracted from the red and green images and compared against each other, which results in four distinct populations. Each population corresponds to a base.").

48. For example, the NovaSeq System Explorer video depicts excitation of a green fluorescent label attached to Thymine molecules:



Ex. O (annotated with arrow); *see also* Ex. P at 2:00-2:05. In the above example, the Thymine binds preferentially to the Adenine, such that the signal(s) detected by the NovaSeq 6000 result in identification of the Thymine that was incorporated and its complementary Adenine nucleotide.

v. "ii) detecting, at the position on the surface occupied by the nucleic acid template, the presence or absence of fluorescent signal(s) associated with the complementary nucleotide; wherein . . ."

49. Illumina's website indicates that the NovaSeq 6000 utilizes a method known as "two-channel sequencing." Ex. B. On information and belief, during "two-channel sequencing," the identity of each nucleotide is deduced from two signals. *Id*. ("The 2-channel SBS method requires only 2 images per cycle, instead of 4[.]"). On information and belief, the NovaSeq 6000 detects two wavelength ranges, one for green light and one for red light. On information and belief, light within these two ranges of wavelength are the two signals detected by the NovaSeq 6000. The "NovaSeq 6000 System Guide" explains in detail how the NovaSeq 6000 deduces the identity of nucleotides using two signals:

> Base calling determines a base (A, C, G, or T) for every cluster of a given tile at a specific cycle. ***The NovaSeq 6000 Sequencing System uses two-channel sequencing, which requires only two images to encode the data for four DNA bases, one from the red channel and one from the green channel***. A no call is identified as N. No calls occur when a cluster does not pass filter, registration fails, or a cluster is shifted off the image. ***Intensities for each cluster are extracted from the red and green images and compared against each other, which results in four distinct populations. Each population corresponds to a base***. The base calling process determines which population each cluster belongs to.

Ex. M at 68 (emphasis added). The NovaSeq System Guide further explains that "[t]he NovaSeq 6000 uses one camera with bidirectional scanning technology to quickly image the flow cell in ***two color channels simultaneously***." *Id*. at 1 (emphasis added).

50. The NovaSeq System detects two fluorescent signals (red and green) to determine the identity of the complementary nucleotides during sequencing.

51. Table 22 of the NovaSeq 6000 System Guide depicts how the NovaSeq 6000 determines nucleotide identity based on the two signals detected by the instrument:

Table 22 Base Calls in 2-Channel Sequencing

Base	Red Channel	Green Channel	Result
A	1 (on)	1 (on)	Clusters that show intensity in both the red and green channels.
C	1 (on)	0 (off)	Clusters that show intensity in the red channel only.
G	0 (off)	0 (off)	Clusters that show no intensity at a known cluster location.
T	0 (off)	1 (on)	Clusters that show intensity in the green channel only.

Id. at 68 (Table 22).

vi. "1) detecting a first fluorescent signal and not a second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C;"

52. As shown in Table 22 of the NovaSeq 6000 System Guide, when the NovaSeq 6000 detects the red signal but not the green signal (*i.e.*, the "Red Channel" is "1 (on)" but the "Green Channel" is "0 (off)"), the base will be identified as "C" for Cytosine.

vii. "2) detecting the second fluorescent signal and not the first fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from the nucleotide selected in (1);"

53. As shown in Table 22 of the NovaSeq 6000 System Guide, when the NovaSeq 6000 detects the green signal but not the red signal (*i.e.*, the "Green Channel" is "1 (on)" but the "Red Channel" is "0 (off)"), the base will be identified as "T" for Thymine.

viii. "3) detecting both the first fluorescent signal and the second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from nucleotides selected in (1) and (2); and"

54. As shown in Table 22 of the NovaSeq 6000 System Guide, when the NovaSeq 6000 detects both the red signal and the green signals (*i.e.*, both the "Red Channel" and "Green Channel" are "1 (on)"), the base will be identified as "A" for Adenine.

ix. "4) detecting neither the first fluorescent signal nor the second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from the nucleotides selected in (1), (2) and (3);"

55. As shown in Table 22 of the NovaSeq 6000 System Guide, when the NovaSeq 6000 detects neither a red nor green signal (*i.e.*, both the "Green Channel" and the "Green Channel" are "0 (off)"), the base will be identified as "G" for Guanine.

x. "iii) deducing the identity of the nucleotide at the detection position in the nucleic acid template based on the identity of the complementary nucleotide."

56. Illumina's "two-channel" sequencing systems, such as the NovaSeq 6000, deduce the identity of the nucleotide at the detection position of the template strand based on the signal detected from excitation of the fluorophore bound to the complementary molecule.

57. By way of background, in the genome, DNA is a double-stranded molecule made of up to four different nucleotides: Adenine (A), Thymine (T), Cytosine (C), and Guanine (G). The nucleotides naturally bind in the following sets of complementary nucleotides: A to T and C to G. This complementarity is integral to the proper functioning of Illumina's sequencers, which rely on the tendency for nucleotides to bind specifically and selectively with their complement. *See* Ex. N at 4 ("As all four reversible terminator-bound dNTPs are present during each

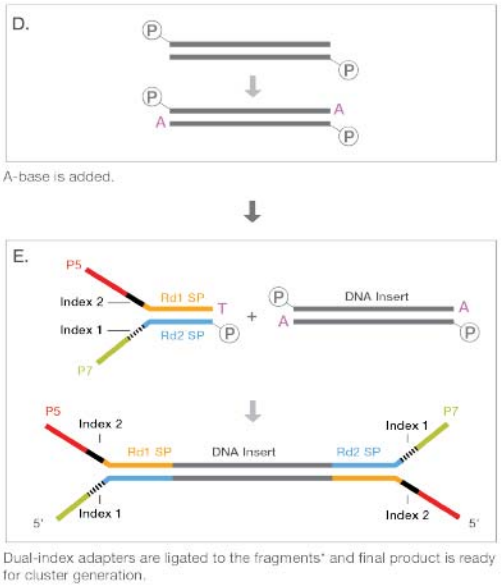
sequencing cycle, natural competition minimizes incorporation bias and greatly reduces raw error rates[.]").

58. Because the nucleotides necessarily bind in complementary pairs, the determination of the identity of the incorporated nucleotide also results in the deduction of the complementary nucleotide in the template strand.

59. On information and belief, Illumina's "two-channel" sequencing systems, such as the NovaSeq 6000, also explicitly deduce the identity of the nucleotides at the detection positions based on the identity of the incorporated nucleotides in order to align the sequences.

60. This is necessary because approximately half of the sequenced single-stranded templates will have been derived from the forward strand of the original double-stranded DNA sample, and the other half will have been derived from the reverse strand. Sequences from templates derived from one of these strands (*e.g.*, the reverse strand) will not align to the reference genome. Thus, in order to align the sequencing data, the reverse-complement of the incorporated strand's sequence must be deduced so that both orientations are considered during alignment with the sequences of the other templates or to a reference genome.

61. For example, as depicted in Illumina's TruSeq DNA Nano brochure, the sample preparation process appends adapter to both strands of the sample DNA:



Ex. Q (TruSeq™ DNA Nano, https://www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/datasheet_truseq_nano_dna_sample_prep_kit.pdf) at 2. Therefore, approximately half of the surface-bound template fragments will be derived from the forward strand of the sample DNA and the other half of the surface-bound template fragments will be derived from the reverse strand.

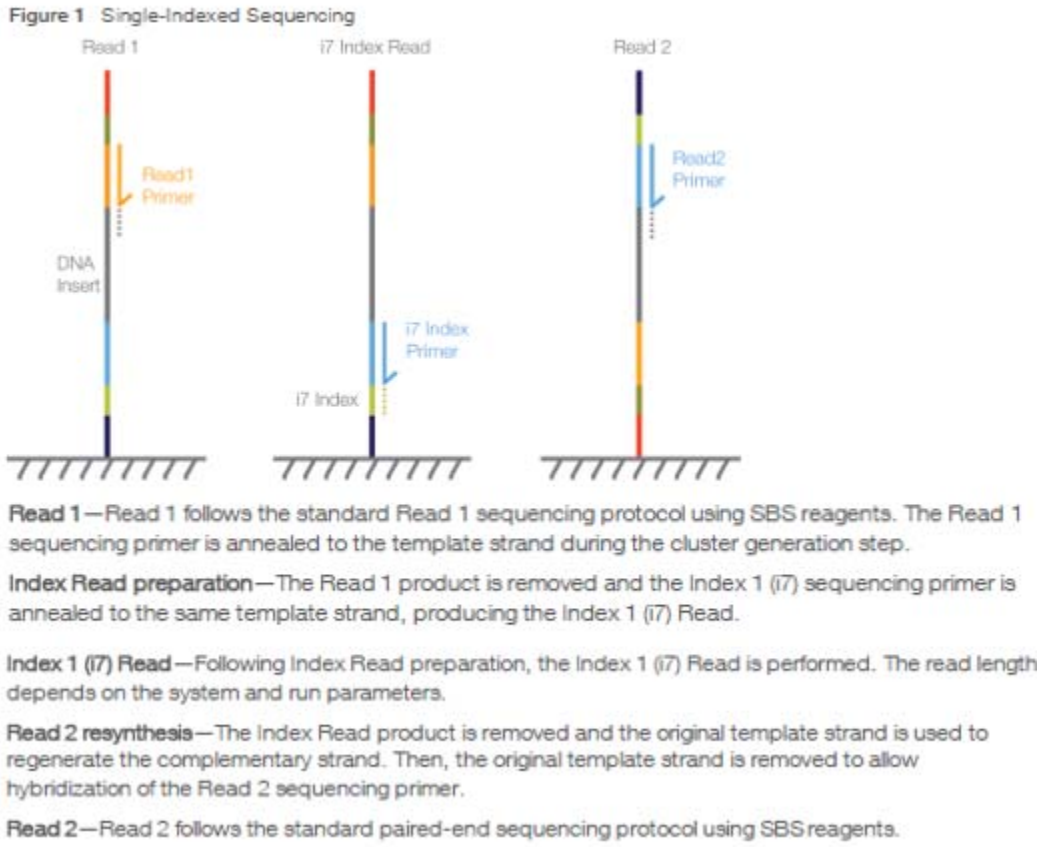
62. On information and belief, the user aligns the sequence fragments to a single-stranded reference genome through applications made available by Illumina, during the normal and intended use of the NovaSeq 6000. This process is depicted in the following excerpt from Illumina's "Introduction to Next Generation Sequencing" brochure:

Ex. N at 5. During sequencing, only half of the sequences generated (*e.g.*, those derived from forward strand fragments) will align directly to the single-stranded reference genome; the remaining sequences (*e.g.*, those derived from reverse strand fragments) will necessarily be in the reverse-complement orientation. Therefore, roughly 50% of the sequences generated during the operation of the NovaSeq 6000 necessarily have to be converted to their reverse-complement before they can be aligned to this reference genome. During this process, the system deduces the identity of the nucleotides in the template strand from which the sequence was derived.

63. Furthermore, when the NovaSeq 6000 is used for paired-end sequencing, such use necessarily involves performing this step, regardless of the orientation of the original sample strand.

64. The Illumina Indexed Sequencing Guide depicts the protocol run by the NovaSeq 6000 when running a single-index paired-end read. As demonstrated in the Figure below, this

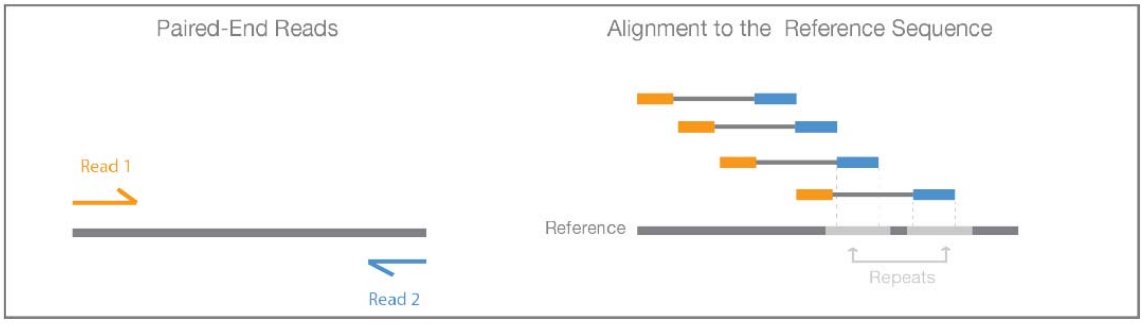
process entails two "Reads" in which an unknown target sequence and its reverse-complement are sequenced using sequencing by synthesis.



Ex. R (Indexed Sequencing Guide, https://www.illumina.com/content/dam/illumina-marketing/documents/products/illumina_sequencing_introduction.pdf) at 3. The Indexed Sequencing Guide states that this "single-indexed sequencing workflow applies to all Illumina sequencing platforms." *Id.* As shown above, the "the original template strand" (*i.e.*, the "DNA insert" used for Read 1 will be "used to regenerate the complementary strand," which is then used for Read 2.

65. Thus, to utilize the sequencing data from both reads (*e.g.*, to compare them both to a reference sequence), the reverse-complement of one of the reads must be deduced, as recited in Claim 1.

66. The Figure below, obtained from Illumina's website, depicts the alignment of paired-end reads to the same reference genome.



Ex. S (Paired-End Sequencing, https://www.illumina.com/science/technology/next-generation-sequencing/paired-end-vs-single-read-sequencing.html). As described above, the sequences of at least one of "Read 1" and "Read 2" were taken from a complementary template strand. This is depicted in the figure above, which shows Read 1 and Read 2 oriented in an antiparallel directions. *See id.* When both reads are aligned to the same reference sequence, as shown in the Figure above, at least one of these sequences must be converted to the reverse-complement, thereby deducing the identity of the nucleotides on the template sequence.

67. A similar process is performed during dual-index sequencing, which also necessarily performs this step of deducing the identity of a nucleotide in the template strand. Dual-index sequencing on the NovaSeq 6000 follows what Illumina describes as "Workflow A." Ex. R at 4 ("Dual-index sequencing on a paired-end flow cell follows one of two workflows,

depending on the system: Workflow A is performed on the NovaSeq™ 6000[.]"). Like the single-index read, "Workflow A" requires two reads, one of which utilizes the "original template strand" and the other utilizes the "complementary strand." *Id*. at 5. Thus, during a dual-index read on a NovaSeq 6000, the reverse-complement of one of the sequences must be deduced, as recited in Claim 1.

68. On information and belief, most researchers currently use the paired-end approach. *See* Ex. N at 5.

69. As noted above, NovaSeq users align the sequences to the reference genome using applications provided by Illumina, such as those offered on Illumina's BioSpace Sequencing Hub. According to Illumina's website, "***BaseSpace Sequence Hub is a direct extension of your Illumina instruments***. Encrypted data flow from the instrument into BaseSpace Sequence Hub, enabling you to manage and analyze your data easily with a curated set of analysis apps." Ex. T (BaseSpace Sequence Hub, https://www.illumina.com/products/by-type/informatics-products/basespace-sequence-hub.html). As described in the "NovaSeq™ 6000 Sequencing System" brochure, "[d]ata from the NovaSeq 6000 System can be streamed into BaseSpace Sequence Hub, a user-friendly genomics cloud computing platform optimized for processing large data volumes." Ex. L at 3.

70. Many of the applications available on the BaseSpace Sequencing Hub are specifically designed for aligning sequences to reference genomes. For example, the Burrows-Wheeler Aligner application (marketed as the "BWA Aligner") "aligns samples (consisting of FASTQ files) using the BWA-MEM aligner to a reference genome[.]" Ex. U (BWA Aligner, https://www.illumina.com/products/by-type/informatics-products/basespace-sequence-

hub/apps/bwa-aligner.html). In addition, BaseSpace Sequencing Hub offers many other applications that perform sequence alignment, such for example, the BWA Enrichment, Enrichment, Whole Genome Sequencing, TruSeq® Amplicon, TruSight Tumor 15, Amplicon DS, and Novoalign Generic DNA Pipeline applications. *See, e.g.*, Ex. V (BaseSpace Quick Guide, https://www.illumina.com/content/dam/illumina-marketing/documents/applications/basespace/basespace-handout-sequence-hub-apps-quick-guide-web.pdf).

71. Moreover, Illumina makes and sells the "BaseSpace Onsite Sequence Hub," which is "a local version of BaseSpace Sequence Hub that offers a secure data storage and computing solution that does not require an internet connection." Ex. W (BaseSpace Onsite, https://www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/datasheet-basespace-onsite.pdf) at 1. The BaseSpace Onsite Hub allows users to perform analysis, including alignment of sequences to a reference genome, on a local private system. *See id.* The BaseSpace Onsite Hub is designed to be compatible with at least the MiSeq and NextSeq Series systems. *Id.*

72. In addition, use of Illumina's "two-channel" sequencing systems, such as the NovaSeq 6000, also facilitates users' output of the base calling data in a FASTQ format in the form of the "reverse-complement," *i.e.*, by deducing and exporting the identity of the nucleotides of the template strand based on the detection of the nucleotide on the complementary molecule. *See, e.g.*, Ex. X (Local Run Manager, Generate FASTQ Analysis Module, Workflow Guide, https://support.illumina.com/content/dam/illumina-support/documents/documentation/software_documentation/local-run-manager/local-run-manager-generate-fastq-workflow-guide-100000003344-02.pdf) at 4.

73. Thus, for at least the preceding reasons, the identity of the complementary nucleotide is deduced based on the identity of the labeled nucleotides during the normal and intended use of the NovaSeq 6000.

b. Infringement of Claim 2 of the ’132 Patent

74. Claim 2 of the ’132 Patent recites “The method of claim 1 wherein the nucleic acid templates comprise adaptors.”

75. The NovaSeq™ 6000 Sequencing System brochure states that “[t]he NovaSeq 6000 System is compatible with various Illumina library preparation kits, supporting a wide range of methods, from expression profiling to WGS and beyond.” Ex. L at 2.

76. Table 2 of the NovaSeq 6000 brochure identifies Illumina sample preparation kits that are available for common sequencing methods:

Table 2: Examples of common sequencing methods

Whole-genome sequencing
TruSeq™ DNA PCR-Free[a]
Nextera™ DNA Flex[a]
IDT for Illumina-TruSeq DNA UD Indexes (24 indexes, 96 samples)[b,c]
IDT for Illumina-TruSeq DNA UD Indexes (96 indexes, 96 samples)[b,c]
Targeted resequencing
Nextera Flex for Enrichment + Illumina Exome Panel
TruSeq Workflow with IDT Enrichment and Exome[b]
Nextera Workflow with IDT Enrichment and Exome[b]
TruSeq RNA Exome Enrichment[a]
RNA sequencing
TruSeq Stranded Total RNA[a]
TruSeq Stranded mRNA[a]
IDT for Illumina-TruSeq RNA UD Indexes (24 indexes, 96 samples)[b,c]
IDT for Illumina-TruSeq RNA UD Indexes (96 indexes, 96 samples)[b,c]
Methylation sequencing
TruSeq Methyl Capture EPIC
Library prep methods listed are only examples of those available for use with the NovaSeq 6000 System. For a complete list, visit www.illumina.com.
a. An Illumina Qualified Method is available b. IDT = Integrated DNA Technologies c. UD Indexes = Unique Dual Indexes

Ex. L at 3.

77. By way of example only, Table 2 of the NovaSeq 6000 Brochure suggests using Illumina's "TruSeq DNA PCR-Free" and "Nextera DNA Flex" sample preparation kits for "whole-genome sequencing." The Brochure further states that for these sample preparation kits, "An Illumina Qualified Method is available." Ex. L at 3.

78. The "Illumina Sequencing Technology" video states that "[t]here are a number of different ways to prepare samples. ***All preparation methods add adaptors to the ends of the DNA fragments.***" Ex. Y (Excerpts of Illumina Sequencing by Synthesis Video,

https://www.illumina.com/company/video-hub/fCd6B5HRaZ8.html) at 0:22-:034. Thus, the use of Illumina sample preparation kits (such as the TruSeq DNA PCR-Free and Nextera DNA Flex sample preparation kits) results in nucleic acid templates that comprise adaptors.

c. Infringement of Claim 3 of the '132 Patent

79. Claim 3 of the '132 Patent recites: "The method of claim 2 wherein the nucleic acid templates are formed from a plurality of genomic fragments."

80. Illumina provides "optimized kits" for certain sequencing methods on the NovaSeq, including whole genome sequencing ("WGS"), as shown below:

Methods for the NovaSeq System

Method	Recommended read length	Optimized kits
Genome		
WGS (large genomes)	2 x -150 bp	TruSeq DNA PCR-Free Library Prep Kit
		TruSeq Nano DNA Library Prep Kit
		Nextera DNA Library Prep Kit
		Nextera Mate Pair Library Prep Kit
WGS (small genomes)	2 x -150 bp	Nextera XT DNA Library Prep Kit
		Nextera Mate Pair Library Prep Kit
Exome sequencing	2 x -100 bp	TruSeq Rapid Exome Library Prep Kit
		TruSeq Exome Library Prep Kit
Cancer research sequencing panels	2 x 150 bp	TruSight Tumor 170
		TruSight Cancer Sequencing Panel
	2 x 75 bp	TruSight RNA Fusion
		TruSight Pan RNA Sequencing Panel
Genetic conditions sequencing panels	2 x 150 bp	TruSight One Sequencing Panel
		TruSight One Expanded Sequencing Panel
		TruSight Cardio Sequencing Panel
Metagenomics	2 x 150 bp	TruSeq DNA PCR-Free Library Prep Kit
		TruSeq DNA Nano Library Prep Kit
		Nextera DNA Library Prep Kit
		Nextera XT DNA Library Prep Kit
Custom sequencing	2 x 75 bp	Nextera Rapid Capture Custom Enrichment Kit

Ex. Z (Illumina Methods Guide, https://genlabperu.com/wp-content/uploads/2018/08/methods-guide-770-2014-018-.pdf) at 119 (annotated).

81. By way of example only, when the optimized kits listed above are used to prepare a sample for whole genome sequencing on the NovaSeq system, the nucleic acid templates will be "formed from a plurality of genomic fragments," as recited in Claim 3.

d. Infringement of Claim 4 of the '132 Patent

82. Claim 4 of the '132 Patent recites "The method of claim 3 wherein the genomic fragments are human genomic DNA."

83. Illumina provides qualified methods for human whole genome sequencing on its two-channel sequencing systems, such as the NovaSeq 6000 system.

84. For example, Illumina's "application note," titled "Human Whole-Genome Sequencing with the NovaSeq 6000 Sequencing System," states that "the NovaSeq 6000 System delivers the highest daily throughput and exceptional data quality for ***human whole-genome sequencing***." Ex. AA at 1 (Human WGS with the NovaSeq 6000, https://www.illumina.com/content/dam/illumina-marketing/documents/products/appnotes/novaseq-wgs-app-note-770-2017-015.pdf) (emphasis added). The application note specifically advertises the advantages of WGS using the NovaSeq 6000, stating that "***human WGS*** can now be completed easily in a more cost-effective manner." *Id*. at 2.

85. For example, when the NovaSeq 6000 system is used for sequencing of human DNA (such as, for example, human WGS), the nucleic acid templates that are sequenced are formed from a plurality of fragments of human genomic DNA, as recited in Claim 4 of the '132 Patent.

B. Indirect Infringement of the Claims 1-4 of the ’132 Patent

86. Illumina has and continues to induce infringement by their customers pursuant to 35 U.S.C. § 271(b). Illumina’s customers directly infringe at least claims 1-4 the ’132 patent when they use Illumina’s two-channel sequencing systems, in combination with the recommended Illumina’s sample preparation and sequencing kits. Illumina actively induces infringement by its customers by selling the NovaSeq 6000, its sample preparation kits and sequencing kits for use in a manner that infringes at least claims 1-4 of the ’132 patent, instructing its customers to use these products together in an infringing manner and providing qualification of the infringing methods, and by providing marketing materials, user guides, technical literature, and bioinformatics software applications to support its customers’ infringing use.

87. On information and belief, Illumina has had knowledge of the ’132 patent since at least December 29, 2015 (the issue date of the ’132 patent) or shortly thereafter. U.S. Published Patent Application No. 2014/037821 A1, which eventually issued as the ’132 patent, was repeatedly cited during prosecution of Illumina’s patent application No. 13/624,200. In particular, the ’821 published application was cited on November 4, 2015—less than two months before the issuance of the ’132 Patent—and was substantively discussed by Illumina in subsequent responses to rejections by the Patent Office. At the very least, service of this complaint provides Illumina with notice the ’132 patent.

88. On information and belief, Illumina acted with knowledge that the induced acts constitute infringement or willful blindness with regards to its customers’ underlying infringement of the ’132 patent.

89. On information and belief, Defendants have and continue to contribute to infringement by their customers pursuant to 35 U.S.C. § 271(c). Illumina contributes to its customers' direct infringement by offering to sell, selling within the United States, or importing into the United States "two-channel" sequencing systems, sample preparation kits, and sequencing kits that are specially designed and optimized for use in practicing claims 1-4 of the '132 patent. Illumina sells these products with the specific intent that their customers use them in a manner that infringes at least claims 1-4 of the '132 patent, and provides qualified methods and instructions directing their customers to perform infringing methods.

90. On information and belief, at least some of these systems and related kits, such as the sample preparation kits designed for whole genome sequencing on the NovaSeq 6000 system, do not have a substantial non-infringing use with respect to claims 1-4. Illumina sells these reagent kits to be exclusively compatible with one sequencer series (*e.g.*, NovaSeq 6000, NextSeq 500/550 Series, and MiSeq). These highly specialized products are not staple articles of commerce; they are specifically designed to be used in a manner that infringes the '132 patent. On information and belief, Illumina acted with knowledge that the induced acts constitute infringement or willful blindness with regards to its customers' infringement of the '132 patent.

91. On information and belief, Illumina's infringement of the '132 patent has been willful and deliberate since learning of the issuance of the '132 patent.

COUNT I – INFRINGEMENT OF U.S. PATENT NO. 9,222,132

92. CGI hereby re-alleges and incorporates by reference the allegations contained in paragraphs 1 through 91 as if fully set forth herein.

93. Illumina and its customers have directly infringed and continue to directly infringe at least claims 1-4 of the ’132 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by using “two-channel” sequencing systems (such as the NovaSeq 6000) in combination with sample preparation kits, and sequencing kits within the United States. Specifically, Illumina has used the accused methods in the United States in connection with research, development, installation, testing, and qualification activities. Illumina’s customers have used the accused methods in the United States in connection with at least DNA sequencing activities.

94. On information and belief, Illumina has had knowledge of the ’132 patent since at least December 29, 2015 (the issue date of the ’132 patent) or shortly thereafter.

95. U.S. Published Patent Application No. 2014/037821 A1, which eventually issued as the ’132 patent, was repeatedly cited during prosecution of Illumina’s patent application No. 13/624,200. In particular, the ’821 published application was cited on November 4, 2015—less than two months before the issuance of the ’132 Patent—and was substantively discussed by Illumina in subsequent responses to rejections by the Patent Office.

96. On information and belief, with knowledge of the ’132 patent, Illumina has and will continue to actively induce others to infringe at least claims 1-4 of the ’132 patent in violation of 35 U.S.C. §271(b) by, at least, causing, instructing, urging, encouraging, and/or aiding others to directly infringe at least claims 1-4 of the ’132 patent by using Illumina’s “two-channel” sequencing systems, sample preparation kits, and sequencing kits to perform the claimed methods, as detailed in Paragraphs 1 to 91, above.

97. On information and belief, Illumina acted with knowledge that the induced acts constitute infringement or willful blindness with regards to its customers' underlying infringement of the '132 patent.

98. Illumina is liable for contributory infringement of the '132 patent pursuant to 35 U.S.C. § 271(c). Specifically, Illumina has contributed to the infringement by its customers of the '132 patent by selling and offering to sell within the United States "two-channel" sequencing systems, sample preparation kits, and sequencing kits for practicing the claimed invention of the '132 patent, including at least the NovaSeq 6000, the NextSeq, and the MiSeq Systems, as well as their compatible sample preparation kits and sequencing kits, as described in paragraphs 1 to 91, above. The aforementioned products, which are designed, supplied and supported by Illumina, constitute a material part of the claimed invention of the '132 patent and they are not a staple article or commodity of commerce suitable for substantial noninfringing use.

99. On information and belief, Illumina's infringement of the '132 patent has been willful and deliberate since learning of the issuance of the '132 patent.

100. Illumina's infringement of the '132 patent has injured CGI in its business and property rights. CGI is entitled to recovery of monetary damages for such injuries pursuant to 35 U.S.C. § 284 in an amount to be determined at trial.

101. Illumina's infringement of the '132 patent has caused irreparable harm to CGI and will continue to cause such harm unless and until their infringing activities are enjoined by this Court.

JURY DEMAND

102. Plaintiff demands a jury trial on all issues so triable.

PRAYER FOR RELIEF

A. A judgment that Illumina has directly and indirectly infringed the ’132 patent;

B. An order enjoining Illumina and its officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting in active concert therewith from further infringement of the ’132 patent;

C. An award of damages pursuant to 35 U.S.C. § 284, including an award of costs, and pre- and post-judgment interest;

D. A declaration that Defendants’ infringement was willful and deliberate, and an increase to the award of damages of three times the amount found or assessed by the Court, in accordance with 35 U.S.C. § 284;

E. A declaration that this case is exceptional pursuant to 35 U.S.C. § 285, and an award of attorneys’ fees and costs; and

F. An award of such other and further relief as the Court may deem just and proper.

Dated: May 28, 2019

YOUNG CONAWAY STARGATT & TAYLOR, LLP

/s/ Pilar G. Kraman

Adam W. Poff (No. 3990)
Pilar G. Kraman (No. 5199)
Rodney Square
1000 North King Street
Wilmington, DE 19801
(302) 571-6600
apoff@ycst.com
pkraman@ycst.com

Attorneys for Plaintiff Complete Genomics, Inc.

OF COUNSEL:
Jennifer Sklenar
ARNOLD & PORTER KAYE SCHOLER LLP
777 South Figueroa Street, 44th Floor
Los Angeles, CA 90017
jennifer.sklenar@arnoldporter.com
(213) 243-4027

Katie J.L. Scott
Joshua D. Seitz
ARNOLD & PORTER KAYE SCHOLER LLP
3000 El Camino Real

Five Palo Alto Square, Suite 500
Palo Alto, CA 94306
katie.scott@arnoldporter.com
joshua.seitz@arnoldporter.com
(650) 319-4529