

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

COLD SPRING HARBOR LABORATORY,

Plaintiff,

v.

GUARDANT HEALTH, INC.,

Defendant.

C.A. No. 25-263-JCG

JURY TRIAL DEMANDED

PLAINTIFF’S FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Cold Spring Harbor Laboratory (“CSHL”), for its Complaint against Defendant Guardant Health, Inc., (“Guardant”), hereby alleges as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 10,947,589 (“the ’589 patent”) and 12,234,510 (“the ’510 patent”) (collectively the “Patents-in-Suit”), arising under the Patent Laws of the United States, 35 U.S.C. §§ 271 *et seq.*

THE PARTIES

2. Plaintiff CSHL is a New York not-for-profit education corporation chartered by action of the Board of Regents of the State of New York, with its principal place of business at One Bungtown Road, Cold Spring Harbor, NY 11724.

3. CSHL was established for the purposes of conducting investigations and research in the biological sciences and related subjects, furthering discovery and development therein, diffusing information, and providing instruction and training related thereto.

4. CSHL conducts expansive research efforts in cancer, neuroscience, genomics, quantitative biology, and plant biology, among other areas.

5. CSHL is recognized as one of only seven National Cancer Institute-designated Basic Laboratory Cancer Centers and has been particularly influential in investigating relationships between cancer and genomics.

6. CSHL's research has various applications, including in early cancer detection tests and liquid biopsies. CSHL's research has resulted in the issuance of several patents, including the Patents-in-Suit.

7. Defendant Guardant is a company organized and existing under the laws of Delaware, with its principal place of business at 3100 Hanover Street, Palo Alto, CA 94304. Guardant has appointed Incorporating Services, Ltd., 3500 S Dupont Highway, Dover, DE 19901, as its agent for service of process. (Ex. 3 at 1 (Delaware Department of State: Division of Corporations).)

8. Defendant Guardant, itself and/or through its subsidiaries and affiliates, makes, uses, and commercializes blood tests that include DNA library preparation, DNA sequencing, and DNA analysis steps to provide genomic profiles, including genetic copy number information.

9. Guardant, itself and/or through its subsidiaries and affiliates, makes, uses, and commercializes tests marketed under the tradename "Guardant360" that include DNA library preparation, DNA sequencing, and DNA analysis steps to provide genomic profiles, including genetic copy number information.

10. Guardant offers and markets tests under the trade name Guardant Complete Portfolio throughout the United States, including through the website <https://guardanthealth.com/products/tests-for-patients-with-early-and-advanced-stage-cancer/>. (See generally Ex. 4 (<https://guardanthealth.com/products/tests-for-patients-with-early-and-advanced-stage-cancer/>).)

JURISDICTION AND VENUE

11. CSHL incorporates by reference paragraphs 1–10.

12. This action arises under the patent laws of the United States, including 35 U.S.C. §§ 271 *et seq.* The jurisdiction of this Court over the subject matter of this action is proper under 28 U.S.C. §§ 1331 and 1338(a).

13. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and (c), and 1400(b), because Guardant is an entity organized under the laws of Delaware and resides in Delaware for purposes of venue under 28 U.S.C. § 1400(b).

14. Guardant conducts business in Delaware, at least by offering for sale and selling products and services through their websites, which are accessible in Delaware.

15. Guardant has committed and continues to commit acts of infringement in this District.

16. This Court has personal jurisdiction over Guardant because Guardant conducts business in Delaware by at least offering for sale or selling products and services through its website, which is accessible in Delaware, and because infringement has occurred and continues to occur in Delaware.

17. Personal jurisdiction also exists over Guardant because it is an entity organized under the laws of Delaware.

BACKGROUND OF THE INVENTION

18. CSHL incorporates by reference paragraphs 1–17.

19. CSHL is a world-renowned research and education institution.

20. CSHL has employed eight Nobel Prize winners and has been home to many groundbreaking discoveries in varied scientific fields, including genetics and cancer.

21. CSHL is a National Cancer Institute-designated Cancer Center.

22. CSHL's cancer research includes efforts aimed at identifying new paths to cancer treatment and diagnostics.

23. Dr. Michael Wigler is a named inventor on the Patents-in-Suit. Dr. Wigler oversees a research laboratory at CSHL ("the Wigler Lab") that has made significant contributions to the genetics and cancer fields by developing and discovering relationships between genetic mutations and human diseases and disorders, including cancer and autism. The Wigler Lab has also developed methods and tools to detect genetic changes in tumors and single cells leading to the design of protocols for early detection of cancer and cancer recurrence.

24. While he was a Ph.D. student at Columbia University, Dr. Wigler helped engineer genetic techniques that facilitated gene transfer and expression within mammalian cells. His research allowed scientists to further study the correlation between genetics and diseases, such as cancer, and also enabled large scale production of biologic drugs that are now widely used to treat various diseases.

25. Dr. Wigler moved to CSHL in 1978 and continued his previous research, becoming one of the first researchers to insert a human cancer gene, or an oncogene, into normal human cells. This discovery started worldwide research on isolating and studying specific oncogenes and tumor suppressor genes.

26. The Wigler Lab continued to study genetic mutations, and its research efforts led to the discovery that copy number variation (e.g., variations in the numbers of copies of particular genes) can be a key genetic indicator for cancer as well as other disorders.

27. The Wigler Lab discovered that, unlike certain mutations, copy number variations could be challenging to accurately quantify using prior DNA sequencing techniques, for example

as a result of difficulties created by a phenomenon known as amplification distortion. Examples of amplification distortion include non-uniform amplification of nucleic acids, such as DNA, that can occur during amplification and/or sequencing. Amplification distortion could create a significant barrier to determining accurate numbers of copies of particular genes in a given genome, or to determining copy number variations, by making it difficult to distinguish between amplified copies of a particular gene and original copies of that particular gene.

28. Dr. Wigler's research provided a solution to prior problems by developing a method to obtain accurate copy number information from a DNA sample, laying the groundwork for the Patents-in-Suit and early cancer detection tests.

THE PATENTS-IN-SUIT

29. CSHL incorporates by reference paragraphs 1–28.

30. The '589 patent, entitled "Varietal Counting Of Nucleic Acids For Obtaining Genomic Copy Number Information" was duly and legally issued by the United States Patent and Trademark Office on March 16, 2021. The inventors of the '589 patent are James Hicks, Nicholas Navin, Jenifer Troge, Zihua Wang, and Michael Wigler. A copy of the '589 patent is attached hereto as Exhibit 1.

31. CSHL is the exclusive owner of all rights, title, and interest in the '589 patent, and has the right to bring this suit for injunctive relief and to recover damages for any current or past infringement of the '589 patent. (Ex. 2 ('589 Patent Assignment to CSHL).)

32. The '589 patent is directed to, among other things, an unconventional, non-routine method of obtaining copy number information from a sample. For example, claim 1 of the '589 patent recites:

A method comprising:

a) obtaining segments of genomic nucleic acids from a sample;

- b) tagging the segments with nucleic acid tags, thereby generating a plurality of unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;
- c) subjecting the plurality of the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified tagged nucleic acid molecules;
- d) generating tag associated sequence reads by sequencing the amplified tagged nucleic acid molecules of step (c);
- e) assigning each of the amplified tagged nucleic acid molecules to a location on a reference genome from the same species from which the sample has been obtained by mapping each of the tag associated sequence reads of step (d) to a location of the reference genome; and
- f) at a plurality of locations on the reference genome, counting the number of unique tagged nucleic acid molecules that have been assigned to the same location on the reference genome based on the mapping step to obtain a count for each location of the plurality of locations on the reference genome, thereby obtaining copy number information from genomic nucleic acids in the sample.

33. The '589 patent explains that its methods allow for obtaining accurate copy number information. The '589 patent explains that the method overcame prior problems—as one example, amplification bias producing inaccurate copy number information—with a novel and innovative solution:

The invention provides the following advantages: (1) the method is simple; (2) with statistical analysis the confidence of a measurement can be determined with great accuracy; (3) this is a sequence based method, which in the long run will be cheaper than arrays; (4) long read lengths are not necessary, providing savings; (5) because tagged nucleic acid molecules are counted, many processing methods that create distortion in yields can be applied without major loss in the tagged nucleic acid molecule count; (6) among these processing methods are hybrid selection (aka capture microarrays), which restrict the sequence information to regions of importance, and thus reduce cost by reducing the total number of reads per sample needed for determination of the desired information; (7) the molecules from one sample can be combined with tags and a sample tag, creating sample tagged nucleic acid molecules which can then be pooled, and after processing and

sequencing, the sample tags decoded, giving a profile for each sample; (8) pooling adds efficiency and uniformity; (9) the samples can be individual cells, yielding large numbers of single cell measurements cheaply.

(Ex. 1 ('589 patent) at 30:8–29.)

34. The '589 patent teaches that the method of obtaining copy number without errors, for example those introduced by amplification distortion, could be critical to early cancer detection:

The invention described herein has clinical applications...including: (1) determination of the genomic heterogeneity of tumors; (2) detection of tumor cells in needle biopsies, in particular an assessment of the heterogeneity of the cells in a biopsy; (3) assessment of the spread of cancer to regional lymph nodes; and (4) detection of malignant cells in sites such as blood and bone marrow. The presence of cells with the molecular signature of the primary in the blood or bone marrow opens up the possibility of using more general single cell/molecule assays as a first line of defense in the early detection of cancer, i.e. breast cancer in women at risk.

* * *

The single cell/molecule approach allows the assessment of the spread of cancer to regional lymph nodes and to establish the DNA-methylation states at switch regions.

Successful application of single cell/molecule detection in the above contexts will lead to application to the detection of cancer recurrence, and the measurement of cancer load. Detection of recurrence at the earliest possible time may prolong survival for a large class of patients by earlier intervention than they would otherwise receive. Moreover, if cancer load were monitored in the patient, even before the site of the cancer growth is discernible by imaging, then one could measure the response of the cancer to a variety of therapeutic measurements. That is, the most effective choice of therapy could be determined empirically in the patient.

(Ex. 1 ('589 patent) at 30:30–42, 54–67.)

35. The inventive concepts of the '589 patent represented a significant improvement in the early detection of cancer and addressed a need in the field:

As described herein, obtaining accurate genomic copy number information by high-throughput sequencing of genomic

DNA prepared by WGA methods is hampered by the copy number distortions introduced by non-uniform amplification of genomic DNA. Thus, there exists a need for a method that allows for copy number determination free of distortions caused by amplification steps and which allows for accurate and efficient copy number determination of complex samples.

(Ex. 1 ('589 patent) at 2:29–37.)

36. The '510 patent, entitled “Varietal Counting Of Nucleic Acids For Obtaining Genomic Copy Number Information” was duly and legally issued by the United States Patent and Trademark Office on February 25, 2025. The inventors of the '510 patent are James Hicks, Nicholas Navin, Jenifer Troge, Zihua Wang, and Michael Wigler. A copy of the '510 patent is attached hereto as Exhibit 17 ('510 patent).

37. CSHL is the exclusive owner of all rights, title, and interest in the '510 patent, and has the right to bring this suit for injunctive relief and to recover damages for any current or past infringement of the '510 patent. (Ex. 18 ('510 Patent Assignment to CSHL).)

38. The '510 patent is directed to, among other things, an unconventional, non-routine method of obtaining relative copy number information from a sample. For example, claim 1 of the '510 patent recites:

A method comprising:

- a) obtaining segments of genomic nucleic acids from a sample containing the genomic nucleic acids;
- b) randomly tagging the segments of genomic nucleic acids with different nucleic acid tags, thereby generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;
- c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating copies of the unique tagged nucleic acid molecules;
- d) generating tag associated sequence reads by sequencing the copies of the unique tagged nucleic acid molecules of step (c);

- e) assigning each of the unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and
- g) in a plurality of locations in the genome, obtaining relative copy number information of the genomic nucleic acids from the sample based on the number of unique tagged nucleic acid molecules that have been assigned to each of the plurality of locations in the genome.

39. The '510 patent explains that its methods allow for obtaining accurate copy number information. The '510 patent explains that the method overcame prior problems—as one example, amplification bias producing inaccurate copy number information—with a novel and innovative solution:

The invention provides the following advantages: (1) the method is simple; (2) with statistical analysis the confidence of a measurement can be determined with great accuracy; (3) this is a sequence based method, which in the long run will be cheaper than arrays; (4) long read lengths are not necessary, providing savings; (5) because tagged nucleic acid molecules are counted, many processing methods that create distortion in yields can be applied without major loss in the tagged nucleic acid molecule count; (6) among these processing methods are hybrid selection (aka capture microarrays), which restrict the sequence information to regions of importance, and thus reduce cost by reducing the total number of reads per sample needed for determination of the desired information; (7) the molecules from one sample can be combined with tags and a sample tag, creating sample tagged nucleic acid molecules which can then be pooled, and after processing and sequencing, the sample tags decoded, giving a profile for each sample; (8) pooling adds efficiency and uniformity; (9) the samples can be individual cells, yielding large numbers of single cell measurements cheaply.

(Ex. 17 ('510 patent) at 30:8-29.)

40. The '510 patent teaches that the method of obtaining copy number without errors, for example those introduced by amplification distortion, could be critical to early cancer detection:

The invention described herein has clinical applications...including: (1) determination of the genomic

heterogeneity of tumors; (2) detection of tumor cells in needle biopsies, in particular an assessment of the heterogeneity of the cells in a biopsy; (3) assessment of the spread of cancer to regional lymph nodes; and (4) detection of malignant cells in sites such as blood and bone marrow. The presence of cells with the molecular signature of the primary in the blood or bone marrow opens up the possibility of using more general single cell/molecule assays as a first line of defense in the early detection of cancer, i.e. breast cancer in women at risk.

* * *

The single cell/molecule approach allows the assessment of the spread of cancer to regional lymph nodes and to establish the DNA-methylation states at switch regions.

Successful application of single cell/molecule detection in the above contexts will lead to application to the detection of cancer recurrence, and the measurement of cancer load. Detection of recurrence at the earliest possible time may prolong survival for a large class of patients by earlier intervention than they would otherwise receive. Moreover, if cancer load were monitored in the patient, even before the site of the cancer growth is discernible by imaging, then one could measure the response of the cancer to a variety of therapeutic measurements. That is, the most effective choice of therapy could be determined empirically in the patient.

(Ex. 17 ('510 patent) at 30:30–42, 54–67.)

41. The inventive concepts of the '510 patent represented a significant improvement in the early detection of cancer and addressed a need in the field:

As described herein, obtaining accurate genomic copy number information by high-throughput sequencing of genomic DNA prepared by WGA methods is hampered by the copy number distortions introduced by non-uniform amplification of genomic DNA. Thus, there exists a need for a method that allows for copy number determination free of distortions caused by amplification steps and which allows for accurate and efficient copy number determination of complex samples.

(Ex. 17 ('510 patent) at 2:29–37.)

GUARDANT'S INFRINGING ACTIVITIES

42. CSHL incorporates by reference paragraphs 1–41.

A. The Accused Guardant360 Tests

43. In May 2014, Guardant launched the Guardant360 test, a commercial liquid biopsy blood test for providing tumor sequencing information from cell-free tumor DNA. (*See* Ex. 5 at 1 (“Guardant Health Announces US Commercial Launch of Guardant360™: A Breakthrough Blood Test for Real-Time Cancer Patient treatment Management”), available at <https://www.prnewswire.com/news-releases/guardant-health-announces-us-commercial-launch-of-guardant360-a-breakthrough-blood-test-for-real-time-cancer-patient-treatment-management-261229671.html> (“Guardant Health, a healthcare company focused on the development and commercialization of oncology diagnostic products, announced today that its premier product, Guardant360™ is now widely commercially available following recent successful introduction to early access partners.”).)

44. Performance of the Guardant360 test includes obtaining segments of genomic nucleic acids from a sample. For example, the Guardant360 test uses “digital sequencing of cell-free circulating tumor DNA isolated from a simple, non-invasive blood draw.” (*See* Ex. 6 at 3 (Lanman et al.).)

45. Performance of the Guardant360 tests also includes randomly tagging the segments with nucleic acid tags. For example, the Guardant360 test includes tagging cell-free DNA fragments obtained from the sample with “non-unique oligonucleotide heptamer barcodes,” such that the tagged DNA molecules include a segment of the genomic nucleic acids obtained from a sample and a nucleic acid tag. (*See* Ex. 6 at 18 (Lanman et al.) (“Isolated cfDNA fragments are subsequently converted to digital sequence libraries. Briefly, in the digital sequencing workflow, non-unique oligonucleotide heptamer barcodes are ligated to each half of individual double-stranded cfDNA. This generates a duplex library whereby each single-stranded half of the double stranded input cfDNA samples is separately encoded with said oligonucleotides. This digital

conversion process occurs with high efficiency with greater than 80% of the original plasma of cfDNA molecules converted.”); Ex. 7 at 3540 (Odegard et al.) (“Five to 30 ng of extracted cfDNA (66% of samples processed with 30 ng input) was labeled with nonrandom oligonucleotide barcodes (IDT, Inc.) and used to prepare sequencing libraries, which were then enriched by hybrid capture (Agilent Technologies, Inc.), pooled, and sequenced by paired-end synthesis (NextSeq 500 and/or HiSeq 2500, Illumina, Inc.).”), 3542 (“Individual unique input molecules are then bioinformatically reconstructed using barcode and sequence data.”); Ex. 8 (U.S. Patent 10,982,265) at 37:52–56 (“[T]he use of non unique barcodes, in combination with sequence data at the beginning (start) and end (stop) portions of individual sequencing reads and sequencing read length may allow for the assignment of a unique identity to individual sequences.”); *id.* at 39:26–30 (“[D]etection of non unique barcodes in combination with sequence data of beginning (start) and end (stop) portions of sequence reads may allow assignment of a unique identity to a particular molecule.”).)

46. Performance of the Guardant360 test further includes subjecting unique tagged nucleic acid molecules to polymerase chain reaction (PCR). For example, in the Guardant360 test, cfDNA fragments tagged with non-unique oligonucleotide barcodes are amplified using PCR. (*See* Ex. 6 at 18 (Lanman et al.) (“These digital sequence libraries are amplified and then subsequently enriched for target genes using biotinylated custom baits of RNA probes”), 19 (“Because digital sequencing enables tracking and quantification of all unique cfDNA fragments overlapping a given genomic site, PCR duplicates and artifacts of amplification during library preparation can easily be removed.”).)

47. Performance of the Guardant360 test further includes sequencing amplified copies of tagged nucleic acid molecules. For example, the Guardant360 test includes sequencing

amplified tagged nucleic acid molecules using an Illumina sequencing platform, such as the HiSeq2500 or NextSeq 550 platforms. (*See* Ex. 6 at 17 (Lanman et al.) (“The enriched digital sequence libraries are then analyzed using HiSeq 2500 Sequencing System (Illumina) paired-end sequencing with fluorescent reversible terminator deoxyribonucleotides.”); Ex. 7 at 3540 (Odegard et al.) (“Five to 30 ng of extracted cfDNA (66% of samples processed with 30 ng input) was labeled with nonrandom oligonucleotide barcodes (IDT, Inc.) and used to prepare sequencing libraries, which were then enriched by hybrid capture (Agilent Technologies, Inc.), pooled, and sequenced by paired-end synthesis (NextSeq 500 and/or HiSeq 2500, Illumina, Inc.).”)).

48. Performance of the Guardant360 test further includes assigning tag associated sequence reads to a location of a reference genome. For example, the Guardant360 test includes using software to align tagged and sequenced oligonucleotides with a reference genome. (*See* Ex. 6 at 19 (Lanman et al.) (“Software utilized includes CASAVA (version 1.8.4), the open source BWA-MEM aligner, and a custom read pile-up process that utilizes information encoded by digital-sequencing oligonucleotides to reconstruct the set of unique cfDNA molecules. First, 150bp paired-end reads are aligned to the reference genome.”); Ex. 7 at 3540 (Odegard et al.) (“Processed reads were then aligned to hg19 using BWA-MEM (arXiv: 1303.3997v2) and used to build double-stranded consensus representations of original unique cfDNA molecules using both inferred molecular barcodes and read start/stop positions.”); Ex. 8 (US Patent 10,982,265) at 30:52–60 (“In some cases, in which copy number variation analysis is desired, sequence data may be: 1) aligned with a reference genome; 2) filtered and mapped; 3) partitioned into windows or bins of sequence; 4) coverage reads counted for each window; 5) coverage reads can then be normalized using a stochastic or statistical modeling algorithm; 6) and an output file can be generated reflecting discrete copy number states at various positions in the genome.”)).

49. Performance of the Guardant360 test further includes obtaining copy number information from genomic nucleic acids in a sample. For example, the Guardant360 test includes obtaining copy number by quantifying unique DNA fragments. (See Ex. 6 (Lanman et al.) at 19 (“Leveraging the ability of digital sequencing technology (DST) to absolutely quantify the number of unique DNA fragments in a sequenced sample, the copy number of a given gene in plasma may also be ascertained. To determine the CNV or amplification of a given gene, we first measure the total number of unique fragments covering each gene comprised of both halves of the original parent molecules.”), 17 (“The Guardant360 cfDNA NGS panel identifies SNVs via sequencing of 54 genes spanning approximately 78,000 base pairs, including complete exon coverage in all exons in 18 genes and the critical exons in 36 genes (gene list in S1 Table) as well as copy number variations (CNVs) in *ERB2*, *EGFR*, and *MET*.”); (Ex. 8 (US Patent 10,982,265) at 30:52–60 (“In some cases, in which copy number variation analysis is desired, sequence data may be: 1) aligned with a reference genome; 2) filtered and mapped; 3) partitioned into windows or bins of sequence; 4) coverage reads counted for each window; 5) coverage reads can then be normalized using a stochastic or statistical modeling algorithm; 6) and an output file can be generated reflecting discrete copy number states at various positions in the genome.”) Ex. 9 (Guardant 2018 IPO Prospectus) at 121 (“Copy number variants manifest in higher than expected coverage, or number of unique molecules mapping to a given amplified region of the genome, compared to that expected for a typical diploid genome. Since observed coverage is highly variable from region to region depending on sequence composition and efficiency of amplification for each individual sample, it is highly non-uniform even when no copy number variants are present. As such, copy number variation is significantly harder to identify than small sequence variants, such as SNVs, insertions, and deletions considered in the previous figure.”).)

50. Guardant performs its Guardant360 tests in its laboratories located in Redwood City, California, and San Diego, California. (Ex. 10 at 10-11 (Guardant 2023 Form 10-K Filing) (“We currently perform our tests in our laboratories located in Redwood City, California, and San Diego, California. . . . Our testing process includes sample collection, laboratory processing, analysis and reporting.”).)

B. The Accused Guardant360 CDx Test

51. In August 2020, Guardant launched the Guardant360 CDx test. (See Ex. 11 at 1 (FDA Approval Order); Ex. 12 at 1 (“Guardant Health Guardant360® CDx First FDA-Approved Liquid Biopsy for Comprehensive Tumor Mutation Profiling Across All Solid Cancers”), available at <https://investors.guardanthealth.com/press-releases/press-releases/2020/Guardant-Health-Guardant360-CDx-First-FDA-Approved-Liquid-Biopsy-for-Comprehensive-Tumor-Mutation-Profilng-Across-All-Solid-Cancers/default.aspx>).)

52. Performance of the Guardant360 CDx test includes obtaining segments of genomic nucleic acids from a sample. (Ex. 13 (Guardant360 CDx Technical Information) at 5 (“Whole blood specimens are processed in the Guardant Health Clinical Laboratory within 7 days of blood collection. A minimum of 5 mL of blood must be received in order to achieve optimal performance for the Guardant360 CDx assay. . . . Plasma is isolated via centrifugation and cfDNA is extracted.”).)

53. Performance of the Guardant360 CDx test also includes randomly tagging the segments with nucleic acid tags. (Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“During library preparation, cfDNA fragment ends are repaired and library adapters containing inline barcodes are attached using blunt-end ligation.”); Ex. 13 at 5 (Guardant360 CDx Technical Information) (“Plasma is isolated via centrifugation and cfDNA is

extracted from plasma. cfDNA, 5 to 30 ng, is then used to prepare sequencing libraries which are enriched by hybridization capture.”.)

54. Performance of the Guardant360 CDx test further includes subjecting unique tagged nucleic acid molecules to polymerase chain reaction (PCR). (Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“The resulting DNA is amplified by PCR to create libraries suitable for enrichment....Each enriched library is amplified by PCR using a unique index primer that also contains a sequencing flow cell attachment sequence.”); Ex. 13 at 5 (Guardant360 CDx Technical Information) (“The enriched libraries are then sequenced using next generation sequencing on the Illumina NextSeq 550 platform.”); *id.* at 6 (listing “Illumina NextSeq 550 Sequencing System” as an instrument for use with the Guardant360 CDx Assay).)

55. Performance of the Guardant360 CDx test further includes sequencing amplified copies of tagged nucleic acid molecules. (Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“Paired-end sequencing by synthesis is performed with the Illumina NextSeq 550 Sequencing system. The amplified cfDNA is analyzed by parallel sequencing of amplified target genes to an average depth of coverage of greater than 2,700 unique molecules.”); Ex. 13 (Guardant 360CDx Technical Information) at 5 (“The enriched libraries are then sequenced using next generation sequencing on the Illumina NextSeq 550 Platform.”).)

56. Performance of the Guardant360 CDx test further includes assigning tag associated sequence reads to a location of a reference genome. (Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“The sequence data then undergoes an alignment process where it is mapped to the human genome (hg19) and an analysis of sequence alteration data is performed.”); (Ex. 8 (US Patent 10,982,265) at 30:52–60 (“In some cases, in

which copy number variation analysis is desired, sequence data may be: 1) aligned with a reference genome; 2) filtered and mapped; 3) partitioned into windows or bins of sequence; 4) coverage reads counted for each window; 5) coverage reads can then be normalized using a stochastic or statistical modeling algorithm; 6) and an output file can be generated reflecting discrete copy number states at various positions in the genome.”.)

57. Performance of the Guardant360 CDx test further includes obtaining copy number information from genomic nucleic acids in a sample. (Ex. 13 at 1 (Guardant360 CDx Technical Information) (“Guardant360® CDx is a qualitative next generation sequencing-based *in vitro* diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of . . . copy number amplifications (CNAs) in two (2) genes”); Ex. 14 at 1 (Guardant360 CDx SSED – January 27, 2023); *id.* at 3-4 (Table 2—reporting copy number amplifications of genes *ERBB2* and *MET*); (Ex. 8 (US Patent 10,982,265) at 30:52–60 (“In some cases, in which copy number variation analysis is desired, sequence data may be: 1) aligned with a reference genome; 2) filtered and mapped; 3) partitioned into windows or bins of sequence; 4) coverage reads counted for each window; 5) coverage reads can then be normalized using a stochastic or statistical modeling algorithm; 6) and an output file can be generated reflecting discrete copy number states at various positions in the genome.”).)

58. Guardant performs its Guardant360 CDx tests in its laboratories located in Redwood City, California, and San Diego, California. (Ex. 10 at 10-11 (Guardant 2023 Form 10-K Filing) (“We currently perform our tests in our laboratories located in Redwood City, California, and San Diego, California. . . . Our testing process includes sample collection, laboratory processing, analysis and reporting.”).)

C. Guardant's Knowledge of CSHL's Patents

59. The Patents-in-Suit claim breakthroughs in genetic testing in the early cancer detection industry in which Guardant actively participates.

60. On information and belief, Guardant has been aware of the Patents-in-Suit and the fact that performance of its tests practices the claimed inventions of the Patents-in-Suit since at least the issue dates of the Patents-in-Suit.

61. Guardant has been and is the assignee of a number of patents and patent applications that are related to subject matter similar to the Patents-in-Suit and that were filed after the '589 patent was published, including patents titled "Systems and Methods to Detect Rare Mutations and Copy Number Variation." (See Ex. 15 (U.S. Patent 9,902,992).) On information and belief, in researching the patentability of its own patents, Guardant did become aware of the '589 patent and its related patents, including the published applications that led to the '589 patent, the '510 patent, and the earlier applications and patents to which the Patents-in-Suit claim priority, as early as May 2015.

62. On January 25, 2019, an opposition against CSHL's European patent titled "Varietal Counting Of Nucleic Acids For Obtaining Genomic Copy Number Information," European Patent No. EP2630263, was filed at the European Patent Office.

63. CSHL's European Patent No. EP2630263 bears the same title as the Patents-in-Suit. (See Ex. 16 (EP 2630263) (titled "Varietal Counting of Nucleic Acids for Obtaining Genomic Copy Number Information").)

64. CSHL's European Patent No. EP2630263 contains similar disclosures to the Patents-in-Suit. For example, claim 1 of CSHL's European Patent No. EP2630263 recites:

A method for obtaining from genomic material genomic copy number information unaffected by amplification distortion, comprising:

- a) obtaining segments of the genomic material;
- b) tagging the segments with a sufficiently large number of distinct nucleic acid tags, to generate unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises one segment of the genomic material from step (a) and a tag;
- c) subjecting the tagged nucleic acid molecules to amplification by polymerase chain reaction (PCR);
- d) generating tag associated sequence reads by sequencing the product of step (c);
- e) assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding to a segment of the genomic material to a location on the genome; and
- h) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the genome, thereby obtaining genomic copy number information unaffected by amplification distortion.

65. CSHL's European Patent No. EP2630263 claims priority to the same provisional patent applications that the Patents-in-Suit claim priority to: Application Nos. 61/510,579 (filed July 22, 2011) and 61/406,067 (filed October 22, 2010). (Ex. 16 (EP 2630263) at 1.)

66. On information and belief, Guardant, itself and/or through its subsidiaries, affiliates, or agents, initiated the European opposition against CSHL's European Patent No. EP2630263.

67. On information and belief, Guardant evaluated CSHL's European Patent No. EP2630263, and when doing so became aware of the related patents in the same family, including the Patents-in-Suit.

68. On information and belief, Guardant continued to monitor the patent family that included CSHL's European Patent No. EP2630263 following the filing of the European opposition, and when doing so became aware of the related patents in the same family, including the Patents-in-Suit.

69. At a minimum, to the extent Guardant claims it was unaware of the Patents-in-Suit when evaluating CSHL's European Patent No. EP2630263, Guardant was willfully blind to the existence of the Patents-in-Suit and of its infringement.

70. On March 17, 2021, oral proceedings were held in the European opposition against CSHL's European Patent No. EP2630263.

71. During the March 17, 2021 oral proceedings in the European opposition against CSHL's European Patent No. EP2630263, counsel from Carpmaels & Ransford LLP argued on behalf of the party that initiated the opposition proceeding.

72. On information and belief, counsel from Carpmaels & Ransford LLP communicated with and/or worked with Guardant in preparation for the March 17, 2021 oral proceedings in the European opposition against CSHL's European Patent No. EP2630263.

73. On information and belief, a representative from Guardant joined the videoconference for at least part of the March 17, 2021 oral proceedings in the European opposition against CSHL's European Patent No. EP2630263.

74. On March 6, 2025, CSHL filed a complaint for infringement of the '589 patent. On March 7, 2025, CSHL served the original complaint on Guardant.

75. The March 6, 2025 complaint provided Guardant with further knowledge of the '589 patent, and of Guardant's infringement of the '589 patent.

76. On information and belief, after receiving the March 6, 2025 complaint, Guardant evaluated the patents and application related to the '589 patent, including the '510 patent.

77. Guardant was provided additional notice of the Patents-in-Suit, and its infringement of the Patents-in-Suit, with an April 25, 2025 communication from CSHL's counsel identifying the '589 patent and '510 patent and providing details regarding Guardant's infringement of the

'589 patent and the '510 patent by the Guardant360 and Guardant360 CDx tests. Ex. 19 (April 25, 2025 Letter).

78. Despite its knowledge of the Patents-in-Suit and of its infringement of the Patents-in-Suit, Guardant has continued to willfully infringe the Patents-in-Suit so as to obtain significant benefits of CSHL's innovations without paying compensation to CSHL. For example, Guardant has continued to use the claimed methods in their Guardant360 and Guardant360 CDx tests without a license, and, on information and belief, has generated hundreds of millions of dollars in revenue from its infringement. Additionally, after becoming aware of the Patents-in-Suit, Guardant proceeded to commercialize the Guardant360 tests, and continues to commercialize its tests, built on and including the claimed inventions of the Patents-in-Suit without entering into a license to the Patents-in-Suit.

COUNT I

(Infringement Of The '589 Patent)

79. CSHL incorporates by reference paragraphs 1–78.

80. The '589 patent is valid and enforceable.

81. Guardant has infringed, and continues to infringe, one or more claims of the '589 patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, products and/or methods encompassed by those claims, including for example, by making, using, selling, offering for sale, and/or importing the Guardant360 and Guardant360 CDx tests.

82. Guardant currently performs all of its tests on samples sent to Guardant's laboratories in Redwood City, California, and San Diego, California, for its Guardant360 and

Guardant360 CDx tests. (*See* Ex. 10 (Guardant 2023 Form 10-K) at 10-11 (“We currently perform our tests in our laboratories located in Redwood City, California, and San Diego, California....Our testing process includes sample collection, laboratory processing, analysis and reporting.”).)

83. To date, over 500,000 patient samples have been analyzed using Guardant’s tests.

84. As one example of Guardant’s infringement, Guardant infringes at least claim 1 of the ’589 patent by using the Guardant360 and Guardant360 CDx tests. For example, use of the Guardant360 and Guardant360 CDx tests includes using a method comprising:

- a. obtaining segments of genomic nucleic acids (such as cfDNA) from a sample (such as a blood sample) (*see, e.g.*, Ex. 6 (Lanman et al.) at 5 (“cfDNA is extracted from a routine blood draw.”); Ex. 13 (Guardant360 CDx Technical Information) at 5 (“Whole blood specimens are processed in the Guardant Health Clinical Laboratory within 7 days of blood collection. A minimum of 5 mL whole blood must be received in order to achieve optimal performance for the Guardant360 CDx assay. . . . Plasma is isolated via centrifugation and cfDNA is extracted.”));
- b. tagging the segments with nucleic acid tags, thereby generating a plurality of unique tagged nucleic acid molecules (*see, e.g.*, Ex. 6 at 18 (Lanman et al.) (“Isolated cfDNA fragments are subsequently converted to digital sequence libraries. Briefly, in the digital sequencing workflow, non-unique oligonucleotide heptamer barcodes are ligated to each half of individual double-stranded cfDNA. This generates a duplex library whereby each single-stranded half of the original double-stranded input cfDNA sample is separately encoded with said oligonucleotides.”); Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023)

- at 7 (“During library preparation, cfDNA fragment ends are repaired and library adapters containing inline barcodes are attached using blunt-end ligation.”));
- c. subjecting the plurality of unique tagged acid molecules to a polymerase chain reaction, thereby generating amplified tagged nucleic acid molecules (*see, e.g.*, Ex. 6 at 18 (Lanman et al.) (“These digital sequence libraries are amplified and then subsequently enriched for target genes using biotinylated custom baits of RNA probes”); Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“The resulting DNA is amplified by PCR to create libraries suitable for enrichment....Each enriched library is amplified by PCR using a unique index primer that also contains a sequencing flow cell attachment sequence.”));
 - d. generating tag associated sequence reads by sequencing the amplified tagged nucleic acid molecules (*see e.g.*, Ex. 6 at 17 (Lanman et al.) (“The enriched digital sequence libraries are then analyzed using HiSeq 2500 Sequencing System (Illumina) paired-end sequencing with fluorescent reversible terminator deoxyribonucleotides.”); Ex. 13 at 5 (Guardant360 CDx Technical Information) (“The enriched libraries are then sequenced using next generation sequencing on the Illumina NextSeq 550 platform.”));
 - e. assigning each of the amplified tagged nucleic acid molecules to a location on a reference genome from the same species from which the sample has been obtained by mapping each of the tag associated reads to a location of the reference genome (*see e.g.*, Ex. 7 at 3540 (Odegaard et al.) (“Processed reads were then aligned to hg19 using BWA-MEM (arXiv: 1303.3997v2) and used to build double-stranded consensus representations of original unique cfDNA molecules using both inferred

molecular barcodes and read start/stop positions.”); Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“The sequence data then undergoes an alignment process where it is mapped to the human genome (hg19) and an analysis of sequence alteration data is performed.”));

- f. at a plurality of locations on the reference genome, counting the number of unique tagged molecules that have been assigned to the same location on the reference genome based on the mapping step to obtain a count for each location of the plurality of locations on the reference genome, thereby obtaining copy number information from genomic nucleic acids in a sample (*see e.g.*, Ex. 6 (Lanman et al.) at 19 (“Leveraging the ability of digital sequencing technology (DST) to absolutely quantify the number of unique DNA fragments in a sequenced sample, the copy number of a given gene in plasma may also be ascertained. To determine the CNV or amplification of a given gene, we first measure the total number of unique fragments covering each gene comprised of both halves of the original parent molecules.”); Ex. 13 (Guardant360 CDx Technical Information) at 1 (“Guardant360® CDx is a qualitative next generation sequencing-based *in vitro* diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of . . . copy number amplifications (CNAs) in two (2) genes”); Ex. 14 at 1 (Guardant360 CDx SSED – January 27, 2023); *id.* at 3-4 (Table 2—reporting copy number amplifications of genes *ERBB2* and *MET*)).

85. CSHL has been and continues to be damaged by Guardant’s infringement of the ’589 patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

86. Guardant’s infringement of the ’589 patent was, and continues to be, willful.

87. Guardant's conduct in infringing the '589 patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

COUNT II

(Infringement Of The '510 Patent)

88. CSHL incorporates by reference paragraphs 1–87.

89. The '510 patent is valid and enforceable.

90. Guardant has infringed, and continues to infringe, one or more claims of the '510 patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, products and/or methods encompassed by those claims, including for example, by making, using, selling, offering for sale, and/or importing the Guardant360 and Guardant360 CDx tests.

91. Guardant currently performs all of its tests on samples sent to Guardant's laboratories in Redwood City, California, and San Diego, California, for its Guardant360 and Guardant360 CDx tests. (*See* Ex. 10 (Guardant 2023 Form 10-K) at 10-11 (“We currently perform our tests in our laboratories located in Redwood City, California, and San Diego, California....Our testing process includes sample collection, laboratory processing, analysis and reporting.”).)

92. To date, over 500,000 patient samples have been analyzed using Guardant's tests.

93. As one example of Guardant's infringement, Guardant infringes at least claim 1 of the '510 patent by using the Guardant360 and Guardant360 CDx tests. For example, use of the Guardant360 and Guardant360 CDx tests includes using a method comprising:

- a) obtaining segments of genomic nucleic acids (such as cfDNA) from a sample (such as a blood sample) containing the genomic nucleic acids (*see, e.g.*, Ex. 6 (Lanman et al.)

- at 5 (“cfDNA is extracted from a routine blood draw.”); Ex. 13 (Guardant360 CDx Technical Information) at 5 (“Whole blood specimens are processed in the Guardant Health Clinical Laboratory within 7 days of blood collection. A minimum of 5 mL whole blood must be received in order to achieve optimal performance for the Guardant360 CDx assay. . . . Plasma is isolated via centrifugation and cfDNA is extracted.”));
- b) randomly tagging the segments of genomic nucleic acids with different nucleic acid tags, thereby generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags (*see, e.g.*, Ex. 6 at 18 (Lanman et al.) (“Isolated cfDNA fragments are subsequently converted to digital sequence libraries. Briefly, in the digital sequencing workflow, non-unique oligonucleotide heptamer barcodes are ligated to each half of individual double-stranded cfDNA. This generates a duplex library whereby each single-stranded half of the original double-stranded input cfDNA sample is separately encoded with said oligonucleotides.”); Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“During library preparation, cfDNA fragment ends are repaired and library adapters containing inline barcodes are attached using blunt-end ligation.”));
- c) subjecting the unique tagged acid molecules to a polymerase chain reaction (PCR), thereby generating copies of the unique tagged nucleic acid molecules (*see, e.g.*, Ex. 6 at 18 (Lanman et al.) (“These digital sequence libraries are amplified and then subsequently enriched for target genes using biotinylated custom baits of RNA

- probes”); Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“The resulting DNA is amplified by PCR to create libraries suitable for enrichment....Each enriched library is amplified by PCR using a unique index primer that also contains a sequencing flow cell attachment sequence.”));
- d) generating tag associated sequence reads by sequencing the copies of the unique tagged nucleic acid molecules of step (c) (*see, e.g.*, Ex. 6 at 17 (Lanman et al.) (“The enriched digital sequence libraries are then analyzed using HiSeq 2500 Sequencing System (Illumina) paired-end sequencing with fluorescent reversible terminator deoxyribonucleotides.”); Ex. 13 at 5 (Guardant360 CDx Technical Information) (“The enriched libraries are then sequenced using next generation sequencing on the Illumina NextSeq 550 platform.”));
- e) assigning each of the unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome (*see, e.g.*, Ex. 7 at 3540 (Odegaard et al.) (“Processed reads were then aligned to hg19 using BWA-MEM (arXiv: 1303.3997v2) and used to build double-stranded consensus representations of original unique cfDNA molecules using both inferred molecular barcodes and read start/stop positions.”); Ex. 14 (Guardant360 CDx Summary of Safety and Effectiveness Data – January 27, 2023) at 7 (“The sequence data then undergoes an alignment process where it is mapped to the human genome (hg19) and an analysis of sequence alteration data is performed.”));
- f) in a plurality of locations in the reference genome, obtaining relative copy number information of the genomic nucleic acids from the sample based on the number of unique tagged nucleic acid molecules that have been assigned to each of the plurality

of locations in the genome (*see, e.g.*, Ex. 6 (Lanman et al.) at 19 (“Leveraging the ability of digital sequencing technology (DST) to absolutely quantify the number of unique DNA fragments in a sequenced sample, the copy number of a given gene in plasma may also be ascertained. To determine the CNV or amplification of a given gene, we first measure the total number of unique fragments covering each gene comprised of both halves of the original parent molecules.”); Ex. 13 (Guardant360 CDx Technical Information) at 1 (“Guardant360® CDx is a qualitative next generation sequencing-based in vitro diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of . . . copy number amplifications (CNAs) in two (2) genes”); Ex. 14 at 1 (Guardant360 CDx SSER – January 27, 2023); *id.* at 3-4 (Table 2—reporting copy number amplifications of genes ERBB2 and MET).).

94. CSHL has been and continues to be damaged by Guardant’s infringement of the ’510 patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

95. Guardant’s infringement of the ’510 patent was, and continues to be, willful.

96. Guardant’s conduct in infringing the ’510 patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, CSHL prays for judgment as follows:

- A. That Guardant has infringed the Patents-in-Suit;
- B. That Guardant’s infringement of the Patents-in-Suit has been willful;
- C. That CSHL be awarded all damages adequate to compensate it for Guardant’s past infringement and any continuing or future infringement of the Patents-in-Suit up until the date

such judgment is entered, including pre- and post-judgment interest, costs, and disbursements as justified under 35 U.S.C. § 284;

D. That any award of damages be enhanced under 35 U.S.C. § 284 as result of Guardant's willful infringement;

E. That this case be declared an exceptional case within the meaning of 35 U.S.C. § 285 and that CSHL be awarded the attorney fees, costs, and expenses incurred in connection with this action;

F. That CSHL be awarded either a permanent injunction, or, at least, a compulsory ongoing licensing fee; and

F. That CSHL be awarded such other and further relief at law or equity as this Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiff CSHL hereby demands a trial by jury on all issues so triable.

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Dated: May 1, 2025

/s/ Kelly E. Farnan

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