

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

GUARDANT HEALTH, INC.,

Plaintiff,

v.

PERSONAL GENOME DIAGNOSTICS,
INC.,

Defendant.

C.A. No. 17-cv-1623-LPS-CJB

JURY TRIAL DEMANDED

SECOND AMENDED COMPLAINT

Plaintiff Guardant Health, Inc. (“Guardant”), on behalf of itself, by Guardant’s attorneys, hereby alleges as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, against Defendant Personal Genome Diagnostics, Inc. (“Personal Genome”).

2. Guardant brings this action to halt Personal Genome’s infringement of Guardant’s rights under the Patent Laws of the United States 35 U.S.C. § 1, et seq., which arise under U.S. Patent Nos. 9,598,731 (“the ’731 patent”) (attached as Exhibit 1), 9,834,822 (“the ’822 patent”) (attached as Exhibit 2), 9,840,743 (“the ’743 patent”) (attached as Exhibit 3), and 9,902,992 (“the ’992 patent”) (attached as Exhibit 4).

PARTIES

3. Guardant is a corporation organized and existing under the laws of the state of Delaware, having its principal place of business at 505 Penobscot Dr., Redwood City, CA 94063.

4. Guardant was founded in 2012 by pioneers in DNA sequencing and cancer diagnostics. Since its inception, Guardant has focused its expertise on the development of liquid biopsy cancer assays. It was the first company to develop and commercialize a comprehensive liquid biopsy assay to identify genomic biomarkers for advanced solid tumors using “cell-free circulating tumor DNA,” or “ctDNA,” from simple, non-invasive blood draws.

5. Today, Guardant markets and sells the Guardant360® ctDNA assay (“Guardant360”). Guardant360 uses advanced DNA sequencing methods to identify targeted therapy treatment options based on the specific changes—also known as somatic mutations—that occur within the DNA of cancer cells. Guardant360 has helped thousands of oncologists find accurate and actionable information about tens of thousands of cancer patients, while avoiding the high costs and added risks of tissue biopsies.

6. On information and belief, Personal Genome is a corporation organized and existing under the laws of the state of Delaware, having its principal place of business at 2809 Boston Street, Suite 503, Baltimore, MD 21224. Personal Genome markets and sells a liquid biopsy test known as the PlasmaSELECT 64® assay (“PlasmaSELECT 64” or “the PlasmaSELECT 64 test”). On information and belief, Personal Genome performs PlasmaSELECT 64 at its facility in Baltimore, MD.

JURISDICTION AND VENUE

7. This action arises under the patent laws of the United States, 35 U.S.C. §§ 100, *et seq.*, and this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

8. Venue is proper in this Court under 28 U.S.C. §§ 1391 and 1400(b).

9. This Court has jurisdiction over Personal Genome because, upon information and belief, Personal Genome is a Delaware corporation.

10. This Court also has jurisdiction over Personal Genome because, upon information and belief, Personal Genome, directly or indirectly, uses, offers for sale, and/or sells PlasmaSELECT 64 throughout the United States and in this judicial district.

11. Further, the Court has jurisdiction over Personal Genome because, inter alia, this action arises from actions of Personal Genome directed toward Delaware, and because Personal Genome has purposefully availed itself of the rights and benefits of Delaware law by engaging in systematic and continuous contacts with Delaware. Upon information and belief, Personal Genome regularly and continuously transacts business within Delaware, including by selling PlasmaSELECT 64 in Delaware, either on its own or through its affiliates. Upon information and belief, Personal Genome derives substantial revenue from the sale of PlasmaSELECT 64 in Delaware and has availed itself of the privilege of conducting business within Delaware.

12. For these reasons, and for other reasons that will be presented to the Court if jurisdiction is challenged, the Court has personal jurisdiction over Personal Genome.

BACKGROUND

13. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

14. On information and belief, in the late-2016 time frame, Personal Genome began commercializing PlasmaSELECT 64. According to a Personal Genome press release, “PlasmaSELECT 64 identifies clinically actionable and functionally important sequence mutations and structural alterations across multiple cancer types without the need for invasive biopsies.” Exhibit 5.

15. In August 2017, scientists affiliated with Personal Genome published the article “Direct detection of early-stage cancers using circulating tumor DNA” (attached hereto as Exhibit 6) in the journal Science Translational Medicine. This article describes an approach that Personal Genome refers to as “TEC-Seq,” an overview of which is presented in the figure below:

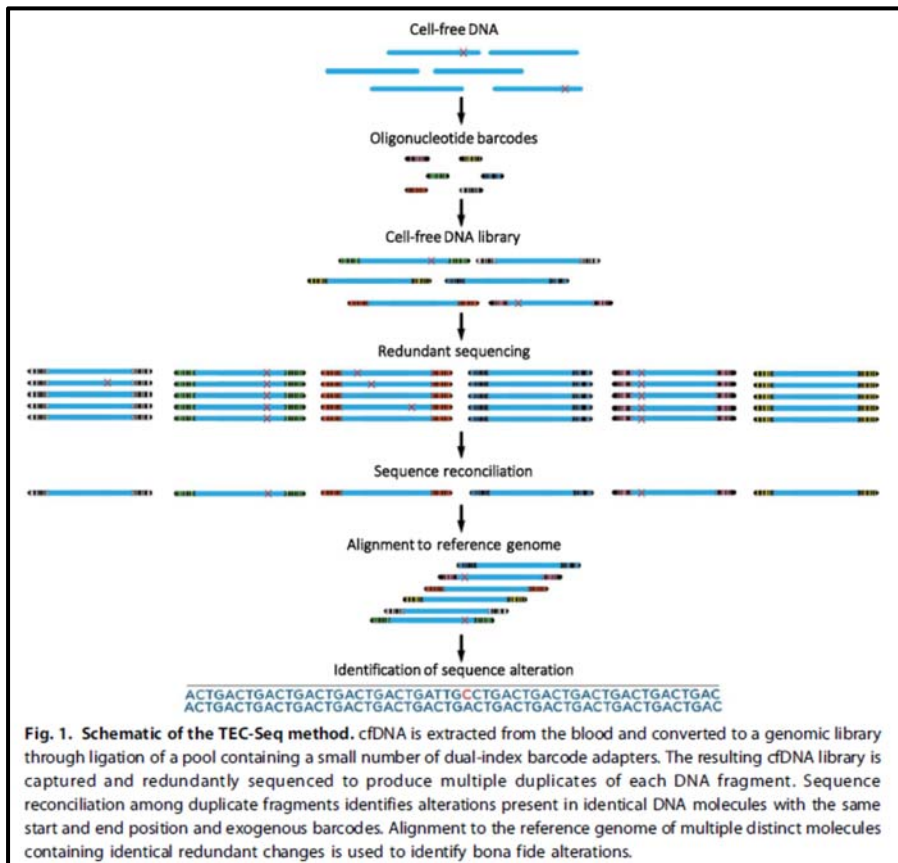


Exhibit 6 at Fig. 1.

16. Personal Genome scientists have confirmed publicly that PlasmaSELECT 64 incorporates that “TEC-Seq” method. For instance, in April 2017, Personal Genome scientist Monica Nesselbush confirmed to the trade publication GenomeWeb that “TEC-Seq is an element of PlasmaSelect.” See Exhibit 7. Likewise, when Personal Genome’s publication in Science Translational Medicine appeared, GenomeWeb reported that the “work was co-authored by

investigators from the liquid biopsy firm and Johns Hopkins spinout Personal Genome Diagnostics, which uses TEC-Seq as part of its PlasmaSelect protocol.” Exhibit 8.

17. Personal Genome infringes, literally or under the doctrine of equivalents, the ’731 patent through its activities connected to its performance of the PlasmaSELECT 64 test that uses TEC-Seq. For instance, representative claim 1 of the ’731 patent is listed below:

1. A method for quantifying single nucleotide variant tumor markers in cell-free DNA from a subject, comprising:
 - (a) providing at least 10 ng of cell-free DNA obtained from a bodily sample of the subject;
 - (b) attaching tags comprising barcodes having from 5 to 1000 distinct barcode sequences to said cell-free DNA obtained from said bodily sample of the subject, to generate non-uniquely tagged parent polynucleotides, wherein each barcode sequence is at least 5 nucleotides in length;
 - (c) amplifying the non-uniquely tagged parent polynucleotides to produce amplified non-uniquely tagged progeny polynucleotides;
 - (d) sequencing the amplified non-uniquely tagged progeny polynucleotides to produce a plurality of sequence reads from each parent polynucleotide, wherein each sequence read comprises a barcode sequence and a sequence derived from cell-free DNA;
 - (e) grouping the plurality of sequence reads produced from each non-uniquely tagged parent polynucleotide into families based on i) the barcode sequence and ii) at least one of: sequence information at a beginning of the sequence derived from cell-free DNA, sequence information at an end of the sequence derived from cell-free DNA, and length of the sequence read, whereby each family comprises sequence reads of non-uniquely tagged progeny polynucleotides amplified from a unique polynucleotide among the non-uniquely tagged parent polynucleotides;
 - (f) comparing the sequence reads grouped within each family to each other to determine consensus sequences for each family, wherein each of the consensus sequences corresponds to a unique polynucleotide among the non-uniquely tagged parent polynucleotides;
 - (g) providing one or more reference sequences from a human genome, said one or more reference sequences comprising one or more loci of reported tumor markers, wherein each of the reported tumor markers is a single nucleotide variant;
 - (h) identifying consensus sequences that map to a given locus of said one or more loci of reported tumor markers; and

- (i) calculating a number of consensus sequences that map to the given locus that include the single nucleotide variant thereby quantifying single nucleotide variant tumor markers in said cell-free DNA from said subject.

18. Performance of Personal Genome's PlasmaSELECT 64 test leads to infringement of this claim in the following way. First, in PlasmaSELECT 64, more than 10 ng of cell free DNA is obtained from a patient blood draw (step a). Tags comprising barcodes are then attached to both ends of the DNA fragments that are present in the sample of cell free DNA (step b). The tagged DNA sample is then subject to PCR amplification (step c). The amplified DNA is then subject to sequencing on the Illumina sequencing platform, resulting in sequence reads that consist of a barcode sequence and a sequence present in the cell free DNA (step d). The sequence reads are (i) grouped into families based on the barcode and additional sequence information, allowing one to collect sequence information that arises from the same DNA molecule (step e), (ii) compared to one another to arrive at a "consensus sequence" that represents a more accurate determination of the sequence of the molecule in question (step f), and (iii) mapped to a reference genome to identify sequences that map to regions of the genome associated with cancer tumor markers (steps f-h). Finally, the number of tumor markers present in the original sample are quantified (step i).

19. As an example, attached hereto as Exhibit 9 is a preliminary and exemplary claim chart detailing Personal Genome's infringement of multiple claims of the '731 patent. This chart is not intended to limit Guardant's right to modify this chart or any other claim chart or allege that other activities of Personal Genome infringe the identified claims or any other claims of the '731 patent or any other patents. Exhibit 9 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 9 that is mapped to the TEC-Seq product shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

20. Personal Genome also infringes, literally or under the doctrine of equivalents, the '822 patent through its activities connected to its performance of the PlasmaSELECT 64 test that uses TEC-Seq. For instance, representative claim 1 of the '822 patent is listed below:

1. A method, comprising:
 - (a) providing a population of cell free DNA (“cfDNA”) molecules obtained from a bodily sample from a subject;
 - (b) converting the population of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides, wherein each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a cfDNA molecule of the population of cfDNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes;
 - (c) amplifying the population of non-uniquely tagged parent polynucleotides to produce a corresponding population of amplified progeny polynucleotides;
 - (d) sequencing the population of amplified progeny polynucleotides to produce a set of sequence reads;
 - (e) mapping sequence reads of the set of sequence reads to one or more reference sequences from a human genome;
 - (f) grouping the sequence reads into families, each of the families comprising sequence reads comprising the same identifier sequence and having the same start and stop positions, whereby each of the families comprises sequence reads amplified from the same tagged parent polynucleotide;
 - (g) at each genetic locus of a plurality of genetic loci in the one or more reference sequences, collapsing sequence reads in each family to yield a base call for each family at the genetic locus; and
 - (h) determining a frequency of one or more bases called at the locus from among the families.

21. Performance of Personal Genome’s PlasmaSELECT 64 test leads to infringement of this claim in the following way. First, in PlasmaSELECT 64, cell free DNA is obtained from a patient blood draw (step a). Tags comprising barcodes are then attached to both ends of the population of DNA fragments that are present in the sample of cell free DNA (step b). The tagged DNA sample is then amplified using polymerase (step c). The amplified DNA is then subject to sequencing on the Illumina sequencing platform, resulting in sequence reads that consist of a

barcode sequence and a sequence present in the cell free DNA (step d). Sequence reads are (i) aligned to a human reference genome (step e), (ii) grouped into families based on the barcode and additional sequence information, allowing one to collect sequence information that arises from the same DNA molecule (step f), and (iii) compared to one another to arrive at a “consensus sequence” that yields a consensus base call at any position in the sequence (step g). Finally, the frequency of specific bases in the form of tumor markers present in the original sample are quantified (step h).

22. As an example, attached hereto as Exhibit 10 is a preliminary and exemplary claim chart detailing Personal Genome’s infringement of multiple claims of the ’822 patent. This chart is not intended to limit Guardant’s right to modify this chart or any other claim chart or allege that other activities of Personal Genome infringe the identified claims or any other claims of the ’822 patent or any other patents. Exhibit 10 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 10 that is mapped to the TEC-Seq product shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

23. Personal Genome also infringes, literally or under the doctrine of equivalents, the ’743 patent through its activities connected to its performance of the PlasmaSELECT 64 test that uses TEC-Seq. For instance, representative claim 10 of the ’743 patent is listed below:

10. A method for detecting a rare mutation in a cell-free or substantially cell-free sample obtained from a subject, comprising:

- (a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads;
- (b) filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold;
- (c) mapping the plurality of sequence reads to a reference sequence;
- (d) determining unique sequence reads corresponding to the extracellular polynucleotides from among the sequence reads;

- (e) identifying a subset of mapped unique sequence reads that include a variant as compared to the reference sequence at each mappable base position;
- (f) for each mappable base position, calculating a ratio of (a) a number of mapped unique sequence reads that include a variant as compared to the reference sequence, to (b) a number of total unique sequence reads for each mappable base position; and
- (g) processing the ratio with a similarly derived number from a reference sample.

24. Performance of Personal Genome's PlasmaSELECT 64 test leads to infringement of this claim in the following way. First, in PlasmaSELECT 64, cell-free DNA extracted from blood, amplified and sequenced using the Illumina platform, generating a plurality of sequence reads (preamble and step a). Second, redundant sequences are grouped together to form consensus sequences and errors in individual sequence reads are removed (step b). The plurality of sequence reads are mapped to a human reference genome (step c). Unique sequences are identified among the plurality of redundant sequences (step d). Next, the test identifies the unique sequence reads that include a variant, and calculates the ratio of sequence reads that include a variant as compared to the total number of unique sequence reads (steps e-f). The ratio of unique sequence reads that include variants are evaluated by comparing with matched tumor tissue and blood cells (step g).

25. As an example, attached hereto as Exhibit 11 is a preliminary and exemplary claim chart detailing Personal Genome's infringement of multiple claims of the '743 patent. This chart is not intended to limit Guardant's right to modify this chart or any other claim chart or allege that other activities of Personal Genome infringe the identified claims or any other claims of the '743 patent or any other patents. Exhibit 11 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 11 that is mapped to the TEC-Seq product shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

26. Personal Genome also infringes, literally or under the doctrine of equivalents, the '992 patent through its activities connected to its performance of the PlasmaSELECT 64 test that uses TEC-Seq. For instance, representative claim 1 of the '992 patent is listed below:

1. A method for detecting genetic aberrations in cell-free DNA ("cfDNA") molecules from a subject, comprising:

- (a) providing cfDNA molecules obtained from a bodily sample of the subject;
- (b) attaching tags comprising barcodes having a plurality of different barcode sequences to the cfDNA molecules to tag at least 20% of the cfDNA molecules, which attaching comprises ligating adaptors comprising the barcodes to both ends of the cfDNA molecules, wherein ligating comprises using more than 10X molar excess of the adaptors as compared to the cfDNA molecules, thereby generating tagged parent polynucleotides;
- (c) amplifying the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;
- (d) sequencing the amplified tagged progeny polynucleotides to produce a plurality of sequence reads from each of the tagged parent polynucleotides, wherein each sequence read of the plurality of sequence reads comprises a barcode sequence and a sequence derived from a cfDNA molecule of the cfDNA molecules;
- (e) mapping sequence reads of the plurality of sequence reads to one or more reference sequences from a human genome;
- (f) grouping the sequence reads mapped in e) into families based at least on barcode sequences of the sequence reads, each of the families comprising sequence reads comprising the same barcode sequence, whereby each of the families comprises sequence reads amplified from the same tagged parent polynucleotide;
- (g) at each of a plurality of genetic loci in the one or more reference sequences, collapsing sequence reads in each family to yield a base call for each family at the genetic locus; and
- (h) detecting, at one or more genetic loci, a plurality of genetic aberrations, wherein the plurality of genetic aberrations comprises two or more different members selected from the group of members consisting of a single base substitution, a copy number variation (CNV), an insertion or deletion (indel), and a gene fusion.

27. Performance of Personal Genome's PlasmaSELECT 64 test leads to infringement of this claim in the following way. First, cfDNA is extracted from blood (step a). Next, barcodes are ligated to each end of cfDNA generating tagged parent polynucleotides (step b). The tagged

parent polynucleotides containing the ligated barcodes are then amplified (step c) and sequenced using an Illumina platform to generate a plurality of sequence reads (step d). This plurality of sequence reads are aligned to a human reference genome (step e) and are then grouped according to their barcode sequence such that sequence reads amplified from the same tagged parent polynucleotide can be identified (step f). Lastly, PlasmaSELECT 64 generates a base call at a plurality of loci from the plurality of sequence reads (step g) and uses that base call to detect a plurality of genetic aberrations including base substitutions, copy number variations, insertions or deletions, and gene fusions (step h).

28. As an example, attached hereto as Exhibit 12 is a preliminary and exemplary claim chart detailing Personal Genome's infringement of multiple claims of the '992 patent. This chart is not intended to limit Guardant's right to modify this chart or any other claim chart or allege that other activities of Personal Genome infringe the identified claims or any other claims of the '992 patent or any other patents. Exhibit 12 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 12 that is mapped to the TEC-Seq product shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

COUNT I

(Infringement of U.S. Patent No. 9,598,731)

29. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

30. On March 21, 2017, the United States Patent and Trademark Office duly and legally issued the '731 patent, entitled "Systems and Methods to Detect Rare Mutations and Copy Number Variation," which is solely assigned to Guardant. Guardant is the owner of all rights, title to and interest in the '731 patent.

31. On information and belief, Personal Genome has infringed and continues to infringe at least claims 1, 2, 5, 6-9, 11-12, 14, 16-17 of the '731 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the PlasmaSELECT 64 test that uses the TEC-Seq method. As an example, attached as Exhibit 8 is a preliminary and exemplary claim chart detailing Personal Genome's infringement of these claims of the '731 patent. This chart is not intended to limit Guardant's right to modify the chart or allege that other activities of Guardant infringe the identified claims or any other claims of the '731 patent or any other patents.

32. Exhibit 9 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 9 that is mapped to Personal Genome's PlasmaSELECT 64 test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

COUNT II

(Infringement of U.S. Patent No. 9,834,822)

33. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

34. On December 5, 2017, the United States Patent and Trademark Office duly and legally issued the '822 patent, entitled "Systems and Methods to Detect Rare Mutations and Copy Number Variation," which is solely assigned to Guardant. Guardant is the owner of all rights, title to and interest in the '822 patent.

35. On information and belief, Personal Genome has infringed and continues to infringe at least claims 1, 3-8, 10, 13-14, 18-19 of the '822 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the PlasmaSELECT 64 test that uses the TEC-Seq method. As an example, attached as

Exhibit 9 is a preliminary and exemplary claim chart detailing Personal Genome's infringement of these claims of the '822 patent. This chart is not intended to limit Guardant's right to modify the chart or allege that other activities of Guardant infringe the identified claims or any other claims of the '822 patent or any other patents.

36. Exhibit 10 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 10 that is mapped to Personal Genome's PlasmaSELECT 64 test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

COUNT III

(Infringement of U.S. Patent No. 9,840,743)

37. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

38. On December 12, 2017, the United States Patent and Trademark Office duly and legally issued the '743 patent, entitled "Systems and Methods to Detect Rare Mutations and Copy Number Variation," which is solely assigned to Guardant. Guardant is the owner of all rights, title to and interest in the '743 patent.

39. On information and belief, Personal Genome has infringed and continues to infringe at least claims 10-21 of the '743 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the PlasmaSELECT 64 test that uses the TEC-Seq method. As an example, attached as Exhibit 10 is a preliminary and exemplary claim chart detailing Personal Genome's infringement of these claims of the '743 patent. This chart is not intended to limit Guardant's right to modify the chart or allege that other activities of Guardant infringe the identified claims or any other claims of the '743 patent or any other patents.

40. Exhibit 11 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 11 that is mapped to Personal Genome's PlasmaSELECT 64 test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

COUNT IV

(Infringement of U.S. Patent No. 9,902,992)

41. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

42. On February 27, 2018, the United States Patent and Trademark Office duly and legally issued the '992 patent, entitled "Systems and Methods to Detect Rare Mutations and Copy Number Variation," which is solely assigned to Guardant. Guardant is the owner of all rights, title to and interest in the '992 patent.

43. On information and belief, Personal Genome has infringed and continues to infringe at least claims 1-6, 11-13, 17-21, and 24 of the '992 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the PlasmaSELECT 64 test that uses the TEC-Seq method. As an example, attached as Exhibit 12 is a preliminary and exemplary claim chart detailing Personal Genome's infringement of these claims of the '992 patent. This chart is not intended to limit Guardant's right to modify the chart or allege that other activities of Guardant infringe the identified claims or any other claims of the '992 patent or any other patents.

44. Exhibit 12 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 12 that is mapped to Personal Genome's PlasmaSELECT 64 test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

JURY DEMAND

45. Guardant demands a jury trial on all issues so triable.

PRAYER FOR RELIEF

WHEREFORE, Guardant prays that this Court grant the following relief:

A. A judgment that Personal Genome has infringed the '731 patent, the '822 patent, the '743 patent, and the '992 patent and that the '731 patent, the '822 patent, the '743 patent, and the '992 patent are valid;

B. Damages or other monetary relief, including, but not limited to, costs and pre- and post-judgment interest, to Guardant;

C. An order enjoining Personal Genome 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 '731 patent, the '822 patent, the '743 patent, and the '992 patent;

D. Such further and other relief as this Court deems proper and just, including, but not limited to, a determination that this is an exceptional case under 35 U.S.C. § 285 and an award of attorneys' fees and costs to Guardant in this action.

Dated: March 23, 2018

Respectfully submitted,

FARNAN LLP

/s/ Michael J. Farnan

Joseph J. Farnan, Jr. (Bar No. 100245)

Brian E. Farnan (Bar No. 4089)

Michael J. Farnan (Bar No. 5165)

919 N. Market St., 12th Floor

Wilmington, DE 19801

Tel: (302) 777-0300

Fax: (302) 777-0301

farnan@farnanlaw.com

bfarnan@farnanlaw.com

mfarnan@farnanlaw.com

Edward R. Reines (admitted *pro hac vice*)

Derek Walter (admitted *pro hac vice*)

WEIL, GOTSHAL & MANGES LLP

201 Redwood Shores Parkway

Redwood Shores, CA 94065

(650) 802-3000

Attorneys for Plaintiff Guardant Health, Inc.