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

| | | |
|---|---|---|
| GUARDANT HEALTH, INC.,<br><br>Plaintiff,<br><br>v.<br><br>FOUNDATION MEDICINE, INC.,<br><br>Defendant. | ) | Civil Action No. 17-1616-LPS-CJB |
| GUARDANT HEALTH, INC.,<br><br>Plaintiff,<br><br>v.<br><br>PERSONAL GENOME DIAGNOSTICS, INC.,<br><br>Defendant. | ) | Civil Action No. 17-1623-LPS-CJB |

## REPORT AND RECOMMENDATION

In these two related actions filed by Plaintiff Guardant Health, Inc. ("Guardant" or "Plaintiff") against Defendants Foundation Medicine, Inc. ("FMI") and Personal Genome Diagnostics, Inc. ("PGDx" and collectively with FMI, "Defendants"), Guardant alleges infringement of United States Patent Nos. 9,598,731 (the "'731 patent"), 9,834,822 (the "'822 patent"), 9,840,743 (the "'743 patent") and 9,902,992 (the "'992 patent" and collectively with the other patents, "the asserted patents"). Presently before the Court is the matter of claim construction. The Court recommends that the District Court adopt the constructions as set forth below.



## I. BACKGROUND AND STANDARD OF REVIEW

The Court hereby incorporates by reference the summary of the background of this matter set out in its September 6, 2019 Report and Recommendation ("September 6 R&R").

(D.I. 354 at 2-3)[1] It additionally incorporates by reference the legal principles regarding claim construction set out in the September 6 R&R. (*Id.* at 3-5) Because Defendants contend that the disputed claim terms addressed herein are indefinite, (*see, e.g.*, D.I. 68 at 15-20), the Court further includes below the applicable standard for definiteness.

The primary purpose of the definiteness requirement is to ensure that patent claims are written in such a way that they give notice to the public of what is claimed, thus enabling interested members of the public (e.g., competitors of the patent owner) to determine whether they infringe. *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779-80 (Fed. Cir. 2002). Put another way, "[a] patent holder should know what he owns, and the public should know what he does not." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002). Even so, the Supreme Court of the United States has recognized that "absolute precision is unattainable" and not required. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014).

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Id.* at 901. Definiteness is to be evaluated from the perspective of a person of ordinary skill in the art ("POSA") at the time the patent was filed. *Id.* at 908.

Like claim construction, definiteness is a question of law for the court. *H-W Tech., L.C. v. Overstock.com, Inc.*, 758 F.3d 1329, 1332 (Fed. Cir. 2014); *Pi-Net Int'l Inc. v. JPMorgan*

---

[1] For simplicity's sake, the Court will refer to the "D.I." number in Civil Action No. 17-1623-LPS-CJB, unless otherwise indicated.

*Chase & Co.*, 42 F. Supp. 3d 579, 586 (D. Del. 2014). The United States Court of Appeals for the Federal Circuit has stated that "[a]ny fact critical to a holding on indefiniteness . . . must be proven by the challenger by clear and convincing evidence." *Intel Corp. v. VIA Techs., Inc.*, 319 F.3d 1357, 1366 (Fed. Cir. 2003); *see also Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1338 (Fed. Cir. 2008).[2]

## II. DISCUSSION

The parties had claim construction disputes regarding 13 terms or sets of terms (hereinafter, "terms" or "term sets"). The Court has addressed five of these terms/term sets in previously-issued Report and Recommendations. (D.I. 354; D.I. 359) In this Report and Recommendation, the Court addresses two additional term sets. The Court will address the remaining terms/term sets in one or more subsequently-issued Report and Recommendation(s).

### A. "detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant" / "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"

The claim term "detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant" is found in claim 2 of the '822 patent, and the claim term "detecting, at one or more genetic loci, a plurality of genetic aberrations, wherein the plurality of genetic aberrations comprises two or more different

---

[2] In *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898 (2014), the Supreme Court left open the question of whether factual findings subsidiary to the ultimate issue of definiteness should, in fact, trigger the application of a "clear-and-convincing-evidence standard[,]" noting that it would "leave th[is] question[] for another day." *Nautilus*, 572 U.S. at 912 n.10. In the absence of Supreme Court precedent to the contrary, the Federal Circuit's case law (utilizing the clear-and-convincing-evidence standard) controls. *See Cal. Inst. of Tech. v. Hughes Commc'ns Inc.*, 35 F. Supp. 3d 1176, 1182 n.4 (C.D. Cal. 2014).

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" is found in claim 1 of the '992 patent. Accordingly, these claims (along with claim 1 of the '822 patent, from which claim 2 depends) are reproduced below, with the disputed terms highlighted:

> **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.

('822 patent, col. 62:18-48)

**2.** The method of claim **1**, further comprising *detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant.*

(*Id.*, col. 62:49-51 (emphasis added))

**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.*

('992 patent, col. 64:2-41 (emphasis added)) The parties' competing proposed constructions for these terms are set out in the chart below:

| **Term** | **Plaintiff's Proposed Construction** | **Defendants' Proposed Construction** |
|---|---|---|
| "detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant" ('822 patent, claim 2) | "[a]cross one or more genetic loci, detecting at least one single nucleotide variant, at least one gene fusion, and at least one copy number variant" | Indefinite. |
| "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" ('992 patent, claim 1) | "[a]cross one or more genetic loci, detecting 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" | |

(D.I. 59 at 18; D.I. 68 at 19) It is undisputed that the patent specification discloses detecting "one individual type of mutation at a locus at a time." (D.I. 59 at 18; *see also* D.I. 74 at 14; Tr. at 159-60)[3] It is also undisputed that the specification does *not* disclose an embodiment in which multiple mutations at a locus are detected. (Tr. at 160, 164-65) However, claim 2 of the '822

[3] For example, the patent specification of the '992 patent explains that "[a]s a consequence, the collection of sequence reads can include a certain percentage of base calls *at a locus* that are not the same as the original base." ('992 patent, col. 31:43-46 (emphasis added); *see also id.*, FIGS. 10-11, cols. 48:15-18, 52:44-46)

patent and claim 1 of the '992 patent clearly recite detecting more than one mutation at the same locus at a time. (*See* D.I. 72 at 15; D.I. 74 at 14)

Defendants assert that claim 2 of the '822 patent and claim 1 of the '992 patent are indefinite because "the methods disclosed in the specification identify only one mutation per locus, but the claims require identifying more than one mutation per locus." (D.I. 74 at 14; *see also* Tr. at 159-60; D.I. 90 at 3) In support of their position, Defendants rely on *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336 (Fed. Cir. 2002). (D.I. 68 at 19; D.I. 74 at 14; Tr. at 159; D.I. 90 at 3) In that case, the Federal Circuit explained that a claim is indefinite under 35 U.S.C. § 112 ("Section 112") if "it would be apparent to one of skill in the art, based on the specification, that the invention set forth in a claim is not what the patentee regarded as his invention[.]" *Allen Eng'g Corp.*, 299 F.3d at 1349.

The Court does not agree that these claims are indefinite under *Allen Eng'g.* Some background with respect to the circumstances of that case is helpful to understanding the Federal Circuit's conclusion therein.

The patent in *Allen Eng'g* was directed to concrete riding trowels (which are machines used to smooth the surface of poured concrete) powered by an internal combustion engine and steered by the manipulation of control sticks. *Id.* at 1342. The steering mechanism of the claimed trowel included a gearbox. *Id.* at 1343, 1349. Certain of the patent's claims limited one of the two pivot steering boxes of the trowel to pivoting "its gear box *only* in a plane *perpendicular to* said biaxial plane[.]" *Id.* at 1349 (internal quotation marks and citation omitted) (emphasis in original). Meanwhile, the specification of the patent described this structure "in contrary terms, stating that 'rotation about the axis established by bolt 272 is not permitted; gearbox 85A *cannot* pivot in a plane *perpendicular to* the biaxial plane.'" *Id.* (citation

omitted) (emphasis in original). And the Federal Circuit noted that the patentee *acknowledged* that the inventor did not regard "a trowel in which the second gear box pivoted only in a plane perpendicular to the biaxial plane to be his invention"—yet that is the invention that was set out in certain of the patent's claims. *Id.* Based on this fundamental "contradiction" between the specification and the claims, the Federal Circuit concluded that the claims at issue were invalid as indefinite "as a matter of law[.]" *Id.*[4]

District courts examining *Allen Eng'g* have thus understandably reasoned that the case teaches that a finding of indefiniteness is required "when there is an irreconcilable contradiction" within the patent, i.e., between the patent specification and patent claims, *Enzo Life Scis., Inc. v. Digene Corp.*, 305 F. Supp. 2d 406, 410 (D. Del. 2004), or, relatedly, a "logical inconsistency or contradiction" between the specification and the claims, *see Juxtacomm-Texas Software, LLC v. Axway, Inc.*, No. 6:10cv011, 2012 WL 7637197, at *4-5 (E.D. Tex. July 5, 2012) (explaining

---

[4] This conclusion in *Allen Eng'g* is in line with the reasoning of other relevant appellate opinions on this subject matter. For example, in *Tr. of Columbia Univ. in the City of New York v. Symantec Corp.*, 811 F.3d 1359 (Fed. Cir. 2016), the Federal Circuit relied on *Allen Eng'g* in affirming the district court's judgment that two claims of the asserted patent were indefinite, where the claims "describe the step of extracting machine code instructions from something that does not have machine code instructions." *Id.* at 1367. The Court explained that such claims were "nonsensical in the way a claim to extracting orange juice from apples would be" and were therefore indefinite. *Id.*

Similarly, in a case of much earlier vintage, the United States Court of Customs and Patent Appeals (a predecessor court to the Federal Circuit) found that certain claims on appeal were indefinite that specifically called for "sealing the oxide surface *with an alkali silicate* in order to ultimately obtain an 'opaque appearance.'" *Application of Cohn*, 438 F.2d 989, 1001 (C.C.P.A. 1971) (emphasis added). Meanwhile, the specification had clearly described an "'opaque finish' [as] a flat-appearing finish which *is not obtained when an alkali metal silicate is used* as a sealant." *Id.* at 1000-01 (emphasis added). The *Cohn* Court thus concluded that the claims were indefinite in light of the "inexplicable inconsistency" between the claims and the specification. *Id.* at 1001.

that to find a claim invalid for indefiniteness based on *Allen Eng'g*, "there must be a showing of a logical inconsistency or contradiction between the claims and the specification" and finding claims indefinite where they "require data transformation to occur within the systems interface, while the specification plainly contradicts such a teaching by disclosing that the systems interface is merely used for defining the scripts that control data flow").[5] When there is no such contradiction between the specification and relevant claims, the claims are not indefinite under *Allen Eng'g*. *See, e.g.*, *Perdiemco, LLC v. Industrack LLC*, Case No. 2:15-cv-727-JRG-RSP, 2:15-cv-1216-JRG-RSP, 2016 WL 5719697, at *8 (E.D. Tex. Sept. 21, 2016) (rejecting defendants' contention that the claims were indefinite under *Allen Eng'g* where there was no "logical contradiction between the asserted claims and the common specification" and noting that "[t]he fact that the asserted claims do not encompass every feature, or even every important feature, disclosed in the specification does not imply a logical contradiction").[6]

---

[5] *See also, e.g.*, *DISA Indus. A/S v. Thyssenkrupp Waupaca, Inc.*, No. 07-C-949, 2009 WL 959564, at *4-5 (E.D. Wis. Apr. 8, 2009) (concluding that a claim was indefinite where the "claim language is *inconsistent* because it teaches something that the guiding means, as defined in the specification, cannot physically do") (emphasis in original), *vacated on other grounds*, 2009 WL 3170511 (E.D. Wis. Sept. 28, 2009); *Network Appliance Inc. v. Sun Microsys. Inc.*, No. C-07-06053 EDL, 2008 WL 4193049, at *39 (N.D. Cal. Sept. 10, 2008) (finding a claim indefinite where "[t]he claim language requires 'one or more storage blocks across a plurality of stripes,' but under the invention, it is impossible for any 'one' storage block to be 'across a plurality of stripes'").

[6] *See also, e.g.*, *Gonzalez v. Infostream Grp., Inc.*, Case No. 2:14-cv-906-JRG-RSP, 2015 WL 5604448, at *9 (E.D. Tex. Sept. 21, 2015) (noting that the claims were found indefinite in *Allen Eng'g* because the "patent described the invention as essentially having two features that could not pivot perpendicularly to each other, yet the claims described two features that could *only* pivot perpendicularly to each other" and finding the claims at issue to be definite where the patents "do not include a definition of the invention in the description that is contrary to the language of the claims") (certain emphasis in original, certain emphasis added); *Safegate Airport Sys., Inc. v. RLG Docking Sys., Inc.*, No. CV-13-00567-PHX-GMS, 2014 WL 4954402, at *2 (D. Ariz. Oct. 1, 2014) (explaining that in *Allen Eng'g*, "the claim was *only* for a motion that the specification stated *cannot* be done" and finding no such "similar contradiction" with respect to

Here, there is no irreconcilable or logical contradiction between the specification and the patent claims at issue. (*See* D.I. 72 at 14-15) Indeed, Defendants do not argue that there is. (D.I. 74 at 14) Instead, Defendants assert that "[c]laim terms need not 'irreconcilably contradict' the specification to be indefinite[,]" and go on to suggest that so long as there is "inconsistency" between the specification and patent claims—in that the specification describes one thing as being inventive and the claim covers something similar to, but also a bit different in scope from, that thing—this is enough to find indefiniteness under *Allen Eng'g*. (*Id.* at 14-15; *see also* Tr. at 159 (Defendants' counsel asserting that the *Allen Eng'g* Court held that claims are indefinite if "you perform a simple comparison of the invention as described in the specification[] to the thing that is actually claimed [and] the scope of those two things" do not match up))

In the Court's view, Defendants read the holding of *Allen Eng'g* too broadly. While it is true that the claims at issue here undisputedly cover an application of the invention that is not disclosed in the specification as an express embodiment, (*see* Tr. at 161-62 (Defendants articulating the problem here as the specification describing detecting a single mutation per locus while the claims "open up and allow for the possibility of multiple mutations per locus")), *Allen Eng'g* and its progeny require more than this for a court to conclude that the claims are indefinite as a matter of law. If the specification stated that detection of multiple mutations at a single locus was an impossible feat, for example, then Defendants would have a much stronger argument that the claims (which allow for such detection) are invalid as indefinite under *Allen Eng'g*. The specification states no such thing, however. Indeed, Guardant pointed out that

---

the patent before it, where the claim covered a single mirror as a means for projecting and the "preferred embodiment in the specification describes a system with multiple mirrors and a stationary LRF, but it does not say that this is the only way to make the invention or that the LRF 'cannot' move") (emphasis in original).

Defendants' expert, Dr. Stacey Gabriel, testified that: (1) it was "not inconceivable" to detect multiple mutations at a single locus (but rather that it was merely "[a]typical"); and (2) a POSA would understand that one could detect multiple mutations at a single locus via the use of the inventions described in the patents. (D.I. 88 at 2-3 (citing *id.*, ex. 2 at 80-82); *see also* D.I. 72 at 15; Tr. at 156-57)

For the above reasons, the Court concludes that the claims at issue are not invalid due to indefiniteness for failing to "set forth . . . what the patentee regarded as his invention" under *Allen Eng'g.*[7] Accordingly, and with there being no other dispute as to the propriety of Guardant's proposed constructions, the Court recommends that those constructions be adopted, and that: (1) "detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant" be construed to mean "[a]cross one or more genetic loci, detecting at least one single nucleotide variant, at least one gene fusion, and at least one copy number variant"; and (2) "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" be construed to mean "[a]cross one or more genetic loci, detecting 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."

---

[7] There might be other Section 112-related defenses that Defendants could raise in the future with regard to claims that contain these terms, but the Court's opinion here offers no view, one way or the other, on the efficacy of such defenses.

### B. "sequence information at a beginning of the sequence derived from cell-free DNA/the cfDNA molecule" / "sequence information at an end of the sequence derived from cell-free DNA/the cfDNA molecule"

The claim terms "sequence information at a beginning of the sequence derived from cell-free DNA/the cfDNA molecule" and "sequence information at an end of the sequence derived from cell-free DNA/the cfDNA molecule" are found in claim 1 of the '731 patent and claims 19 and 20 of the '992 patent. Accordingly, these claims (along with claim 1 and 4 of the '992 patent, from which claims 19 and 20 depend) are reproduced below, with the disputed terms highlighted:

> **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.

('731 patent, col. 62:8-54 (emphasis added))

**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.

('992 patent, col. 64:2-41)

**4.** The method of claim 1, comprising providing between 100 and 100,000 human haploid genome equivalents of the cfDNA molecules, wherein the cfDNA molecules are tagged with between 2 and 1,000,000 unique identifiers.

(*Id.*, col. 64:46-49)

**19.** The method of claim **4**, wherein grouping the sequence reads mapped in e) is further based on one or more of: *sequence information at a beginning of the sequence derived from the cfDNA molecule, sequence information at an end of the sequence derived from the cfDNA molecule*, and length of the sequence read.

(*Id.*, col. 65:34-39 (emphasis added))

**20.** The method of claim **4**, wherein grouping the sequence reads mapped in e) is further based on a plurality of: *sequence information at a beginning of the sequence derived from the cfDNA molecule, sequence information at an end of the sequence derived from the cfDNA molecule*, and length of the sequence read.

(*Id.*, col. 65:40-45 (emphasis added)) The parties' competing proposed constructions for these terms are set out in the chart below:

| **Term** | **Plaintiff's Proposed Construction** | **Defendants' Proposed Construction** |
|---|---|---|
| "sequence information at a beginning of the sequence derived from cell-free DNA/the cfDNA molecule" | No construction necessary. If construed, "sequence information at the 'beginning' of a sequence is sequence information including the identity of the bases in the start region of the sequence read" | Indefinite. |
| "sequence information at an end of the sequence derived from cell-free DNA/the cfDNA molecule" | No construction necessary. If construed, "[s]equence information at the 'end' of a sequence is sequence information including the identity of the bases in the stop region of the sequence read" | |

(D.I. 59 at 16) As reflected in the claims above, these terms are part of the "grouping" steps of claim 1 of the '731 patent and claims 19 and 20 of the '992 patent, which require that sequence reads be grouped into families based on particular information including "sequence information at a beginning of the sequence" and/or "sequence information at an end of the sequence." (*See* D.I. 68 at 16) Defendants contend that these terms are indefinite under Section 112 because the intrinsic record provides no objective boundaries that would allow a POSA to understand what constitutes information at "a beginning" or "an end" of the sequence. (*Id.* at 16-18; D.I. 74 at 12-14)

To illustrate Defendants' position, their expert, Dr. Gabriel, set out a hypothetical sequence that is 16 nucleotides long:

G-G-C-C-G-T-G-C-C-A-G-C-T-T-A-A

(D.I. 69 at ¶ 46; *see also* D.I. 68 at 16)[8] Dr. Gabriel then persuasively points out that "[s]equence information at a beginning of the sequence" could refer to "numerous . . . combinations"—for instance, it might only include the "first nucleotide, 'G[,]'" or it "might include the first two, 'G-G[,]'" or it might "include the third, fourth, fifth, sixth, seventh and eighth nucleotides[,]" or it could even include simply "the third and fourth nucleotides, 'C-C,' but not the first two 'G-G.'" (D.I. 69 at ¶ 46; *see also* D.I. 68 at 16-17)[9] The problem, according to Defendants, is that the intrinsic record provides no guidance as to how sequence reads may be grouped based on, *inter alia*, information at "a beginning" or "an end" of the sequence. (D.I. 69 at ¶ 47; *see also* D.I. 68 at 17-18) Indeed, Dr. Gabriel ultimately opines that a POSA would not have understood the scope of claim 1 of the '731 patent and claims 19 and 20 of the '992 patent, because the POSA would not have understood the meaning of these terms in view of the intrinsic record. (D.I. 69 at ¶¶ 44-53; *see also id.* at ¶ 47 (Dr. Gabriel noting that the "terms 'information at a beginning of a sequence' and 'information at an end of the sequence' are . . . not terms used in the art to refer to a particular portion of a sequence" and are "vague and open-ended")[10]

---

[8] During the *Markman* hearing, Defendants' counsel represented that a typical cell free DNA fragment is approximately 160-170 nucleotides long. (Tr. at 172)

[9] The claim terms' use of "a beginning" and "an end" instead of "the beginning" or "the end" provide further ambiguity here, according to Defendants, because (for example) they would allow for the third and fourth nucleotides in the string to be encompassed by "a beginning," instead of requiring that the first nucleotide (i.e., the one at *the* beginning) be included. (D.I. 68 at 16-17)

[10] According to Dr. Gabriel, the fact that the patents do not "provide guidance on how many nucleotides are encompassed by the term 'sequence information'" is also "significant because the greater the number of nucleotides taken into account, the easier it is to distinguish the sequence reads from one another[.]" (D.I. 69 at ¶ 45)

In its opening brief, Guardant's primary response was to argue that the specification provides objective guidance regarding the scope of these claims. (D.I. 59 at 16) In particular, Guardant there pointed to the following excerpt from the '731 patent specification:

> In some embodiments, sequence reads of unique identity may be detected based on sequence information at the beginning (start) and end (stop) regions of the sequence read and the length of the sequence read. In other embodiments sequence molecules of unique identity are detected based on sequence information at the beginning (start) and end (stop) regions of the sequence read, the length of the sequence read and attachment of a barcode.

('731 patent, col. 3:40-47) Guardant argues that this excerpt (and others in the patent like it) provides the POSA with "two key pieces of information." (D.I. 59 at 16) First, it purportedly demonstrates that "the 'beginning' and 'end' of the sequence corresponds to the 'start' and 'stop' positions, respectively, of the sequence read[,]" with start and stop positions being terms of art referring to the coordinates in a reference genome delineating the endpoints of the sequence read. (*Id.* at 17) Second, according to Guardant, this excerpt tells the POSA that the information at the "beginning" and "end" of the sequence read "must be of sufficient length" to allow the POSA to detect sequence reads of unique identity. (*Id.*)[11]

The Court is not persuaded that this excerpt from the '731 patent specification provides the requisite objective guidance with respect to these claim terms.

---

[11] During the *Markman* hearing, Guardant's counsel elaborated that these claim terms could indeed cover numerous scenarios, depending on the degree of precision that the POSA desired. That is, counsel noted that perhaps for one experiment a POSA would want to use information "from four bases, at other times you might want to use information from [for example] six bases as an identifier." (Tr. at 165; *see also id.* at 167) At one point, the Court asked Guardant's counsel whether "there [is] anything [i.e., any number of nucleotides] that couldn't be included" in the meaning of "at a beginning of" or "at an end of" the sequence. (Tr. at 169) To that, counsel replied only "[t]o me that is [for] expert testimony." (*Id.*)

For example, as to Guardant's first point about the excerpt, left unsaid is that the exact claim terms at issue here ("information at a beginning of the sequence" or "information at an end of the sequence") are *never* referenced in the specification (and, thus, are not found in the excerpt). (*See* D.I. 74 at 13 n.8; Tr. at 173) Moreover, it is notable that the excerpt makes reference to start and stop "*regions*" of the sequence read, not (as Guardant suggests) start and stop "*positions*." (D.I. 68 at 18)[12] And Dr. Gabriel's unrebutted testimony is that "start region" and "stop region" are not themselves terms of art used to describe a specific portion of a sequence. (D.I. 69 at ¶ 50)

Moreover, as to Guardant's second point about the excerpt, the Court disagrees that it (or any other portion of the specification) provides guidance as to what types of sequence reads are of "sufficient length" to allow a POSA to detect sequence reads of a unique identity. Indeed, Guardant's argument just begs the question: "What length is sufficient length?" On that point, the excerpt does not actually say anything helpful. (D.I. 68 at 18 n.14)

Perhaps realizing the specification's inability to provide objective guidance with respect to these claim terms, in its answering brief, Guardant said nothing more about the specification. (D.I. 72 at 13-14) Instead, there it primarily argued that the "claim itself" provides sufficient objective guidance as to the scope of these claim terms, by "provid[ing] the purpose for which the sequence information at a beginning or end of the sequence is used, namely, grouping of the plurality of sequence reads." (*Id.*) According to Guardant, this statement of purpose would

---

[12] The patentee clearly knew how to utilize the particular terms "start position" and "stop position" had it wished to, as is demonstrated by claim 1 of the '822 patent, which recites "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*[.]" ('822 patent, col. 62:37-40 (emphasis added))

provide objective guidance to the POSA, who "would understand what considerations [] would go into the choice of sequence information used." (*Id.* at 14) In support of this assertion, however, Guardant cites to nothing. Nor does it further elaborate on what are the "considerations" that the POSA would contemplate in this regard. (*See* D.I. 74 at 13-14) The Court thus remains in the dark as to how these claims, read in light of the intrinsic record, inform the POSA with reasonable certainty about the scope of the invention.[13]

At the *Markman* hearing, Guardant's argument took on yet a different flavor. There, Guardant primarily relied on the fact that in related *inter partes* review proceedings, Dr. Gabriel opined that certain prior art references read on claim 1 of the '731 patent. According to Guardant, this demonstrates the definiteness of the claims at issue. (Tr. at 166-67; Guardant's Markman Presentation, Slides 113-15; *see also* D.I. 88 at 3) But as Defendants rightly retort, just because "a particular prior art reference [may] fall[] within the scope of a claim limitation[, that] does not mean that the scope of the limitation is clear enough to determine whether *any* accused product practices the limitation." (D.I. 90 at 3 (emphasis in original); *see also* Tr. at 171)

In sum, Defendants have proved by clear and convincing evidence that these claim terms are indefinite. The intrinsic record provides no bounds with respect to what constitutes "a beginning" or "an end[.]" The Court therefore finds claim 1 of the '731 patent and claims 19 and 20 of the '992 patent to be indefinite. *See, e.g.*, *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1363-64 (Fed. Cir. 2018) (affirming district court's indefiniteness determination with respect to the term "archive exhibits minimal redundancy" in light of the lack of objective boundaries or specific

[13] Guardant does not rely on any portion of the prosecution history as apprising the POSA about the scope of these claims/claim terms. (*See* D.I. 69 at ¶ 52)

examples of what constitutes "minimal" in the intrinsic record, and where defendant's expert opined that the patent failed to inform a skilled artisan of the meaning of the term with reasonable certainty); *Rillito River LLC v. Bamboo Indus. LLC*, No. 2:17-cv-00181-TLN-CKD, 2018 WL 4350095, at *9-10 (E.D. Cal. Sept. 11, 2018) (finding the claim term "partially surround" to be insufficiently defined in the intrinsic record, in that the record offered a POSA "no details as to the degree of 'partially surround[,]'" and therefore finding the term to be indefinite); *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, Civil No. 12-2692 (JRT/LIB), 2016 WL 6832623, at *14-17 (D. Minn. Nov. 18, 2016) (finding that claim terms "normal" and "low temperature" failed to inform those skilled in the art about the scope of the asserted patent with reasonable certainty, where "neither the intrinsic evidence nor the extrinsic evidence provide any objective boundaries for determining what constitutes 'normal' or 'low temperature'"); *Arthrex, Inc. v. Smith & Nephew, Inc.*, Case Nos. 2:15-cv-1047-RSP, 2:15-cv-1756-RSP, 2016 WL 4211504, at *42 (E.D. Tex. Aug. 10, 2016) (finding that the phrase "most distal end of the implant" was indefinite, where the claim language and specification provided no objective boundaries for assessing whether a given eyelet is located at the "most distal end of the implant").

## III. CONCLUSION

For the foregoing reasons, the Court recommends that the District Court adopt the following constructions:

1. "detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant" be construed to mean "[a]cross one or more genetic loci, detecting at least one single nucleotide variant, at least one gene fusion, and at least one copy number variant" and "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" be construed to mean "[a]cross one or more genetic loci, detecting 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"

2. "sequence information at a beginning of the sequence derived from cell-free DNA/the cfDNA molecule" and "sequence information at an end of the sequence derived from cell-free DNA/the cfDNA molecule" are indefinite pursuant to 35 U.S.C. § 112.

This Report and Recommendation is filed pursuant to 28 U.S.C. § 636(b)(1)(B), Fed. R. Civ. P. 72(b)(1), and D. Del. LR 72.1. The parties may serve and file specific written objections within fourteen (14) days after being served with a copy of this Report and Recommendation. Fed. R. Civ. P. 72(b)(2). The failure of a party to object to legal conclusions may result in the loss of the right to de novo review in the district court. *See Henderson v. Carlson*, 812 F.2d 874, 878-79 (3d Cir. 1987); *Sincavage v. Barnhart*, 171 F. App'x 924, 925 n.1 (3d Cir. 2006).

The parties are directed to the Court's Standing Order for Objections Filed Under Fed. R. Civ. P. 72, dated October 9, 2013, a copy of which is available on the District Court's website, located at http://www.ded.uscourts.gov.

Dated: October 11, 2019

Christopher J. Burke
UNITED STATES MAGISTRATE JUDGE