IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

II. DISCUSSION

The parties had claim construction disputes regarding 13 terms or sets of terms (hereinafter, "terms" or "term sets"). The Court has addressed seven of these terms/term sets in previously-issued Reports and Recommendations. (D.I. 354; D.I. 359; D.I. 389) The Court addresses four of the remaining six terms/term sets herein; it will not construe the remaining two terms at this stage of the case.[2]

A. "attaching tags . . . to said cell free DNA obtained from said bodily sample" / "attaching tags . . . to the cfDNA molecules" / "ligating . . . to both ends of the cfDNA molecules" (the "attaching/ligating" terms)

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[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.

[2] As to one of those two remaining terms ("determining unique sequence reads corresponding to the extracellular polynucleotides from among the sequence reads"), it appears that the dispute with respect to the term evolved in the parties' extensive supplemental claim construction letter briefing (most significantly with the parties raising a new issue with regard to whether the claims can encompass the use of barcodes to identify unique sequence reads). (*See, e.g.*, D.I. 357 at 2) The Court has minimal guidance from the parties as to how these "new" disputes should be appropriately resolved. As for the other term ("identifying a subset of mapped unique sequence reads that include a variant as compared to the reference sequence at each mappable base position"), Guardant has asserted that FMI has taken the opposite position in the IPR proceedings with respect to this claim term, and it appears (from what little information the Court has before it about what FMI said in the IPR) that Guardant could possibly be correct. (D.I. 136 at 5 (citing D.I. 129, ex. B at 59, 61)) But with the record so sparse on that issue, the Court is hesitant to now make a final claim construction decision there too.

If these two terms are at issue in the parties' forthcoming summary judgment briefing, the parties may address the appropriate constructions for the terms (and the specific issues described above) in that briefing. If not, the parties may otherwise propose a process for further teeing up claim construction anew for these terms.

The attaching/ligating terms are found in claim 1 of the '731 patent and claim 1 of the '992 patent. Accordingly, these claims 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;
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> (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;
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> (c) amplifying the non-uniquely tagged parent polynucleotides to produce amplified non-uniquely tagged progeny polynucleotides;
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> (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 (emphasis added)) The parties' competing proposed constructions for the attaching/ligating terms are set out in the chart below:

Term	**Plaintiff's Proposed Construction**	**Defendants' Proposed Construction**
"attaching tags . . . to said cell free DNA obtained from said bodily sample" / "attaching tags . . . to the cfDNA molecules" / "ligating . . . to both ends of the cfDNA molecules"	No construction necessary.	"attaching/ligating tags to the unmodified cell-free DNA from step (a) without end repair and/or A-tailing"

(D.I. 59 at 4) As reflected by the claim language, claim 1 of the '731 patent and claim 1 of the '992 patent require attaching/ligating tags to cell free DNA (or "cfDNA"). The parties have agreed that the terms "cell-free DNA" and "cfDNA" shall be construed to mean "DNA that exist(s) within a bodily fluid within the body outside of a cell and in solution, including in blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool or tears." (D.I. 53, ex. A at 1) The parties' dispute with regard to the attaching/ligating terms is whether tags may be attached to cell free DNA that has undergone the processes of end repair and/or A-tailing (Plaintiff says yes, Defendants say no). (D.I. 59 at 4; D.I. 68 at 3-4; Tr. at 100)

As a preliminary matter, the parties' briefing (and their technology tutorials) did not make clear what end repair and A-tailing actually are. During the *Markman* hearing, Guardant's

counsel explained that end repair and A-tailing are intermediate steps in the process of attaching adaptors to DNA. (Tr. at 95) When DNA comes out of cells, the ends of the DNA are "messed up" and "jagged." (*Id.*; *see also* D.I. 286, ex. A at 67) End repair is a process for repairing the ends of the DNA in which something is stuck to one of the ends, or the ends are made blunt so that there is no overhang. (Tr. at 95-96; D.I. 286, ex. A at 67-68) A-tailing entails attaching a series of As to the end of the DNA that can be used as a site ligation. (Tr. at 96; D.I. 286, ex. A at 68) Defendants assert that "[t]here is no dispute that end repair and A-tailing modify and add chemical moieties" to the DNA. (D.I. 74 at 4; *see also* Guardant's Markman Presentation, Slide 55) Moreover, the specification makes specific mention of end repair and A-tailing in the following discussion regarding isolation and extraction of "[c]ell free polynucleotides":

> One method of increasing conversion efficiency involves using a ligase engineered for optimal reactivity on single-stranded DNA, such as a ThermoPhage ssDNA ligase derivative. Such ligases *bypass traditional steps in library preparation of end-repair and A-tailing that can have poor efficiencies and/or accumulated losses* due to intermediate cleanup steps, and allows for twice the probability that either the sense or anti-sense starting polynucleotide will be converted into an appropriately tagged polynucleotide. It also converts double-stranded polynucleotides that may possess overhangs that *may not be sufficiently blunt-ended by the typical end-repair reaction.*

('731 patent, cols. 35:42, 54, 36:42-53 (emphasis added))

With both claims at issue requiring the attachment of tags "to said *cell free DNA*" or "to the *cfDNA molecules*[,]" Defendants assert that the parties' agreed-upon construction for cell free DNA/cfDNA (whereby it "exist(s) within a bodily fluid within the body outside of a cell and in solution") compels their proposed construction. (D.I. 68 at 4; D.I. 74 at 4; Tr. at 100, 105) Because the processes of end repair and A-tailing result in DNA that has been *modified*, Defendants argue that such DNA "is not cell-free DNA because it never existed within the

body." (D.I. 68 at 4; *see also* D.I. 74 at 4; Tr. at 103) Accordingly, Defendants propose that the attaching/ligating terms should be construed to require the attaching of tags to cell free DNA that has not been modified by end repair and/or A-tailing. (D.I. 291 at 2 ("Tags must be attached to the unmodified cfDNA obtained from the bodily sample of the subject—not some other altered molecule.")) For the following three reasons, however, the Court is not persuaded by Defendants' argument.

First, attaching barcodes to DNA modified by end repair and/or A-tailing is a "traditional way" of attaching barcodes to DNA molecules. (Tr. at 99, 107; D.I. 136 at 2; D.I. 157 at 1; D.I. 173 at 1) The specification describes the processes of end-repair and A-tailing themselves as "traditional steps" in preparing samples of DNA. ('731 patent, col. 36:45) Importantly, it does so in a section of the specification that is all about the preparation of *cell free* polynucleotide samples. (*Id.*, cols. 35:54, 65, 36:4-6, 13, 32, 38) And the claims at issue simply recite "attaching" and "ligating"—without any indication that these terms should be given special meaning or be construed to exclude such "traditional" processes for attaching and ligating. (*See* D.I. 59 at 5; D.I. 72 at 4; Tr. at 99, 107)[3]

[3] While it is true that the specification acknowledges that end repair and A-tailing "can have poor efficiencies and/or accumulated losses[,]" and describes an alternative method of using ligases that "increas[es] conversion efficiency[,]" ('731 patent, col. 36:42-47), the claims at issue do not indicate that they are limited to this alternative method, (*see* D.I. 59 at 4 ("[T]here is no express language of exclusion or restriction limiting 'attaching' or 'ligating' to such embodiment[]."); *see also* D.I. 72 at 4). Although Defendants at first argued that claim 1 of the '731 patent and claim 1 of the '992 patent *were* "directed to" the alternative "embodiment bypassing 'end-repair and A-tailing'" described in this portion of the specification, (D.I. 68 at 3), they ultimately downplayed this argument at the *Markman* hearing, (Tr. at 103-04 (Defendants noting that "[w]e are not relying on that [embodiment of the specification] in some way [to] limit what [the] term means"); *see also id.* at 105).

Second, certain dependent claims of the patents help to demonstrate that the attaching/ligating terms are broad enough to encompass DNA that has gone through end repair and A-tailing. Dependent claim 8 of the '731 patent recites "[t]he method of claim **1**, wherein the attaching comprises blunt-end ligation or sticky end ligation." ('731 patent, col. 63:12-13)[4] During the *Markman* hearing, Guardant's counsel asserted that claim 8 is evidence that "attaching" in claim 1 of the '731 patent does not exclude cell free DNA that has undergone end repair and/or A-tailing. (Tr. at 97, 107) According to Guardant's counsel, "blunt-end ligation" and "sticky end ligation" are techniques used in the repair of DNA and can include end repair and A-tailing. (*Id.* at 95-96, 98; *see also* D.I. 173 at 1; D.I. 286 at 2) Defendants' response to this line of argument was that blunt-end ligation or sticky-end ligation may not necessarily "involve[] end repair or A-tailing." (Tr. at 110) But Guardant points to certain deposition testimony indicating that these processes *are* indeed related. For example, FMI's scientist Travis Clark, Ph.D. testified that FMI's ligation process involves "repair[ing] the ends" of the cell free DNA "which makes them blunt" and then "add[ing] 1A to the 3 prime end of each side"—i.e., A-tailing—and that the process is a "form of sticky-end ligation[.]" (D.I. 173, ex. 1 at 57-58 (cited in D.I. 173 at 1)) Similarly, PGDx's scientist Andrew Georgiadis testified that "end repair fixes [] overhangs [on pieces of DNA ends] and [] blunt-ends them" and that he thought that ligation using end-repair and A-tailing is a "form of sticky end ligation." (D.I. 286, ex. A at 67-

[4] Similarly, dependent claim 9 of the '992 patent recites "[t]he method of claim **1**, wherein the attaching comprises performing blunt-end ligation or sticky end ligation." ('992 patent, col. 64:62-63)

70 (cited in D.I. 286 at 2))[5] With dependent claim 8 of the '731 patent and dependent claim 9 of the '992 patent reciting "attaching tags comprising barcodes . . . to said cell-free DNA" wherein "the attaching comprises blunt-end ligation or sticky end ligation[,]" and with the evidence demonstrating that end repair and A-tailing are, at minimum, forms of sticky end ligation, the record supports Guardant's position that the attaching/ligating terms should not be construed to exclude end repair and A-tailing.[6]

Third, various testimony in the record demonstrates that a person of ordinary skill in the art would understand that attaching tags to cell free DNA encompasses DNA that has undergone end repair and A-tailing. (*See* D.I. 88 at 2) For example, FMI's expert Dr. Stacey Gabriel testified "the cell-free DNA is . . . end repaired and A-tailed and used and amplified, and then those fragments are what are actually being analyzed here in" step (e) of claim 1 of the '731 patent. (D.I. 88, ex. 2 at 78; *see also id.* at 85 (Dr. Gabriel testifying that cell-free DNA that has been end-repaired or A-tailed is "a modified version of a cell-free DNA fragment. . . it contains the cell-free DNA, but it's also been modified")) And FMI's scientist Dr. Clark testified in describing FMI's ligation process that "the cell-free DNA" undergoes steps to "repair[] the ends" and then "there is an enzymatic step that adds 1A to the 3 prime end of each side." (D.I. 173, ex.

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[5] The patent itself also seems to suggest that end repair and blunt-end ligation are related. ('731 patent, col. 36:50-53 ("It also converts double-stranded polynucleotides that may possess overhangs that may not be sufficiently blunt-ended by the typical end-repair reaction."))

[6] In response to Guardant's reliance on Mr. Georgiadis' testimony, PGDx asserted that such testimony "does not show that 'sticky end' ligation always requires end-repair and A-tailing." (D.I. 291 at 2) While it may be true that sticky end ligation does not *always* require end repair and A-tailing, it is also true that the relevant dependent claims do not *exclude* end repair and A-tailing. Rather, these dependent claims refer to sticky end ligation and blunt end ligation generally.

1 at 57) Thus, this testimony seems to cut against Defendants' position that "the use of end-repair and A-tailing modifies cell-free DNA such that a skilled artisan would not believe the claim term 'attaching tags . . . to said cell free DNA' encompasses the use of end repair and A-tailing." (D.I. 173 at 1; *see also* D.I. 286 at 1)[7]

Having clearly resolved the dispute regarding this term set in Plaintiff's favor, and seeing no other dispute regarding this term set's meaning, the Court recommends that the terms "attaching tags . . . to said cell free DNA obtained from said bodily sample" / "attaching tags . . . to the cfDNA molecules" / "ligating . . . to both ends of the cfDNA molecules" be afforded their plain and ordinary meaning. *See Spectrum Pharms., Inc. v. InnoPharma, Inc.*, Civil Action No. 12-260-RGA-CJB, 2014 WL 3365684, at *9 (D. Del. July 3, 2014).

B. "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject"

The claim term "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject" appears in claims 1 and 10 of the '743 patent. Accordingly, these claims are reproduced below, with the disputed term highlighted:

> **1.** A method for detecting copy number variation, comprising:
>
> a) *sequencing extracellular polynucleotides from a bodily sample from a subject*, wherein each of the extracellular polynucleotides generates a plurality of sequence reads;

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[7] In supplemental letter briefs, PGDx argued that Guardant's position with respect to the attaching/ligating terms is contradicted by its position in connection with *inter partes* review ("IPR") proceedings. (D.I. 162; D.I. 291) In those proceedings, Guardant has asserted that claim 1 of the '731 patent's requirement that barcodes be attached to the cell free DNA molecules obtained from the bodily sample of a subject is *different* than tagging *amplified copies* of DNA; according to PGDx, that assertion underscores that the attaching/ligating terms require attaching barcodes only to unmodified cell free DNA. (D.I. 162 at 1; D.I. 291 at 2) But the Court is not persuaded that Guardant is necessarily taking inconsistent positions. As Guardant asserts, "[t]he use of end-repair and A-tailing does not suggest that one is tagging *amplicons of cell-free DNA* as opposed to the cell-free DNA itself." (D.I. 157 at 1 (emphasis added))

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) quantifying mapped reads or unique sequence reads in a plurality of predefined regions of the reference sequence; and

e) determining copy number variation in one or more of the plurality of predefined regions by:

i) normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other; and/or

ii) processing a number of reads in the plurality of predefined regions or a number of unique sequence reads in the plurality of predefined regions with numbers obtained from a control sample.

('743 patent, col. 62:43-65 (emphasis added))

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 the 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 sequence reads derived from the sequencing onto 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.

(*Id.*, col. 63:26-49 (emphasis added)) The parties' competing proposed constructions for the term are set out in the chart below:

Term	**Plaintiff's Proposed Construction**	**Defendants' Proposed Construction**
"sequencing extracellular polynucleotides from a bodily sample from [a/the] subject"	"[e]xtracellular polynucleotides are polynucleotides that exist(s) within a bodily fluid within the body outside of a cell and in solution, including in blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool or tears. No further construction necessary."	"[s]equencing the extracellular polynucleotides obtained from a bodily sample, as distinguished from the amplicons of such extracellular polynucleotides"

(D.I. 59 at 2) The crux of the parties' dispute here is whether this term should be limited to require sequencing only of extracellular polynucleotides obtained directly from a bodily sample (as Defendants assert), or whether it encompasses the sequencing of amplified copies of such polynucleotides (as Guardant asserts). (*Id.*; D.I. 68 at 1-2; Tr. at 110-11)

Defendants' position has some initial appeal. While independent claims 1 and 10 of the '743 patent recite "sequencing extracellular polynucleotides from a bodily sample[,]" the independent claims of the other asserted patents recite sequencing "*amplified*" polynucleotides. (D.I. 68 at 1 (citing '731 patent, col. 62:21-23; '822 patent, col. 62:32-33; '992 patent, col. 64:16-17)) And while the specification of the '743 patent discusses several embodiments in which polynucleotides are amplified "and the resulting amplified molecules are sequenced[,]" ('743

patent, col. 33:39-40; *see also id.*, col. 34:9-24), the specification also makes clear that "a plurality of sequence reads from a single polynucleotide can be produced *without amplification*[,]" (*id.*, col. 33:59-61 (emphasis added)). According to Defendants, the independent claims of the '743 patent are directed to this latter embodiment (while the independent claims of the other asserted patents are directed to the former embodiments). (D.I. 74 at 2) Defendants also argue that the parties' agreed-upon construction of "extracellular polynucleotides"—i.e., "polynucleotides that exist(s) within a bodily fluid within the body . . ."—support their position with respect to this term, because "[a]mplified *copies* of extracellular polynucleotides never existed 'within a bodily fluid within the body' and [therefore] are *not* 'extracellular polynucleotides.'" (D.I. 68 at 1-2 (emphasis added); *see also* D.I. 74 at 1-2) And they note that the specification explains that the amplification process can introduce errors, such that "a subset of the amplified polynucleotides may contain, at a particular locus, a base that is not the same as the original base at that locus[,]" ('743 patent, col. 31:35-38); Defendants argue that this supports their position here, in that it explains why the patent at issue may have excluded amplicons from the sequencing process, (D.I. 74 at 1-2).

Ultimately, however, the Court agrees with Guardant that the claim term should not be limited as Defendants propose. This is so for the following three reasons.

First, in the specification's discussion of how the invention "may have a wide variety of uses in the manipulation, preparation, identification and/or quantification of *cell free polynucleotides*[,]" it tells us that "[e]xamples of polynucleotides include but are not limited to: . . . amplicons[.]" ('743 patent, col. 35:49-53 (emphasis added)) This suggests that, as a general matter, the term "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject" should not exclude the sequencing of amplicons, because an amplicon (according to the

patent) is an example of a "polynucleotide[.]" (D.I. 59 at 2) Relatedly, Guardant notes that a primary purpose of the patents is to "'eliminate errors introduced by amplification'" and that sequencing amplicons is a "central theme" of the patents. (*Id.* (quoting '743 patent, col. 32:16-18); *see also* D.I. 72 at 2; Tr. at 115; '743 patent, col. 33:39-40 ("Typically, polynucleotides in a tagged library are amplified and the resulting amplified molecules are sequenced.")) All of this is to say that if the '743 patent is replete with statements indicating that the invention is focused on, *inter alia*, manipulation of amplified polynucleotides, then it is going to be an uphill climb for Defendants to convince the Court that the claims have nothing to do with amplified polynucleotides.

Second, the Court agrees with Guardant that dependent claims 3 and 12 of the '743 patent support its position here (i.e., that amplicons of extracellular polynucleotides should not be excluded from the scope of the "sequencing" term at issue found in claims 1 and 10 of the same patent). (D.I. 59 at 2-3; D.I. 72 at 1-2; D.I. 157 at 2; Tr. at 111-14) Dependent claim 3 recites "[t]he method of claim **1**, further comprising generating copies of the extracellular polynucleotides prior to sequencing[,]" ('743 patent, col. 63:1-3), and dependent claim 12 recites "[t]he method of claim **10**, further comprising generating copies of the extracellular polynucleotides prior to sequencing[,]" (*id.*, col. 64:3-5).

The United States Court of Appeals for the Federal Circuit has instructed that independent claims should not be construed to exclude material recited in dependent claims. *See Chamberlain Grp., Inc. v. Techtronic Indus. Co.*, 676 F. App'x 980, 986 (Fed. Cir. 2017) ("The inclusion of a particular limitation in a dependent claim does not suggest that the limitation is eschewed by the claim from which it depends. [] Rather, it compels the opposite conclusion. If claim 1 precluded the inclusion of sensors, a claim dependent on it, such as claim 2, could not

include sensors."); *Trs. of Columbia Univ. in City of N.Y. v. Symantec Corp.*, 811 F.3d 1359, 1370 (Fed. Cir. 2016) ("[W]here dependent claims have no meaningful difference other than an added limitation, the independent claim is not restricted by the added limitation in the dependent claim. [] In such situations, construing the independent claim to exclude material covered by the dependent claim would be inconsistent."); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("[I]f [dependent] claim 2 covers the range from 0.0001% w/v-5% w/v, [independent] claim 1 must cover at least that range.").[8] And therefore, as Guardant asserts, with dependent claims 3 and 12 reciting the generation of amplicons of extracellular polynucleotides prior to sequencing, that means that independent claims 1 and 10, while not *requiring* such a

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[8] District courts construing claims have also emphasized this principle. *See, e.g.*, *Cochlear Ltd. v. Oticon Med. AB*, Civil Action No. 3:18-cv-6684-BRM-DEA, 2019 WL 3943014, at *7 (D.N.J. Aug. 21, 2019) ("Dependent claims may broaden the court's interpretation of the scope of an independent claim to ensure that the dependent claim fits within its scope."); *Fractus, S.A. v. AT&T Mobility LLC*, CIVIL ACTION No. 2:18-CV-00135-JRG, 2019 WL 1641357, at *12 (E.D. Tex. Apr. 16, 2019) (interpreting the claim term "juxtaposition" in independent claim 1 to "encompass[] situations in which the relative positions of elements remain the same as well as situations in which certain elements are repositioned" in light of dependent claim 11's recitation of "reposition[ing]" elements, because "construing the independent claim to exclude material covered by the dependent claim would be inconsistent") (internal quotation marks and citation omitted); *Shire ViroPharma Inc. v. CSL Behring LLC*, Civil Action No. 17-414, 2019 WL 266327, at *7 (D. Del. Jan. 18, 2019) (finding that a dependent claim reciting administration of a drug for prophylactic use dictated that independent claim 1 must include both acute and prophylactic treatment since "[a]n alternative construction would improperly exclude dependent claim 7 from the scope of independent claim 1 from which it depends"); *Merck Sharp & Dohme Corp. v. Hospira Inc.*, 221 F. Supp. 3d 497, 520 (D. Del. 2016) (a construction that "exclude[s] [a] dependent claim from the scope of the claim from which it depends. . . . should be avoided"); *Biedermann Motech GMBH v. Alphatec Spine, Inc.*, 482 F. Supp. 2d 32, 34 (D. Mass. 2007) (concluding that the claim term "hole" was broad enough to cover U-shaped slits and rejecting the accused infringer's contrary argument since it would, *inter alia*, contradict a dependent claim that expressly claimed "slits," because the fact that the dependent claim recited "slits" "indicates that the term 'holes' in broader claim 1 encompasses slits").

step, could indeed encompass the sequencing of such amplicons. (D.I. 59 at 2-3; D.I. 72 at 1-2; Tr. at 111-14; Guardant's Markman Presentation, Slide 65)[9]

Third, even one of the Defendants in these actions, FMI, seems to agree with Guardant's position with respect to this term. While PGDx and FMI filed joint claim construction briefs, (D.I. 68; D.I. 74), FMI did not join in PGDx's series of later-filed supplemental letters relating to the proper construction for this term, (*see, e.g.*, D.I. 154; D.I. 162; D.I. 283). Meanwhile, on February 2, 2019, FMI filed a Petition requesting *inter partes* review ("IPR") of all claims of the '743 patent. (D.I. 129 at 1 & ex. B) In its Petition, FMI argued that the claim element "sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads" in claim 1 of the '743 patent is disclosed in a prior art reference known as "Chiu." (*Id.*, ex. B at 23) More specifically, FMI argued that Chiu discloses this claim element because it "discloses amplifying the DNA

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[9] Defendants do not have a persuasive response to Guardant's argument relating to the dependent claims. They assert that the dependent claims "add additional steps to the process" recited in independent claims 1 and 10 of the '743 patent and that such "[a]dditional steps cannot change the meaning of 'extracellular polynucleotides.'" (D.I. 68 at 2 (emphasis omitted); *see also* D.I. 162 at 1; Tr. at 120-21) And in support they cite to *Power Mosfet Techs., L.L.C. v. Siemens AG*, 378 F.3d 1396, 1409 (Fed. Cir. 2004) for the proposition that "'[c]omprising,' while permitting additional elements not required by a claim, does not remove the limitations that are present." (D.I. 68 at 2) The cited portion of *Power Mosfet*, however, has to do with an independent claim that recites "comprising"—it is not discussing any relationship between independent claims and dependent claims. *Power Mosfet*, 378 F.3d at 1402, 1408-09. And so Defendants never really squarely confront Guardant's position, supported by caselaw, that "'[w]here dependent claims have no meaningful difference other than an added limitation . . . construing the independent claim to exclude material covered by the dependent claim would be inconsistent.'" (D.I. 59 at 3 (quoting *Trustees of Columbia Univ.*, 811 F.3d at 1370)) Here, in line with Guardant's cited authority, the key point is that (for example) dependent claim 3 covers generating "copies" of "extracellular polynucleotides prior to sequencing[,]" and so as to independent claim 1's method for "sequencing extracellular polynucleotides[,]" that method has to allow for the inclusion of polynucleotides that have been copied. ('743 patent, cols. 62:45, 63:1-3)

fragments prior to sequencing, such that multiple copies of the fragments are generated and sequenced, and a plurality of sequence reads is generated for each fragment." (*Id.*) On August 19, 2019, the Patent Trial and Appeal Board ("PTAB") of the United States Patent and Trademark Office issued a Decision instituting review of all claims of the '743 patent. (D.I. 357, ex. C) In its Decision, the PTAB noted that it would apply the "same claim construction standard that would be used to construe the claim" in a civil action in federal district court, since FMI's Petition was filed after November 13, 2018. (*Id.* at 6 & n.5 (internal quotation marks and citation omitted)) While the PTAB did not construe the term "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject" in its Decision, the PTAB found that FMI:

> has demonstrated that the method of Chiu discloses preparing a plurality of sequence reads for each polynucleotide. As [FMI] points out, Chiu discloses amplifying the isolated DNA fragments before sequencing. [] By amplifying the fragments and then sequencing the fragments, Chiu generates a plurality of sequence reads for each polynucleotide.

(*Id.* at 18)

In the Court's view, it is telling that in the context of the IPR proceeding, FMI clearly believes that sequencing amplicons of extracellular polynucleotides satisfies this claim limitation. (D.I. 357 at 3) The Court does not agree that "FMI's petitions are irrelevant to the proper construction of these terms[.]" (D.I. 139 at 5); *cf. Research Frontiers, Inc. v. E Ink Corp.*, Civil Action No. 13-1231-LPS, 2016 WL 1169580, at *3 n.4 (D. Del. Mar. 24, 2016) ("[T]he fact that [defendant] took certain claim construction positions during the IPR proceeding may well be relevant to the Court in resolving claim construction disputes here (as might the PTAB's analysis of a particular term).") (emphasis omitted). Nor does the Court find persuasive

Defendants' argument that "FMI is entitled to make different arguments in different proceedings[.]" (D.I. 139 at 4) Of course that is so; FMI is entitled to be able to do lots of things. But if in a different proceeding, FMI takes advantage of that entitlement and makes Plaintiff's claim construction case here for Plaintiff, that all may have consequences as to the Court's decisionmaking about the right construction for this term.[10]

For all of these reasons, the Court recommends that the term "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject" be construed to mean "sequencing polynucleotides that exist(s) within a bodily fluid within the body outside of a cell and in solution, including in blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool or tears."

C. "grouping the plurality of sequence reads produced from each non-uniquely tagged parent polynucleotide into families" / "grouping the sequence reads into families" / "grouping the sequence reads mapped in e) into families"

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[10] Indeed, even PGDx has previously argued that this claim limitation could be satisfied by "'amplifying the polynucleotides prior to sequencing'" in a now-withdrawn Petition for Post-Grant Review. (D.I. 72 at 3 (quoting D.I. 53, ex. R at 15); Tr. at 116-17) While the broadest reasonable interpretation standard of claim construction applied to this Petition, (D.I. 53, ex. R at 12; Tr. at 116-17), and this fact is therefore not dispositive of the issue, PGDx's prior argument is still relevant to the Court's decision as to what is encompassed by this claim term. *Cf. Ethicon LLC v. Intuitive Surgical, Inc.*, C.A. No. 17-871-LPS, 2018 WL 6831169, at *7 n.4 (D. Del. Dec. 28, 2018).

PGDx, for its part, contends that Guardant has made arguments in the IPR proceedings relevant to the prior attaching/ligating terms (i.e., that barcodes must be attached to cell free DNA molecules as opposed to amplification productions of cell free DNA molecules) that are inconsistent with Guardant's argument here relating to this term (i.e., that sequencing extracellular polynucleotides encompasses the sequencing of amplified copies of polynucleotides). (D.I. 154 at 1-2; D.I. 162 at 1) But as Guardant responds, its arguments in the IPR relate to different claim terms found in patents other than the '743 patent at issue here. (D.I. 157 at 2; D.I. 173 at 1) The intrinsic evidence with respect to the term "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject" demonstrates that it encompasses the sequencing of amplified copies of such polynucleotides.

The claim terms "grouping the plurality of sequence reads produced from each non-uniquely tagged parent polynucleotide into families" / "grouping the sequence reads into families" / "grouping the sequence reads mapped in e) into families" (the "grouping" terms) appear in claim 1 of the '731 patent, claim 1 of the '822 patent and claim 1 of the '992 patent, respectively. Claim 1 of the '731 patent and claim 1 of the '992 patent are reproduced above, and claim 1 of the '822 patent is reproduced below, with the disputed term 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 (emphasis added)) The parties' competing proposed constructions for the grouping terms are set out in the chart below:

Term	**Plaintiff's Proposed Construction**	**Defendants' Proposed Construction**
"grouping the plurality of sequence reads produced from each non-uniquely tagged parent polynucleotide into families" ('731 patent, claim 1(e))	"A family is a collection of sequence reads traceable back to an original parent polynucleotide. No further construction necessary."	"[g]rouping *every one* of the sequence reads generated in step (d) into a family to yield families for every one of the parent polynucleotides from step (c)"
"grouping the sequence reads into families" ('822 patent, claim 1(f))		"[g]rouping *every one* of the sequence reads produced in step (d) into families"
"grouping the sequence reads mapped in e) into families" ('992 patent, claim 1(f))		"[g]rouping *every one* of the sequence reads mapped in step (e) into families"

(D.I. 59 at 11 (certain emphasis in original, certain emphasis omitted)) The crux of the parties' dispute here is whether the claims require that every single sequence read must be put into a family (as Defendants assert), or if they just require that the reads be subject to a "grouping" process such that "families" of sequence reads are generated, but every sequence read need not be grouped (as Guardant argues). (*Id.*; D.I. 68 at 9; Tr. at 121) For the reasons set out below, the Court concludes that Defendants' proposed construction (with a small modification to the construction of "grouping the sequence reads into families" found in claim 1 of the '822 patent) is better aligned with the intrinsic evidence.

Looking first to the language of the claims, the claim limitation requires the grouping of "*the* plurality of sequence reads" or "*the* sequence reads" referred to in the prior step, as demonstrated by the claim excerpts below:

- Claim 1 of the '731 patent recites:
  (d) sequencing the amplified non-uniquely tagged progeny polynucleotides to produce *a plurality of sequence reads* from each parent polynucleotide . . .
  (e) grouping *the plurality of sequence reads* produced from each non-uniquely tagged parent polynucleotide into families[.]
  ('731 patent, col. 62:21-28 (emphasis added))

- Claim 1 of the '822 patent recites:
  (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[.]
  ('822 patent, col. 62:32-37 (emphasis added))

- Claim 1 of the '992 patent recites:
  (d) sequencing the amplified tagged progeny polynucleotides to produce *a plurality of sequence reads . .*
  .
  (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*[.]
  ('992 patent, col. 64:16-25 (emphasis added))

The Federal Circuit has explained that use of definite articles such as "the" and "said" are "anaphoric phrases, referring to the initial antecedent phrase." *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342-43 (Fed. Cir. 2008); *see also Transocean Offshore Deepwater Drilling, Inc. v. Pac. Drilling, Inc.*, Civil Action No. H-13-1088, 2015 WL 3422410, at *33 (S.D. Tex. May 27, 2015) ("The term 'the well' is 'an anaphoric phrase that merely refers back to the initial antecedent phrase.'") (citations omitted); *Vehicle IP, LLC v. Werner Enters., Inc.*, 4 F. Supp. 3d 648, 664 (D. Del. 2013) ("[T]he use of 'the' in those phrases refers back to an initial

antecedent phrase.").[11] The Court therefore agrees with Defendants that (absent some other strong indication to the contrary) "the plain language [of these claims] requires grouping *the same* set of sequence reads referred to in the prior step—not some other selection or subset of sequence reads." (D.I. 68 at 9 (certain emphasis in original, certain emphasis omitted); *see also* D.I. 74 at 8; Tr. at 130); *Harris Corp. v. Fed. Express Corp.*, 502 F. App'x 957, 962-63 (Fed. Cir. 2013) (construing "transmitting the accumulated, stored generated aircraft data" to refer to that same data set as referenced in a previous step because "the later instance refers to 'the' data and therefore begs for some antecedent basis[,]" and rejecting an argument that would permit transmission of a subset of all stored data). After all, the claims do not say "grouping *any* of the plurality of sequence reads" or "grouping *some* of the plurality of sequence reads"—rather, they require grouping of "*the*" sequence reads referred to in the prior step. (D.I. 68 at 9; Defendants' Markman Presentation, Slide 81)[12]

Guardant's arguments to the contrary are not persuasive. In support of its position that the claim term does not require every single sequence read to be put into a family, Guardant

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[11] *Cf. Summit 6, LLC v. Samsung Elecs. Co.*, 802 F.3d 1283, 1291 (Fed. Cir. 2015) ("The use of the term 'said' indicates that this portion of the claim limitation is a reference back to the previously claimed 'pre-processing parameters.'"); *Predicate Logic, Inc. v. Distributive Software, Inc.*, 544 F.3d 1298, 1305-06 (Fed. Cir. 2008) ("The [claimed] '*said* instantiated indexes' must be instantiated indexes with an antecedent basis elsewhere in the claim—namely, the indexes that are instantiated during the 'instantiating' step.") (emphasis in original).

[12] In a supplemental claim construction brief, Guardant asserts that FMI has abandoned its claim construction position with respect to the grouping terms in FMI's IPR filings. (D.I. 136 at 4) According to Guardant, FMI "alleg[es] [in its IPR filings] that the Schmitt reference expressly teaches this element even though it excludes sequence reads prior to grouping." (*Id.*) In support, Guardant does not cite directly to any of FMI's arguments in the IPR, but instead cites to portions of the Schmitt reference relating to filtering out or discarding reads. (*Id.*) But it is not clear enough to the Court from these citations that the filtering out discussed in Schmitt happens prior to grouping. And thus, it is not clear on this record that FMI has taken directly contradictory positions with respect to this claim term.

relies on the fact that some of the sequence reads will be filtered out, as discussed in the specification and in certain dependent claims. (D.I. 59 at 12-13; Tr. at 122) Guardant asserts that "[t]here is nothing in the intrinsic record justifying a claim construction that excludes such embodiments from the scope of the claims." (D.I. 59 at 12-13) To that end, the specification does explain that:

> After sequencing, reads are assigned a quality score. A quality score may be a representation of reads that indicates whether those reads may be useful in subsequent analysis based on a threshold. In some cases, some reads are not of sufficient quality or length to perform the subsequent mapping step. Sequencing reads with a quality score at least 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data. In other cases, sequencing reads assigned a quality scored less than 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In step **106**, the genomic fragment reads that meet a specified quality score threshold are mapped to a reference genome, or a template sequence that is known not to contain copy number variations.

('731 patent, col. 44:37-50; *see also id.*, col. 3:54-56 ("In some embodiments, the method may comprise filtering out reads with an accuracy or quality score of less than a threshold[.]")) And dependent claim 5 of the '731 patent recites "[t]he method of claim **1**, further comprising filtering out sequence reads that fail to meet a set quality control threshold[,]" (*id.*, col. 63:5-7), while claim 10 of the '822 patent recites "[t]he method of claim **1**, further comprising filtering out sequence reads that fail to meet a quality threshold[,]" ('822 patent, col. 63:9-10).

But the existence of these embodiments and dependent claims does not defeat Defendants' position. As an initial matter, claim 1 of the '731 patent, claim 1 of the '822 patent and claim 1 of the '992 patent do not even expressly include a filtering step. The Court agrees with Defendants that "[t]he possibility of additional unclaimed steps, [such as filtering,] cannot

alter the express limitations of the claims." (D.I. 68 at 9)[13] Moreover, while Guardant characterizes claim 5 of the '731 patent and claim 10 of the '822 patent as reciting "[filtering] [r]eads [p]rior [t]o [g]rouping[,]" (Guardant's Markman Presentation, Slides 75, 77), these claims do not actually speak to *when* the sequence reads must be filtered out, and thus do not seem to "preclude filtering sequence reads after grouping[,]" (D.I. 68 at 9; *see also* D.I. 84 at 2; Tr. at 126). Indeed, during the *Markman* hearing, Guardant's counsel acknowledged that sequence reads can be filtered out after the sequence reads have been grouped into families. (Tr. at 122)

Guardant also points to dependent claim 19 of the '822 patent as demonstrating that Defendants' position cannot be correct. (Tr. at 123-25; D.I. 136 at 4) That claim recites "[t]he method of claim **1**, further comprising *removing a subset of the sequence reads from further analysis prior to e).*" ('822 patent, col. 64:17-19 (emphasis added)) According to Guardant, because claim 19 requires the removal of a subset of reads prior to the grouping step in part (f) of claim 1, this demonstrates that the claim limitation "grouping the sequence reads into families" in part (f) does not require grouping every one of the sequence reads. (Tr. at 123-24; Guardant's Markman Presentation, Slides 76-78)

The Court, however, agrees with Defendants that their position with respect to the grouping terms is reconcilable with claim 19—after making a small modification to Defendants' proposed construction for the "grouping the sequence reads into families" claim term found in claim 1 of the '822 patent. (D.I. 84 at 1-2) By its plain language, claim 19 narrows the "set of

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[13] In contrast to claim 1 of the '731 patent, claim 1 of the '822 patent and claim 1 of the '992 patent, independent claims 1 and 10 of the '743 patent expressly recite a step directed to "filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold[.]" ('743 patent, cols. 62:49-50, 63:33-34; *see also* Tr. at 128)

sequence reads" produced in step (d) of claim 1 of the '822 patent—that is, claim 19 requires removal of a subset of the sequence reads "prior to step e)[,]" which results in a smaller remaining "set of sequence reads" to be mapped in step (e). (*Id.*; *see also, e.g.*, Guardant's Markman Presentation, Slide 78 (depicting the removal of a subset of sequence reads required by claim 19 as occurring prior to step (e)) Yet as Defendants explain, that same (smaller) set is then mapped and grouped in steps (e) and (f). (D.I. 84 at 1-2) In other words, while "[c]laim 19 changes the makeup of the 'set' of sequence reads produced in step (d), it does not change the plain language of Claim 1, which requires carrying forward the same set of reads for mapping and grouping." (*Id.* at 2)

As to how the construction for "grouping the sequence reads into families" in claim 1 of the '822 patent should be altered, recall that Defendants' proposed construction requires "[g]rouping *every one of* the sequence reads produced in step (d) into families." However, even Defendants acknowledge that, in light of claim 19, the sequence reads that are mapped in step (e) of claim 1 could encompass all *or a subset of* the sequence reads produced from sequencing polynucleotides in step (d). (*Id.* at 1-2) Thus, Defendants' current proposal does not seem quite correct. Therefore, a construction for the claim term "grouping the sequence reads into families" in claim 1 of the '822 patent that more accurately reflects the intrinsic record is "grouping every one of the sequence reads mapped in step (e) into families."

For the above reasons, the Court recommends that the grouping terms be construed as follows:

(1) "grouping the plurality of sequence reads produced from each non-uniquely tagged parent polynucleotide into families" from claim 1 (e) of the '731 patent should be construed to mean "grouping every one of the sequence reads generated in step (d) into a family to

yield families for every one of the parent polynucleotides from step (c)"

(2) "grouping the sequence reads into families" from claim 1(f) of the '822 patent should be construed to mean "grouping every one of the sequence reads mapped in step (e) into families"

(3) "grouping the sequence reads mapped in e) into families" from claim 1(f) of the '992 patent should be construed to mean "grouping every one of the sequence reads mapped in step (e) into families"

D. "produce a plurality of sequence reads from each parent polynucleotide" / "produce a plurality of sequence reads from each of the tagged parent polynucleotides"

The term "produce a plurality of sequence reads from each parent polynucleotide" is found in claim 1(d) of the '731 patent, and the term "produce a plurality of sequence reads from each of the tagged parent polynucleotides" (collectively, the "produce a plurality of sequence reads" terms) is found in claim 1(d) of the '992 patent. These claims have been previously reproduced above. The parties' competing proposed constructions for these terms are set out in the chart below:

Term	**Plaintiff's Proposed Construction**	**Defendants' Proposed Construction**
"produce a plurality of sequence reads from each parent polynucleotide" (claim 1(d) of the '731 patent) "produce a plurality of sequence reads from each of the tagged parent polynucleotides" (claim 1(d) of the '992 patent)	No construction necessary.	"[p]roduce two or more sequence reads for every one of the parent polynucleotides from step (c)"

(D.I. 59 at 9) The crux of the parties' dispute here is whether this term requires one to generate multiple sequence reads from every single tagged parent polynucleotide (as Defendants assert) or

whether the claims allow for some of those polynucleotides in the sample to not proceed all the way through every step in the claims (as Guardant argues). (*Id.* at 10; D.I. 357 at 2)

Beginning with the claim language, the claims at issue require, *inter alia*:

> **1**. . . (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[.]

('731 patent, col. 62:18-25 (emphasis added))

> **1**. . . (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[.]

('992 patent, col. 64:14-21 (emphasis added)) The plain and ordinary meaning of "each" is "every one." (D.I. 68 at 8 (citing *id.*, ex. 3 at 408)); *see also, e.g.*, *ResQNet.com, Inc. v. Lansa, Inc.*, 346 F.3d 1374, 1379 (Fed. Cir. 2003) (interpreting "each field" in claim limitation to mean "each (and every) field"). And the plain and ordinary meaning of "plurality" is "two or more." (D.I. 68 at 8 (citing *id.*, ex. 3 at 1009)); *see also, e.g.*, *Cheese Sys., Inc v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1348 (Fed. Cir. 2013). Thus, the plain language of the claims recites producing two or more sequence reads from every one of the tagged parent polynucleotides that have been amplified in the previous step.

In arguing to the contrary, Guardant relies on the claims' use of the open-ended transitional term "comprising." It asserts that the use of this term somehow allows for some of

the polynucleotides in the sample to not proceed through every single step of the process. (D.I. 59 at 10-11; D.I. 72 at 9; Tr. at 137-39) And in Guardant's view, in conjunction with "comprising," "each" in step (d) of the claim is simply "defining the subset of parent polynucleotides that are part of the claim" and is not a reference to "each" of the tagged parent polynucleotides that are amplified in step (c). (Tr. at 138-39, 141 ("Th[e] reference to 'each' is telling you which tagged parent polynucleotides are the ones that are subject to the claims. . . . It is not every single parent polynucleotide in the sample. It is not every single parent polynucleotide that gets amplified.") According to Guardant, it is improper to require "unnatural efficiency" such that every single tagged parent polynucleotide must behave perfectly by producing two or more sequence reads. (D.I. 59 at 11; *see also* Tr. at 137, 139 ("It would be unreasonable to contend that every molecule should go through every aspect of the process at every step because there [are] billions and billions of molecules."))

The problem with this argument, though, is one of Guardant's own making. It drafted these method claims to require the production of "a plurality of sequence reads from each [of the tagged] parent polynucleotide[s.]" The Court cannot now rewrite these claims so that they align with how Guardant wishes they would read. The claims' use of the term "comprising" is also of no benefit to Guardant here. The fact that the claims use that term means that infringing methods can include additional unclaimed elements; it does not mean that "comprising" negates existing claim limitations—e.g., limitations that require multiple sequence reads "from each [] parent polynucleotide[]." (*See* D.I. 68 at 8-9); *Raytheon Co. v. Sony Corp.*, 727 F. App'x 662, 672 (Fed. Cir. 2018). And Guardant's position ignores the plain and ordinary meaning of "each"—i.e., each and every one of the tagged parent polynucleotides; instead, it attempts to rewrite the claims to require only that a plurality of sequence reads are produced from "some" of the tagged

parent polynucleotides. (D.I. 68 at 8) That is not what the claims recite. *See, e.g.*, *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1378-79 (Fed. Cir. 2012) (construing claim term "a plurality of modules . . . wherein . . . each heuristic module corresponds to a respective area of search and employs a different, predetermined heuristic algorithm[,]" and rejecting plaintiff's arguments that: (1) "plurality" refers to not all but a subset of modules; and (2) the claim allows for addition of other modules that do not use different heuristic algorithms—even though the claim used the term "comprising"—because such arguments would wipe out the claim's express limitation that require every module to have a unique heuristic algorithm); *cf. In re Skvorecz*, 580 F.3d 1262, 1265, 1267-68 (Fed. Cir. 2009) (explaining that the signal "comprising" "simply means that the device may contain elements *in addition to those explicitly mentioned in the claim*" and finding that the United States Patent and Trademark Office's Board of Patent Appeals and Inferences erred in holding that some wire legs of the device need not have an offset, where the claims stated that the device has "*at least two* [] wire legs with *each wire leg* having two upright sections . . . and . . . a plurality of offsets . . .") (emphasis added).[14]

Turning next to the specification, it discusses embodiments that align with Defendants' position. (D.I. 74 at 6-7) To that end, the specification explains that "the disclosure also

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[14] Guardant's citation to *Raindance Techs., Inc. v. 10X Genomics, Inc.*, Civil Action No. 1:15-cv-00152-RGA, 2017 WL 382235 (D. Del. Jan. 26, 2017) is also unhelpful to it here. (D.I. 72 at 8-9) Guardant relies on *Raindance* to argue that "each" does not mean "every one" as a matter of law, and that in *Raindance*, this Court rejected such a construction of "each." (*Id.*) Guardant is wrong. In *Raindance*, the parties *agreed* that "each" meant "each and every." *Raindance Techs.*, 2017 WL 382235, at *10. Rather, the dispute there was whether additional language should be included in the construction to make clear that "each" was limited to "each and every" plug-fluid *used in the claimed method* (as opposed to every plug-fluid that existed anywhere in the universe). *Id.* This Court found that no such language was necessary because it was clear from the claim language that "each plug-fluid" referred to each of the plug-fluids listed earlier in the claim. *Id.*

provides for a method for detecting a rare mutation" in a sample "obtained from a subject comprising a) sequencing extracellular polynucleotides from a bodily sample from a subject, *wherein each of the extracellular polynucleotides generate a plurality of sequencing reads*[.]" ('731 patent, col. 5:36-41 (emphasis added); *see also, e.g.*, *id.*, cols. 1:64-2:8, 13:55-58, 13:62-66, 14:13-16, 17:52-55) The specification also recognizes that "[i]n some cases, sequence coverage of the genome may be at least . . . 100%." (*Id.*, col. 42:32-36)[15]

Other of Guardant's arguments to the contrary are also not persuasive. For example, Guardant points to certain dependent claims as purportedly "mak[ing] clear that not every DNA molecule in the sample is subject to the claim steps." (D.I. 72 at 9; *see also* D.I. 358; Guardant's Markman Presentation, Slide 88) Specifically, Guardant points to:

(1) Claim 10 of the '731 patent, which is directed to the method of claim 1 and further "comprising selectively enriching regions from the subject's genome or transcriptome prior to sequencing[,]" ('731 patent, col. 63:16-18);

(2) Claim 13 of the '992 patent, directed to the method of claim 1, and further comprising "selectively enriching for polynucleotides mapping to one or more selected reference

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[15] It is certainly true that, as Guardant notes, the specification also contemplates that only a subset of molecules may produce sequence reads. (*See, e.g.*, '731 patent, col. 33:39-41) However, the "claims of the patent need not encompass all disclosed embodiments." *Tip Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008) ("[T]he mere fact that there is an alternative embodiment disclosed in the '828 patent that is not encompassed by [the] district court's claim construction does not outweigh the language of the claim, especially when the court's construction is supported by the intrinsic evidence."); *see also* (Tr. at 146).

Guardant also points out that the specification explains that a large number of parent polynucleotides are not tagged and thus may not be sequenced. (D.I. 72 at 8 (citing '731 patent, col. 33:1-10); *see also* Tr. at 138) To the extent that Guardant suggests that this disclosure supports its position, however, it misunderstands that Defendants' construction requires only that two or more sequence reads be produced for every one of the parent polynucleotides *that are actually tagged.* Therefore, the fact that some parent polynucleotides may not be tagged does not seem relevant for purposes of analyzing Defendants' claim construction position. (*See* Tr. at 145-46; Defendants' Markman Presentation, Slide 89)

sequences prior to the sequencing," ('992 patent, col. 65:5-17); and

(3) Claim 18 of the '992 patent, directed to the method of claim 1 "wherein each base of the tagged parent polynucleotides has at least 99% chance of being represented by at least one sequence read among the sequence reads mapped in e)[,]" (*id.*, col. 65:30-33).

In its initial claim construction briefing, Guardant did not provide much explanation as to *why* it is that these particular dependent claims purportedly render Defendants' proposed construction incorrect. (*See, e.g.*, D.I. 72 at 9 (simply citing to these three claims in support of the statement that "the specification[] makes clear that not every DNA molecule in the sample is subject to the claim steps"); *see also* D.I. 74 at 7 n.6) Meanwhile, Defendants plausibly respond with respect to claim 10 of the '731 patent that it "does not necessarily contemplate removing polynucleotides before sequencing—it can refer to generating copies[,]" and that claim 18 of the '992 patent relates to "sequencing accuracy" and not whether there are multiple sequence reads of each polynucleotide. (D.I. 74 at 7 n.6) On this record, then, the Court is not persuaded that claim 10 or claim 18 should impact the construction for these claim terms.

With all of the above said, however, one of Guardant's arguments—made in a supplemental claim construction letter brief filed after the *Markman* hearing, (D.I. 358)—is persuasive. It regards claim 13 of the '992 patent. That claim contemplates, *inter alia*, "subjecting the amplified progeny polynucleotides to selective sequence capture against the one or more selected reference sequences" "prior to the sequencing[.]" ('992 patent, col. 65:12-15) In other words, this claim "eliminates some parent polynucleotides through a selective capture process" prior to the sequencing step. (D.I. 358 at 1) Guardant therefore asserts that this claim "is directly at odds" with PGDx's position that one must generate multiple sequence reads from

every single tagged parent polynucleotide. (*Id.* at 1-2) The Court agrees that with respect to the claim term at issue in the '992 patent, because independent claim 1 should be construed to encompass material in a dependent claim (for the reasons explained above), then dependent claim 13 indicates that the "each of the tagged parent polynucleotides" in step (d) of claim 1 must refer only to *each of the tagged parent polynucleotides that are sequenced* in that step. In other words, claim 1 requires that the sequencing produce two or more sequence reads for each of the tagged parent polynucleotides that are *sequenced* (as opposed to the production of two or more sequence reads for each of the tagged parent polynucleotides that are *amplified*). Indeed, even Defendants come close to conceding that as to this term in the '992 patent, such a result is required. (D.I. 361 at 2)[16]

For the above reasons, the Court recommends that "produce a plurality of sequence reads from each parent polynucleotide" in claim 1 of the '731 patent be construed to mean "produce two or more sequence reads for every one of the parent polynucleotides from step (c)" and that "produce a plurality of sequence reads from each of the tagged parent polynucleotides" in claim 1 of the '992 patent be construed to mean "produce two or more sequence reads for every one of the parent polynucleotides that is sequenced."

III. CONCLUSION

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

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[16] In supplemental letter briefs, Guardant also asserts that in the IPR proceedings, FMI has taken a position with respect to this claim term that is contrary to Defendants' position here. (D.I. 136 at 2-3; D.I. 357 at 2-3) However, it is not clear enough to the Court that what FMI has asserted in the IPR stands in direct contradiction to Defendants' position with respect to this claim limitation. Thus, the Court does not rely on this argument of Guardant.

1. "attaching tags . . . to said cell free DNA obtained from said bodily sample" / "attaching tags . . . to the cfDNA molecules" / "ligating . . . to both ends of the cfDNA molecules" should be afforded their plain and ordinary meaning

2. "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject" should be construed to mean "sequencing polynucleotides that exist(s) within a bodily fluid within the body outside of a cell and in solution, including in blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool or tears"

3. (a) "grouping the plurality of sequence reads produced from each nonuniquely tagged parent polynucleotide into families" from claim 1(e) of the '731 patent should be construed to mean "grouping every one of the sequence reads generated in step (d) into a family to yield families for every one of the parent polynucleotides from step (c)"

(b) "grouping the sequence reads into families" from claim 1(f) of the '822 patent should be construed to mean "grouping every one of the sequence reads in the set of sequence reads that are mapped in step (e) into families"

(c) "grouping the sequence reads mapped in e) into families" from claim 1(f) of the '992 patent should be construed to mean "grouping every one of the sequence reads mapped in step (e) into families"

4. "produce a plurality of sequence reads from each parent polynucleotide" in claim 1 of the '731 patent should be construed to mean "produce two or more sequence reads for every one of the parent polynucleotides from step (c)" and "produce a plurality of sequence reads from each of the tagged parent polynucleotides" in claim 1 of the '992 patent should be construed to mean "produce two or more sequence reads for every one of the parent polynucleotides that is sequenced"

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: November 1, 2019

Christopher J. Burke
UNITED STATES MAGISTRATE JUDGE