IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TWINSTRAND BIOSCIENCES, INC. & UNIVERSITY OF WASHINGTON,	)	
Plaintiffs and Counterclaim Defendants,	)	
v.	)	Civil Action No. 21-1126-GBW-SRF
GUARDANT HEALTH, INC.,	)	
Defendant and Counterclaim Plaintiff.	)	

REPORT AND RECOMMENDATION

Pending before the court are the parties' claim construction disputes. Plaintiffs TwinStrand Biosciences, Inc. and the University of Washington ("Plaintiffs") assert four patents against defendant Guardant Health, Inc. ("Defendant"): United States Patent Nos. 10,287,631 ("the '631 patent"), 10,689,699 ("the '699 patent"), 10,752,951 ("the '951 patent"), and 10,760,127 ("the '127 patent"). (D.I. 1 at ¶ 1) In its counterclaims, Defendant asserts four patents against Plaintiffs: United States Patent Nos. 10,801,063 ("the '063 patent"), 10,889,858 ("the '858 patent"), 11,118,221 ("the '221 patent"), and 11,149,306 ("the '306 patent"). (D.I. 30 at ¶¶ 130-33) All of the asserted patents generally relate to similar methods of error-correcting DNA sequencing. This decision sets forth the court's recommendations of constructions following a review of the parties' joint claim construction brief and consideration of the arguments presented at the *Markman* hearing held on December 6, 2022. (D.I. 129)

The joint claim construction brief confirms that the parties have agreed upon constructions for ten claim terms. I recommend that the court adopt the parties' agreed-upon constructions as follows:

Term	**Recommended Construction**
"uniquely labels" '631 patent, claim 1	Plain and ordinary meaning
"Quantifying at least two of (i) said paired sequence reads, (ii) said unpaired sequence reads, (iii) read depth of said paired sequence reads, and (iv) read depth of said unpaired sequence reads" '951 patent, claim 1	Plain and ordinary meaning
"partially single-stranded adapters" '127 patent, claim 22	Plain and ordinary meaning with the understanding that the term can include both Y-shaped and U-shaped adaptors
"partially complementary, asymmetrical double-stranded adapter-DNA molecules" '127 patent, claim 1	Plain and ordinary meaning with the understanding that the term can include both Y-shaped and U-shaped adaptors
"other fragment regions" '631 patent, claim 18	Plain and ordinary meaning
"circulating DNA molecule(s)" '699 patent, claims 1, 8, 9, 12, 17-20, 24, 25	DNA molecules that circulate within the circulatory system, which can include cell-free DNA and cellular DNA
"double-stranded circulating nucleic acid molecules" '951 patent, claims 11, 12, 15, 16, 18	Double-stranded nucleic acid molecules that circulate within the circulatory system, which can include cell-free DNA and cellular DNA
"cell-free deoxyribonucleic acid (cfDNA)" '063 patent, claims 15, 24 '858 patent, claims 1, 3, 5 '221 patent, claims 1-5 '306 patent, claims 17, 19, 20	DNA that exist(s) outside of a cell while in the body, including in blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool, cerebral spinal fluid, or tears
"a family of the families" '063 patent, claim 17	A single family from the plurality of families
"a subject having cancer" '221 patent, claim 2	Plain and ordinary meaning

Eleven terms remain in dispute. For the reasons set forth below, I recommend that the court adopt the following constructions for the parties' disputed terms:

Term	**Recommended Construction**
"non-uniquely tagged parent polynucleotide(s)" '699 patent, claims 1, 18	A population of parent polynucleotide molecules affixed to polynucleotide barcodes, wherein the same polynucleotide barcode sequence is affixed to multiple parent polynucleotide molecules in the [population / sample], and wherein the polynucleotide barcode sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule
"non-unique tag" '951 patent, claim 25	A tag that is affixed to a parent polynucleotide molecule and having a nucleotide sequence, wherein the same tag nucleotide sequence is affixed to multiple parent polynucleotide molecules in the sample, and wherein the tag nucleotide sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule
"substantially unique" '699 patent, claims 1, 20	Plain and ordinary meaning; not indefinite
"degenerate . . . sequence(s)" '631 patent, claims 1, 12, 13, 15 '951 patent, claim 23 '127 patent, claim 13	A nucleotide sequence that is known or unknown in which every nucleotide position is unrestricted in its nucleotide variability
"semi-degenerate . . . sequence(s)" '631 patent, claims 1, 12, 13, 15 '951 patent, claim 23 '127 patent, claim 13	A nucleotide sequence that is known or unknown in which at least one, but not all, nucleotide positions are fixed or restricted in their nucleotide variability
"high accuracy consensus sequence read" '631 patent, claims 1, 4, 7, 16, 23	Plain and ordinary meaning; not indefinite
"fragment features" '631 patent, claims 16, 18	Plain and ordinary meaning; not indefinite
"DNA fragment-specific information" '127 patent, claim 22	Plain and ordinary meaning; not indefinite
"fragment ends" '631 patent, claim 1	Plain and ordinary meaning
"comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules" '221 patent, claim 3 '306 patent, claim 19	Plain and ordinary meaning

I. LEGAL STANDARDS

A. Claim Construction

The purpose of the claim construction process is to "determin[e] the meaning and scope of the patent claims asserted to be infringed." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370, 388-90 (1996). Construing the claims of a patent presents a question of law, although subsidiary fact finding is sometimes necessary. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 837-38 (2015) (citing *Markman*, 52 F.3d at 977-78). An actual dispute regarding the proper scope of a claim term must be resolved by a judge, as opposed to the jury. *Markman*, 52 F.3d at 979.

"[T]here is no magic formula or catechism for conducting claim construction." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1324 (Fed. Cir. 2005). Instead, the court may attach the appropriate weight to appropriate sources "in light of the statutes and policies that inform patent law." *Id.* The words of the claims "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312-13 (internal citations and quotation marks omitted). If the meaning of a claim term is not readily apparent, the court considers sources including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004).

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312

(Fed. Cir. 2005) (internal quotation marks omitted). Accordingly, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." *Id.* at 1314. Claim terms are typically used consistently throughout the patent, and "usage of a term in one claim can often illuminate the meaning of the same term in other claims." *Id.* Also, "[d]ifferences among claims can also be a useful guide . . . . For example, the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Id.* at 1314-15 (internal citation omitted).

The claims must be read in view of the specification, which "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316 (citing *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)). The specification may also contain a disclaimer or disavowal of claim scope. *Id.* However, "[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004) (internal quotation marks omitted). The specification "is not a substitute for, nor can it be used to rewrite, the chosen claim language." *SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004).

The court should also consider the patent's prosecution history, which is intrinsic evidence and "consists of the complete record of the proceedings before the [Patent and

Trademark Office] and includes the prior art cited during the examination of the patent." *Phillips*, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.* Statements made during inter partes review ("IPR") may also be considered. *Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1362 (Fed. Cir. 2017).

A court may sometimes rely on "extrinsic evidence," which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. Expert testimony can be useful "to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Id.* Nonetheless, courts must not lose sight of the fact that "expert reports and testimony [are] generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." *Id.* Overall, extrinsic evidence is less reliable than intrinsic evidence, and its consideration "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Phillips*, 415 F.3d at 1318-19. Where the intrinsic record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583).

B. Indefiniteness

"Definiteness is a statutory requirement for patentability." *Niazi Licensing Corp. v. St. Jude Med. S.C., Inc.*, 30 F.4th 1339, 1346 (Fed. Cir. 2022). The primary purpose of the definiteness requirement articulated in 35 U.S.C. § 112(b) "is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public . . . can determine whether or not they infringe." *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779-80 (Fed. Cir. 2002). Definiteness is a question of law, although the court must sometimes make factual findings based on extrinsic evidence. *See Sonix Tech. Co. v. Publications Int'l, Ltd.*, 844 F.3d 1370, 1376 (Fed. Cir. 2017). "Any 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).

Like claim construction, definiteness should be evaluated from the viewpoint of a person of ordinary skill in the art at the time the patent was filed. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 908 (2014); *Nature Simulation Sys. Inc. v. Autodesk, Inc.*, 50 F.4th 1358, 1360 (Fed. Cir. 2022). A patent claim is indefinite "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. The reasonable certainty standard is intended to strike a balance between providing clear notice of what is claimed and recognizing the "inherent limitations" of language. *Niazi*, 30 F.4th at 1346 (quoting *Nautilus*, 572 U.S. at 909).

II. CONSTRUCTION OF DISPUTED TERMS

A. The "non-unique" terms

Claim term	Plaintiff's proposal	Defendant's Proposal	Court's construction
"non-uniquely tagged parent polynucleotide(s)" ('699 patent, claims 1, 18)	A population of parent polynucleotide molecules affixed to polynucleotide barcodes, wherein the same polynucleotide barcode sequence is affixed to multiple parent polynucleotide molecules in the [population / sample], and wherein the polynucleotide barcode sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule	Indefinite	A population of parent polynucleotide molecules affixed to polynucleotide barcodes, wherein the same polynucleotide barcode sequence is affixed to multiple parent polynucleotide molecules in the [population / sample], and wherein the polynucleotide barcode sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule
"non-unique tag" ('951 patent, claim 25)	A tag that is affixed to a parent polynucleotide molecule and having a nucleotide sequence, wherein the same tag nucleotide sequence is affixed to multiple parent polynucleotide molecules in the sample, and wherein the tag nucleotide sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule	Indefinite	A tag that is affixed to a parent polynucleotide molecule and having a nucleotide sequence, wherein the same tag nucleotide sequence is affixed to multiple parent polynucleotide molecules in the sample, and wherein the tag nucleotide sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule
"substantially unique" ('699 patent, claims 1, 20)	Plain and ordinary meaning; not indefinite	Indefinite	Plain and ordinary meaning; not indefinite

1. "Non-unique"

I recommend that the court construe the terms "non-uniquely tagged parent polynucleotide(s)" and "non-unique tag" in accordance with Plaintiffs' proposed constructions, which are consistent with the claim language and the specifications of the '699 and '951 patents.

The terms "non-unique" and "non-uniquely" do not appear in the specifications of the '699 and '951 patents, and the prosecution histories of those patents likewise fail to provide any guidance on the scope of these terms. (D.I. 130, Ex. 9 at ¶¶ 49-51; D.I. 131, Ex. 20 at ¶¶ 76-77) However, the meaning of the "non-unique" terms is ascertainable from a review of the claim language in combination with the specification's description of the hybrid method for identifying parent polynucleotide molecules, which uses a combination of shorter n-mer tags and information contained in the tagged parent polynucleotide molecule. (D.I. 129 at 12-13) There is no dispute that the claimed "non-unique" tags pertain to the hybrid method of molecular identification described in the specification. (D.I. 188 at 7:5-8, 21:21-23; D.I. 131, Ex. 20 at ¶ 68)

The specification discloses "[a] hybrid method using a combination of sheared ends and a shorter n-mer tag" to serve as molecular identifiers. (D.I. 130, Ex. 2 at 9:38-42) This hybrid method corresponds with claims 1 and 18 of the '699 patent, and claim 25 of the '951 patent, which recite methods of molecular identification using a combination of sequence information from the parent polynucleotide molecule and a non-unique tag sequence:

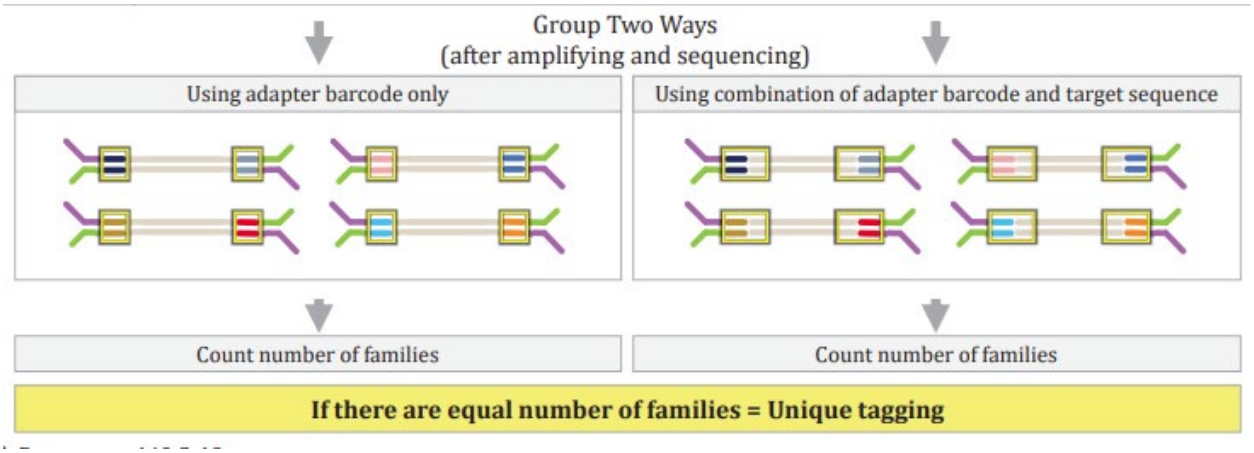
> a population of non-uniquely tagged parent polynucleotides, wherein each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a circulating DNA molecule of the population of circulating DNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes, such that each non-uniquely tagged parent polynucleotide is substantially unique with respect to other non-uniquely tagged parent polynucleotides in the population[.]

(*Id.*, Ex. 2 at 37:50-59; *see also id.* at 39:43-51; *id.*, Ex. 3 at 40:13-29) The specification explains that "[c]ombining information regarding the shear points of DNA with the Single Molecule Identifier ("SMI") tag sequence would allow a shorter SMI to be used, thus minimizing loss of sequencing capacity due to sequencing of the SMI itself." (*Id.*, Ex. 2 at 18:49-52) The intrinsic record is therefore consistent with Plaintiffs' proposed constructions for the "non-unique" terms.

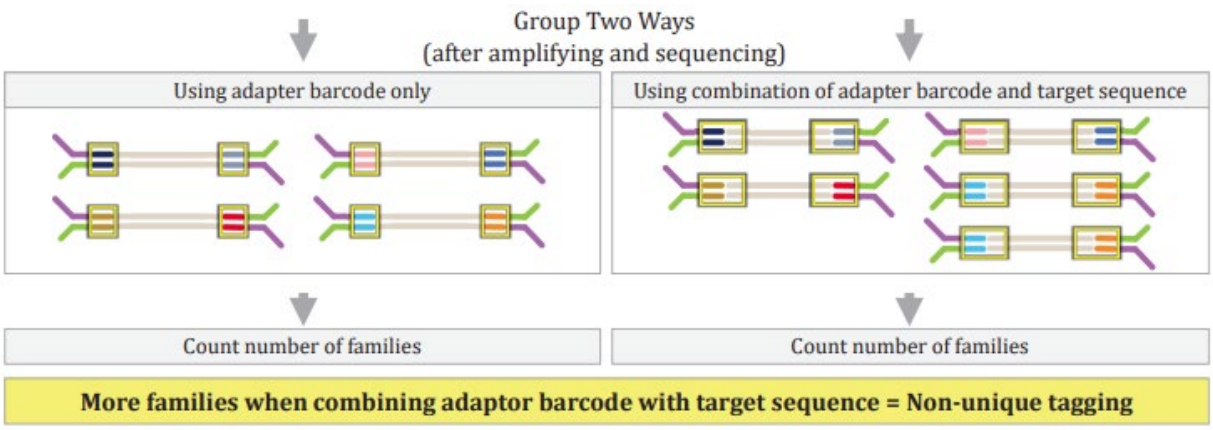
Defendant takes the position that the limited discussion of the hybrid method in the specification is not enough to provide adequate guidance on the meaning of the "non-unique" terms. (D.I. 129 at 19; D.I. 131, Ex. 20 at ¶¶ 80-82) But the "non-unique" terms can be understood with reasonable certainty in terms of their function, in which shorter n-mer tags are combined with other information from the parent polynucleotide molecule to achieve molecular identification. *See Exmark Mfg. Co. Inc. v. Briggs & Stratton Power Prods. Grp., LLC*, 879 F.3d 1332, 1346 (Fed. Cir. 2018) ("Functional language can promote[ ] definiteness because it helps bound the scope of the claims by specifying the operations that the [claimed invention] must undertake." (internal citations and quotation marks omitted)). The evidence supports Plaintiffs' position that a person of ordinary skill would understand the shorter tags alone cannot reliably distinguish the parent polynucleotide molecules by themselves, and they must be combined with molecular sequence information before they can serve as a molecular identifier. (D.I. 133, Ex. 42 at ¶¶ 18-19)

Defendant argues that the non-unique terms are indefinite because Plaintiffs' proposed constructions do not adequately distinguish between unique and non-unique tagging. (D.I. 129 at 11, 16) But the record shows that the difference would be clear to a person of ordinary skill in the art. In the unique tagging method of molecular identification, the unique tag sequences are

sufficiently distinct to identify the parent polynucleotide molecules without additional information. (D.I. 130, Ex. 2 at 6:67-7:13) A person of ordinary skill would understand that unique tagging requires enough diversity of information in the tags alone to distinguish DNA polynucleotide molecules in the population. (D.I. 130, Ex. 2 at 2:16-23, 3:55-61, 19:20-23; D.I. 131, Ex. 20 at ¶ 76; D.I. 133, Ex. 42 at ¶ 17) For example, if unique tags were attached to four parent polynucleotide molecules, the unique tags represented by the different colored portions in boxes would be enough to differentiate the parent polynucleotide molecules without additional information:



In contrast, an example of non-unique tagging shows that the tag information is not enough to accurately identify five parent polynucleotide molecules because the tags attached to the fourth and fifth molecules are identical, as represented by the turquoise and orange tag colors. Using only the tag sequences in this example, four families would be identified instead of five. But when the non-unique tag sequences are combined with other information from the target DNA molecules, all five parent polynucleotide molecules can be identified:



Defendant focuses on the Miner reference described in the specification as an example of unique tagging because that reference discloses a 0.31% chance that "unique" tagging will result in polynucleotide molecules labeled with a non-unique, identical tag. (D.I. 129 at 16; D.I. 130, Ex. 10 at 2; Ex. 2 at 2:16-19) Without citing any intrinsic support, Defendant argues that these identical tag sequences must be combined with molecular sequence information to achieve molecular identification, creating a situation where the unique tagging falls under Plaintiffs' proposed construction for non-unique tagging. (D.I. 188 at 17:17-18:21, 24:1-5) Defendant contends there is no reasonably certain demarcation between "unique" and "non-unique" tagging because Plaintiffs' expert offered varying estimates of what would constitute an acceptable amount of tag sharing, ranging from the 0.31% disclosed in the Miner reference to 5%. (*Id.* at 23:6-10)

The record establishes that some amount of tag sharing is unavoidable in unique tagging, and there is no "sharp demarcation" between unique tags and non-unique tags based on the level of tag sharing. (D.I. 133, Ex. 42 at ¶ 30; D.I. 157, Ex. 48 at 63:12-22) Plaintiffs' expert was nonetheless able to provide a range of .31% to 5% for tag sharing tolerance. (D.I. 188 at 23:20-23) This range is consistent with the tag sharing levels disclosed in Defendant's own patents, which contemplate up to 5% tag sharing in unique tagging. (*See, e.g.*, D.I. 130, Ex. 6 at 18:61-

66) Defendant has not shown that this level of tag sharing would prevent an ordinarily skilled artisan from understanding the scope of the non-unique terms under Plaintiffs' proposed construction. *See Exmark*, 879 F.3d at 1346 ("All that is required is some standard for measuring the term of degree.").

Moreover, the specification suggests that instances of tag sharing are discarded as noise in the data, instead of being combined with molecular sequence information under the non-unique tagging method: "Reads having common (i.e., identical) SMI sequences were grouped together, and were collapsed to generate a consensus read. Sequencing positions were discounted if the consensus group covering the position consisted of fewer than 3 members, or if fewer than 90% of the sequences at that position in the consensus group had the identical sequence." (D.I. 130, Ex. 2 at 21:32-38; D.I. 188 at 37:2-11) While the intrinsic record may not provide absolute certainty as to the meaning of the "non-unique" terms, it is sufficient to provide reasonable certainty to a person of ordinary skill in the art, and Defendant has not produced clear and convincing evidence to the contrary. *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

2. "Substantially unique"

I recommend that the court adopt Plaintiffs' proposed construction and construe the term "substantially unique" in accordance with its plain and ordinary meaning because this construction is consistent with the claim language. As used in claim 1 of the '699 patent, the term "substantially unique" does not modify the tag by itself, but rather the molecular identifier that results from the combination of the tag and the molecular sequence information:

> wherein each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a circulating DNA molecule of the population of circulating DNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes, such that each non-uniquely tagged parent polynucleotide is

> substantially unique with respect to other non-uniquely tagged parent polynucleotides in the population[.]

(D.I. 130, Ex. 2 at 37:51-59) The parties' experts agree that this claim language means a "substantially unique" parent polynucleotide molecule should have enough distinguishing information to distinguish the molecule from other DNA molecules. (D.I. 133, Ex. 42 at ¶¶ 36, 43; Ex. 43 at ¶ 86)

The disclosure of the '699 patent describes how a person of ordinary skill would determine how much information is needed to distinguish parent polynuculeotide molecules from each other using a molecular identifier. (*See, e.g.*, D.I. 130, Ex. 2 at 19:7-11) The word "substantially" also acknowledges the reality that some parent polynucleotide molecules may have identical molecular identifiers. (D.I. 129 at 23) The use of a term of degree in this context to accommodate the "level of precision appropriate to the technology" does not render the claim indefinite. *See Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1119-20 (Fed. Cir. 2002) ("Expressions such as 'substantially' are used in patent documents when warranted by the nature of the invention, in order to accommodate the minor variations that may be appropriate to secure the invention."). Because a person of ordinary skill in the art may objectively determine whether a parent polynucleotide molecule is substantially unique by analyzing whether it is differentiated from other parent polynucleotide molecules in the population, this term of degree is not inherently indefinite. *Exmark Mfg. Co. Inc. v. Briggs & Stratton Power Prods. Grp., LLC*, 879 F.3d 1332, 1346 (Fed. Cir. 2018) (finding that the term "elongated and substantially straight" was not indefinite despite a lack of numerical precision because its meaning could be ascertained relative to other claim elements).

B. "Degenerate . . . sequence(s)" and "semi-degenerate . . . sequence(s)"

Claim term	Plaintiff's proposal	Defendant's Proposal	Court's construction
"degenerate . . . sequence(s)" ('631 patent, claims 1, 16)	A nucleotide sequence that is known or unknown in which every nucleotide position is unrestricted in its nucleotide variability	[single molecule identifier (SMI) / oligonucleotide] sequence in which all of the nucleotides have been randomly generated	A nucleotide sequence that is known or unknown in which every nucleotide position is unrestricted in its nucleotide variability
"semi-degenerate . . . sequence(s)" ('631 patent, claims 1, 12, 13, 15; '951 patent, claim 23; '127 patent, claim 13)	A nucleotide sequence that is known or unknown in which at least one nucleotide position is fixed or restricted in its nucleotide variability	[single molecule identifier (SMI) / oligonucleotide] sequence in which some of the nucleotides have been randomly generated	A nucleotide sequence that is known or unknown in which at least one, but not all, nucleotide positions are fixed or restricted in their nucleotide variability

I recommend that the court construe the term "degenerate . . . sequence(s)" in accordance with Plaintiffs' proposed construction and "semi-degenerate . . . sequence(s)" in accordance with a modified version of Plaintiffs' proposal set forth during the *Markman* hearing: "a nucleotide sequence that is known or unknown in which at least one, *but not all*, nucleotide positions are fixed or restricted in their nucleotide variability. (D.I. 188 at 49:7-11) In the briefing, the parties primarily disagree on whether "degenerate" sequences require only variability of the nucleotide positions, or whether those nucleotide positions must be randomly generated. (D.I. 129 at 38-55) Plaintiffs' proposed constructions are consistent with the claim language and the patent specifications, which do not establish randomness as a required characteristic of degenerate and semi-degenerate sequences.

Plaintiffs' proposed constructions find support in the intrinsic record. The specifications contemplate that each nucleotide in a degenerate sequence can be any of the four possible nucleotides—A, C, G, or T—with "N" representing the degenerate barcode base positions:

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the primer strand:
                                        (SEQ ID NO: 1)
AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCT

TCCGATCT;
and

the template strand:
                                        (SEQ ID NO: 2)
/5phos/ACTGNNNNNNNNNNNNAGATCGGAAGAGCACACGTCTGAACTC

CAGTCAC.
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(D.I. 130, Ex. 1 at 7:6-10, 19:32-42, 33:63) By comparison, a semi-degenerate sequence "need not contain all possible bases at each position;" rather, at least one (but not all) nucleotide(s) in a semi-degenerate barcode sequence is fixed or otherwise restricted. (*Id.*, Ex. 1 at 7:22-23; Ex. 9 at ¶¶ 61-62) These portions of the specifications support the "nucleotide variability" language in Plaintiffs' proposed constructions because the degenerate portions of the nucleotide sequence can be any of the four possible nucleotides.

The extrinsic evidence describing semi-degenerate sequences further confirms that the "degenerate" and "semi-degenerate" terms relate to the variability of the nucleotide positions. One reference describes semi-degenerate nucleotide sequences as sequences that "contain a known (fixed) nucleotide at a specific (query) position and any nucleotide in the other positions," consistent with Plaintiff's proposed construction of "semi-degenerate . . . sequence(s)." (*Id.*, Ex. 13 at 131) Another defines "degenerate oligonucleotide-primed PCR" as using semi-degenerate oligonucleotide sequences "that have been synthesized in parallel to have the same base at certain nucleotide positions, while differing at other positions." (*Id.*, Ex. 14 at 124) Neither of these sources require the degenerate portions of the sequences to be "random."

Defendant relies on extrinsic evidence that defines the term "degenerate" to mean "random." (D.I. 129 at 47-50; D.I. 188 at 58:15-61:7) This evidence supports a conclusion that degenerate sequences can be randomized, but it stops short of establishing that randomization is

a requirement of degenerate sequences. (*See, e.g.*, D.I. 131, Ex. 25 at 2590) (describing the construction of DS adapters "by annealing two oligonucleotides, one of which contains a 12-nt single-stranded randomized tag sequence. A DNA polymerase is used to copy the degenerate tag sequence[.]"). Similarly, the patents and patent applications cited by Defendants establish that the patentee equated the terms "degenerate" and "random" in those specific references, but they do not compel a conclusion that this reflected the understanding of a person of ordinary skill in the art, as opposed to the inventor's own lexicography. (D.I. 131, Ex. 23 at col. 18, Table 1; Ex. 24 at [0048], [0076]); *see Phillips*, 415 F.3d at 1316 (explaining that "the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess."). The extrinsic evidence cited by Plaintiffs shows that the disputed terms are not always so narrowly construed by a person of ordinary skill in the art. Regardless, the intrinsic evidence does not support Defendant's proposed construction, reducing the persuasive value of Defendant's extrinsic references. *See Phillips*, 415 F.3d at 1318-19 (explaining that extrinsic evidence "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence.").

Defendant maintains that random generation is a required characteristic of degenerate and semi-degenerate sequences because otherwise, the term "degenerate" would be rendered meaningless and could include sequences that are known or unknown, designed or not designed. (D.I. 129 at 44-50; D.I. 188 at 50:2-51:7) But Defendant goes on to argue that a random sequence can be known or designed, making it less clear how Defendant's proposed construction provides any more guidance than Plaintiffs' proposal. (D.I. 188 at 52:11-53:5) In fact, Plaintiffs' counsel indicated that, "[i]f random sequences can be designed, it's not clear to me why we are fighting over it." (*Id.* at 90:17-18) The Power Ball analogy offered at oral argument

does not clarify Defendant's interpretation of "random"—if the generation of random numbers by the lottery machine could be "known," the odds of winning the lottery would presumably be much higher. (*Id.* at 52:18-21) Defendant also acknowledges that a degenerate sequence is different from a fixed sequence, a concession that provides meaning to the term "degenerate" as captured by Plaintiffs' proposed construction requiring variability. (*Id.* at 57:18-21)

The degenerate and semi-degenerate terms can reasonably be defined based on the variability of the nucleotide positions without imposing the supposedly narrower requirement that those nucleotides must be randomly generated. The word "random" does not appear in the claims. (*See, e.g.*, D.I. 130, Ex. 1 at 39:41-40:31) Instead, it appears only in the specifications' description of "some" embodiments, (*id.*, Ex. 1 at 6:51-53, 7:6-8), or in particular examples or figures set forth in the specification, (*id.*, Ex. 1 at Fig. 2, 20:46-48). The patentees' decision not to modify "degenerate" and "semi-degenerate" sequences with the word "random" in the claims is significant, and it counsels against importing the limitation from the specification into the claims. *See Novartis Pharms. Corp. v. Actavis, Inc.*, C.A. No. 12-366-RGA-CJB, 2013 WL 6142747, at *10 (D. Del. Nov. 21, 2013).

The specification also fails to support Defendant's position that the nucleotide sequences must always be randomly generated. The '631 patent specification explains that, "[i]n some embodiments, the degenerate or semi-degenerate SMI sequence may be a random degenerate sequence," implying that random generation of the sequence is not required in all embodiments. (D.I. 130, Ex. 1 at 6:51-53); *see Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1349 (Fed. Cir. 2020) (concluding that the written description's use of phrases like "may also include," "e.g.," "such as," and "etc." indicated that "the patentee did not intend this excerpt of the written description to define" the disputed term). The specification subsequently elaborates that, "[i]n

some embodiments, the SMI tag nucleotide sequence may be completely random and degenerate," whereas in other embodiments,

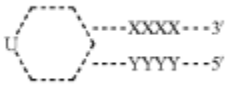
> [t]he degenerate or semi-degenerate n-mer sequences may be generated by . . . preparing and annealing a library of individual oligonucleotides of known sequence. Alternatively, any degenerate or semi-degenerate n-mer sequences may be a randomly or non-randomly fragmented double stranded DNA molecule from any alternative source that differs from the target DNA source.

(*Id.*, Ex. 1 at 7:6-7, 7:23-31)

By describing the nucleotide sequence as both random and degenerate, the specification suggests that "random" and "degenerate" describe distinct characteristics of the nucleotide sequences. (*Id.*, Ex. 1 at 7:6-7; Ex. 9 at ¶ 72) This interpretation is supported by the ensuing language that explains degenerate and semi-degenerate sequences may be generated either randomly or from a library of known sequences. (*Id.*, Ex. 1 at 7:23-31) Defendant does not address this portion of the specification in its argument that "random" and "degenerate" mean the same thing, nor does Defendant's "shiny, silver pole" analogy compel a conclusion that random and degenerate mean the same thing—a brass pole can also be shiny, but is not accurately described as silver, and a silver pole can be tarnished, which is no longer shiny. (D.I. 188 at 56:18-22, 70:11-18; D.I. 129 at 58)

Both parties discuss at length an embodiment describing how SMI adaptor molecules containing a double-stranded, complementary, degenerate or semi-degenerate SMI tag can be made. (D.I. 129 at 40, 47, 51-53, 58-59; D.I. 130, Ex. 1 at 12:64-13:39) Plaintiffs argue that this embodiment describes a degenerate SMI sequence that can be known or designed. (D.I. 129 at 51-52) Defendant counters that the embodiment refers to the design of the oligonucleotide adaptor containing the SMI sequence, as opposed to the design of the SMI sequence itself. (*Id.* at 47, 58-59)

Plaintiffs' interpretation of this embodiment is supported by the specification, which confirms that the SMI tag sequences in the SMI adaptor molecules are degenerate or semi-degenerate. (D.I. 130, Ex. 1 at 12:64-66) The embodiment specifies that the oligonucleotide can be designed with regions of self-complementarity to anneal into the following form:



(*Id.*, Ex. 1 at 15-24) It is the design of the complementary SMI sequence that is disclosed in this excerpt, as opposed to the design of the macromolecule as a whole. The example goes on to describe "a set of nucleotides of known sequence where X and Y represent the complementary SMI sequences [that] can be synthesized on an array[.]" (*Id.*, Ex. 1 at 13:36-38) Defendant's proposed construction would therefore contravene the "strong presumption against a claim construction that excludes a disclosed embodiment." *Immunex Corp. v. Sanofi-Aventis U.S. LLC*, 977 F.3d 1212, 1220 (Fed. Cir. 2020).

C. The "high accuracy" terms

Claim term	**Plaintiff's proposal**	**Defendant's Proposal**	**Court's construction**
"high accuracy sequence reads" ('631 patent, claims 1, 16)	Plain and ordinary meaning; not indefinite	Indefinite	Plain and ordinary meaning; not indefinite
"high accuracy consensus sequence read" ('631 patent, claims 1, 4, 7, 16, 23)	Plain and ordinary meaning; not indefinite	Indefinite	Plain and ordinary meaning; not indefinite

I recommend that the court adopt Plaintiffs' proposed constructions and construe the "high accuracy" terms in accordance with their plain and ordinary meaning. Claims 1 and 16 of

the '631 patent include the term "high accuracy sequence reads," and claims 1, 4, 7, 16, and 23 of the '631 patent include the term "high accuracy consensus sequence read." (D.I. 130, Ex. 1)

Defendant argues that the "high accuracy" terms are indefinite because both the intrinsic and extrinsic evidence fail to attach a quantitative accuracy or error rate to the phrase "high accuracy," and deletion of the phrase would not alter claim scope in any way. (D.I. 129 at 27-28) Plaintiffs respond that the claims themselves provide sufficient guidance on what a high accuracy sequence read is and how it is generated:

> generating a high accuracy consensus sequence read for each of the double-stranded target nucleic acid molecules in the population that includes only the nucleotide positions where the compared first and second strand sequence reads are complementary.

(*Id.* at 29; *see also* D.I. 130, Ex. 1 at 38:37–41, 40:27–31) Thus, Plaintiffs contend that there is no numerical accuracy or error rate requirement, and a person skilled in the art would understand that the complementary relationship between the DNA strands is what establishes the claimed method's high accuracy. (D.I. 129 at 29-30)

Plaintiffs' proposal is consistent with the claim language and the specification. "The ordinary meaning of a claim term is its meaning to an ordinary artisan after reading the entire patent." *Mfg. Res. Int'l, Inc. v. Civiq Smartscapes*, *LLC*, 397 F. Supp. 3d 560, 568 (D. Del. 2019) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1321 (Fed. Cir. 2005)). The claims of the '631 patent support an understanding that "high accuracy sequence reads" and "high accuracy consensus sequence read" are terms that describe sequence reads resulting from the leveraging of information stored in complementary, as opposed to non-complementary, strands of DNA. (D.I. 130, Ex. 1 at 38:37-41, 40:27-31) These disputed terms represent a method to improve the accuracy of sequence reads, and any improvement in accuracy over the prior art methods is sufficient to satisfy the meaning of the term.

A person of ordinary skill in the art evaluating the claimed method steps for DNA sequencing would understand how those steps lead to a more accurate result than prior art sequencing methods. (D.I. 133, Ex. 42 at ¶¶ 68, 70); *see Niazi*, 30 F.4th at 1347 ("[D]escriptive words . . . in a claim may inherently result in broader claim scope than a claim defined with mathematical precision. But a claim is not indefinite just because it is broad."). The specification compares the claimed sequencing method to previous sequencing methods and confirms that the claimed complementary sequencing method "represents a greater than 3 million fold improvement over the error rate . . . that was obtained by a standard sequencing approach." (D.I. 130, Ex. 1 at 28:49-51; *see also* 16:45-17:7, 21:55-59) This improvement over the prior art method is sufficient to provide a point of comparison for a person of ordinary skill in the art. *See Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325 (Fed. Cir. 2010). On this record, Defendant has not shown by clear and convincing evidence that the "high accuracy" claim terms are indefinite. *See Nature Simulation Sys. Inc. v. Autodesk, Inc.*, 50 F.4th 1358, 1360-61 (Fed. Cir. 2022) (describing the judicial role of "constru[ing] the claim as a matter of law, on review of appropriate sources of relevant information," including the claim language and the state of the art).

Defendant asks the court to apply two Federal Circuit cases which stand for the proposition that "claims 'must be interpreted with an eye toward giving effect to all terms in the claim.'" *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1257 (Fed. Cir. 2010) (quoting *Bicon, Inc. v. Straunmann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006)). But those cases are distinguishable from the facts before the court. In *Becton*, the Federal Circuit construed a term to require both a spring member and a hinged arm structure because without both elements, the spring means limitation would be functionally meaningless. *Id.* In *Bicon*, the

Federal Circuit rejected a construction that would read out multiple steps of the claimed method. *Bicon*, 441 F.3d at 951. In contrast, the "high accuracy" terms in this case do not provide structure or recite a method step. Plaintiffs' expert and Plaintiffs' counsel have both conceded that the words "high accuracy" are not necessary to the meaning of the claims. (D.I. 130, Ex. 9 at 40:12-41:8; D.I. 188 at 77:13-14) But as Plaintiffs' counsel has indicated, "[t]he fact that there is one word that . . . isn't doing a lot of work, doesn't mean the claim is indefinite." (D.I. 188 at 86:4-7) Defendant has not cited any analogous authority to the contrary.

D. "Fragment features" and "DNA fragment-specific information"

Claim term	**Plaintiff's proposal**	**Defendant's Proposal**	**Court's construction**
"fragment features" ('631 patent, claims 16, 18)	Plain and ordinary meaning; not indefinite	Indefinite	Plain and ordinary meaning; not indefinite
"DNA fragment-specific information" ('127 patent, claim 22)	Plain and ordinary meaning; not indefinite	Indefinite	Plain and ordinary meaning; not indefinite

I recommend that the court adopt Plaintiffs' proposals and construe the terms "fragment features" and "DNA fragment-specific information" in accordance with their plain and ordinary meaning, which in this case means the claimed "features" and "information are limited to "DNA sequence information." The parties agree that a "fragment" is a piece of a larger nucleic acid molecule containing the four nitrogenous bases of DNA: adenine ("A"), guanine ("G"), thymine ("T"), and cytosine ("C"). (D.I. 129 at 35; D.I. 133, Ex. 42 at ¶ 47; Ex. 44 at 12:17-21, 17:11-20) The parties' dispute centers on the scope of the claimed "features" and "information." For the reasons set forth below, Defendant has not shown by clear and convincing evidence that these claim terms are indefinite. *See Nature Simulation*, 50 F.4th at 1360-61.

Like the "high accuracy" terms, the "fragment features" and "DNA fragment-specific information" terms are not used in the specification and are not substantively discussed in the prosecution history. Nonetheless, the meaning of the terms would be apparent to a person of ordinary skill in the art based on the context provided by the claim language. Claim 16 of the '631 patent discloses that the "fragment features" are used to "distinguish the individual double-stranded target nucleic acid molecules from other double-stranded target nucleic acid molecules in the population." (D.I. 130, Ex. 1 at 39:43-47) This is achieved by producing first and second strand sequence reads, and then grouping those sequence reads based on "one or more distinguishing fragment features shared by each strand of the double-stranded target nucleic acid molecule[.]" (*Id.*, Ex. 1 at 40:9-17) By associating the claimed fragment features with information that can be obtained from the sequence reads, the claims equate the fragment features with the order of nucleotides in the DNA fragments. (D.I. 133, Ex. 42 at ¶¶ 50, 52-54) The term "DNA fragment-specific information," as used in claim 22 of the '127 patent, is likewise tied to the generation of sequence reads. (D.I. 130, Ex. 4 at 40:8-11) Thus, these terms may be given their ordinary and customary meaning, consistent with their usage in the claims. *Phillips*, 415 F.3d at 1312-13.

Defendant argues that the definition of these terms cannot be limited to DNA sequence information because Plaintiffs' own expert stated that other characteristics such as fragment weight are fragment features. (D.I. 129 at 37) But Plaintiffs' expert testified that, in the context of the asserted claim, fragment features would be limited to the DNA sequence information because no other features of DNA are discussed in the claim. (D.I. 157, Ex. 48 at 67:1-68:15) And Plaintiff's counsel explained that this is because no other information is present after the sequencing step. (D.I. 188 at 98:8-11) The reply expert declaration reiterates that "[a] person of

ordinary skill in the art would know that these terms are circumscribed by the type of information obtainable from sequence reads so long as the information or features distinguish one molecule from another" and "would readily identify which few pieces of data from the sequence read of the fragment function in the context of the claimed methods." (D.I. 133, Ex. 42 at ¶ 55) Defendant's counsel maintains that the intrinsic evidence is not sufficient to support limiting the claimed "features" and "information" to "DNA sequence information," while acknowledging that this limitation cures the alleged indefiniteness of the terms. (D.I. 188 at 105:13-18) ("[T]he point is the same, which is that however – short of defining these as sequence, which is just not merited by the intrinsic evidence, there is just no way to know – however you, sort of, describe them, there is no way to know what falls inside the claim and what falls outside.").

E. "Fragment ends"

Claim term	Plaintiff's proposal	Defendant's Proposal	Court's construction
"fragment ends" ('631 patent, claim 1)	Plain and ordinary meaning	Each fragment end is made up of fewer nucleotides than the entire fragment at the terminal end of the fragment after shearing and trimming	Plain and ordinary meaning

I recommend that the court adopt Plaintiffs' proposed construction and construe the term "fragment ends" in accordance with its plain and ordinary meaning, which Plaintiffs articulate to be "the distal or terminal parts of the fragment." (D.I. 129 at 61) As previously stated at § II.D, *supra*, the parties agree that the word "fragment" does not warrant construction. Defendant's proposed construction imposes additional requirements on the term by importing limitations from the specification into the claims. *See Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367,

1372-73 (Fed. Cir. 2014) (declining to import limitations from the specification into the claims absent limiting language).

The focus of the parties' dispute is on whether the fragment end is limited to what remains "after shearing and trimming." (D.I. 129 at 61-66) There is no dispute that claim 1 of the '631 patent does not include such a requirement. (D.I. 130, Ex. 1 at 37:29-41) Instead, Defendant argues that the limitations of shearing and trimming should be imported into the claim language because every embodiment in the specification supports this limitation. (D.I. 129 at 62-63) The intrinsic record does not support Defendant's position.

As with the degenerate and semi-degenerate sequence terms, the specification uses the permissive word "may" to describe shearing of fragment ends: "In one embodiment, the double-stranded target nucleic acid molecule may be a sheared double-stranded DNA or RNA fragment." (D.I. 130, Ex. 1 at 15:10-12) Although many embodiments describe fragments generated by shearing, there is no limiting language or disclaimer in the intrinsic record that would restrict the claims in that manner. *See Hill-Rom*, 755 F.3d at 1372-73. In fact, the specification describes an embodiment in which "specific PCR primers can selectively amplify specific regions of genome when the adaptor that is ligated to the other end of the molecule is a hairpin[.]" (D.I. 130, Ex. 1 at 14:5-7) The record confirms that a person of ordinary skill would interpret this passage to mean that fragment ends can be generated using polymerase chain reaction ("PCR"). (D.I. 133, Ex. 42 at ¶ 104) Defendant's own expert, Dr. John Quackenbush, testified that " 'shearing' here, in Guardant's proposed construction, was referring to the process described in the examples. One skilled in the art would understand that there are other methods." (*Id.*, Ex. 44 at 58:8-11; *see also* 63:10-17 ("So 'shearing' here really does refer to that process of fragmentation. As I said, it's the one which is most commonly used. The patent does allow

other methods to be used for fragmentation. But fragmentation, whether it's shearing or any other approach, in fact is necessary to create these fragment ends.")).

With respect to "trimming," Defendant's argument is limited to two brief portions of the specification, the first of which does not use the word "trim" or "trimming." (D.I. 129 at 63, citing D.I. 130, Ex. 1 at 20:53-56, 21:13-14) Both cited excerpts relate to a single example in the specification. (*Id.*) This is not sufficient to establish "trimming" as a required feature of "fragment ends." *See Honeywell Inc. v. Victor Co. of Japan, Ltd.*, 289 F.3d 1317, 1326 (Fed. Cir. 2002) (stating that a description of a preferred embodiment explaining the benefits of that embodiment does not limit the scope of the claims). Thus, even if the court were to accept Defendant's argument regarding shearing, Defendant's proposed construction would still fail due to the trimming requirement, which is not adequately supported by the intrinsic record and would require improperly importing limitations from the specification into the claims.

F. "Comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules"

Claim term	**Plaintiff's proposal**	**Defendant's Proposal**	**Court's construction**
"comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules" ('221 patent, claim 3; '306 patent, claim 19)	1 ng or greater of cfDNA molecules	Plain and ordinary meaning	Plain and ordinary meaning

I recommend that the court adopt Defendant's proposal and construe the term "comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules" in accordance with its plain and ordinary meaning. The focus of the parties' dispute is on whether the word "comprises" broadens the scope of the claim term beyond the specified range. Plaintiffs' proposal to construe

the term broadly as "1 ng or greater of cfDNA molecules" is not supported by established principles of claim construction.

The Federal Circuit has consistently interpreted the word "comprises" to mean "that the listed elements (i.e., method steps) are essential but other elements may be added." *Lucent Tech., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1214 (Fed. Cir. 2008) (citing *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1344-45 (Fed. Cir. 2003)). For instance, if a patent claim calls for a car "comprising" three wheels, then a car with ten wheels would infringe the claim. But when the word "comprises" appears in the body of the claim and precedes a precise numerical range, the Federal Circuit has rejected attempts to construe such a claim in a manner that exceeds the bounds of the claimed numerical range because such a construction "would read out of [the claim] the express claim ranges." *Jeneric/Pentron, Inc. v. Dillon Co., Inc.*, 205 F.3d 1377, 1382-83 (Fed. Cir. 2000).

Here, the word "comprises" appears in the body of dependent claims and precedes a precisely defined numerical range of 1 to 100 ng of cfDNA molecules. (D.I. 130, Ex. 7 at 61:42-44; Ex. 8 at 63:1-3) The dependent claims at issue do not contain qualifying words such as "about" or "at least" that might otherwise introduce ambiguity to the claimed range. (*Compare* D.I. 130, Ex. 7 at 61:42-44, *with id.* at 61:49-51) In these circumstances, Federal Circuit precedent supports a construction that preserves the specified range as claimed. *See Jeneric*, 205 F.3d at 1381-83; *Takeda Pharm. Co. Ltd. v. Zydus Pharms. USA Inc.*, 743 F.3d 1359, 1364 (Fed. Cir. 2014) (finding no indication that the patentee intended to mean anything other than exactly 400 μm in the absence of qualifying language or "any other indicator of imprecision"); *Amgen Inc. v. Amneal Pharm. LLC*, 945 F.3d 1368, 1378-79 (Fed. Cir. 2020) (remanding for consideration of whether an accused infringer's formulation satisfied a claim requiring a

pharmaceutical composition comprising "from about 1% to about 5% by weight of at least one binder").

Plaintiffs argue that *Jeneric* should not control the analysis here because a case from this district rejected the application of *Jeneric* in the context of claim construction. (D.I. 129 at 70-71); *see Dow Chem. Co. v. NOVA Chem. Corp. (Canada)*, 629 F. Supp. 2d 397, 408 (D. Del. 2009). But consideration of *Dow Chemical* is of limited utility here, as the claim term at issue there—"Comprising (A) . . . And (B)"—did not involve a clearly defined numerical range. *Id.* at 407-08. Other cases favorably cite *Jeneric* in a manner that supports Defendant's proposed construction to limit the disputed term to the specified numerical range. *See Otsuka Pharm. Co., Ltd. v. Lupin Ltd.*, C.A. No. 21-900-RGA, 2022 WL 2952759, at *2 (D. Del. July 26, 2022) ("[B]ecause the claim term lacks 'broadening words,' the numerical range in this claim involves a 'strict numerical boundary.'"); *see also Cobalt Boats, LLC v. Sea Ray Boats, Inc.*, 2016 WL 11645459, at *6 (E.D. Va. Dec. 21, 2016) (citing *Jeneric* for the canon of construction that "[o]rdinarily, absent broadening language, numerical ranges are construed exactly as written"); *Maury Microwave, Inc. v. Focus Microwaves, Inc.*, 2022 WL 9161988, at *30 (C.D. Cal. July 30, 2012) ("*Jeneric* stands for the proposition that numbers in a claim term set outer limits on what is claimed"); *Johnson Matthey, Inc. v. Noven Pharm., Inc.*, 2009 WL 2208214, at *6 (E.D. Tex. July 21, 2009) (reasoning that the Federal Circuit "adopted a literal interpretation of a numerical range" in *Jeneric*); *Ideal Instruments, Inc. v. Rivard Instruments, Inc.*, 498 F. Supp. 2d 1131, 1162 (N.D. Iowa 2007) (concluding that claimed weight percentage ranges for elements comprising "stainless steel" were properly construed as "strict numerical boundaries" under *Jeneric*).

Plaintiffs also argue that the *Jeneric* court relied on express narrowing of the claimed range by the patentee during prosecution to overcome the prior art, which did not occur in the instant case. (D.I. 129 at 70-71) But the *Jeneric* court's holding that "the district court correctly limited the weight ranges to those recited precisely in the table of claim 1" was based on the language of the claims. *See Jeneric*, 205 F.3d at 1381. The Federal Circuit went on to explain that its reading "finds additional support in the written description" and the prosecution history of the asserted patent. *Id.* at 1381-82. A proper reading of the case does not suggest that the Federal Circuit would have reached a different outcome on this issue had it not been for evidence of narrowing in the prosecution history.

Plaintiffs also rely on the Federal Circuit's decision in *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1366 for the proposition that "'comprises' is no less open-ended just because the claim language also recites a numerical range." (D.I. 129 at 170) But this reading of *Invitrogen* does not extend to the disputed claims in this case. In *Invitrogen*, the disputed claim read:

> 1. A process for producing transformable E. coli cells of improved competence by a process comprising the following steps in order:
> (a) growing E. coli cells in a growth-conducive medium at a temperature of 18° C. to 32° C.;
> (b) rendering said E. coli cells competent; and
> (c) freezing the cells.

Invitrogen, 327 F.3d at 1366. The Federal Circuit determined that the use of the word "comprising" in this manner left open the door to additional, unclaimed steps occurring before the recited steps. *Id.* at 1368. As a result, an alleged infringer who met all the recited steps and included an additional, prior step of growing cells at 37º Celsius would fall within the scope of the claim. *Id.* The word "comprising" did not eliminate the requirement that the temperature range of 18° C to 32° C must be satisfied at step (a) of the claimed method; instead, it simply

meant that additional steps could occur before the claimed method steps. Therefore, the Federal Circuit's holding in *Invitrogen* is not inconsistent with the court's recommendation in this case.

Plaintiffs attempt to distinguish *Jeneric* and *Ideal Instruments* by arguing that those cases dealt with weight percentages in tandem with other chemicals to create a composition, while the numerical range here pertains to a single element. (D.I. 129 at 70-71) Plaintiffs also maintain that Defendant could have preceded the numerical range with the phrase "consists of" if it intended the claims to mean exactly between 1 and 100 ng. (*Id.*) Ultimately, however, the *Jeneric* line of cases show that the outer limitations of a numerical range control, and "[c]omprising is not a weasel word with which to abrogate claim limitations." *Wis. Alumni Rsch. Found. v. Apple, Inc.*, 905 F.3d 1341, 1348 n.8 (Fed. Cir. 2008) (quoting *Spectrum Int'l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1380 (Fed. Cir. 1998)).

III. CONCLUSION

For the reasons set forth above, I recommend that the court construe disputed terms as follows:

Term	**Recommended Construction**
"non-uniquely tagged parent polynucleotide(s)" '699 patent, claims 1, 18	A population of parent polynucleotide molecules affixed to polynucleotide barcodes, wherein the same polynucleotide barcode sequence is affixed to multiple parent polynucleotide molecules in the [population / sample], and wherein the polynucleotide barcode sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule
"non-unique tag" '951 patent, claim 25	A tag that is affixed to a parent polynucleotide molecule and having a nucleotide sequence, wherein the same tag nucleotide sequence is affixed to multiple parent polynucleotide molecules in the sample, and wherein the tag nucleotide sequence serves as a molecular identifier only when combined with other

	information from the tagged parent polynucleotide molecule
"substantially unique" '699 patent, claims 1, 20	Plain and ordinary meaning; not indefinite
"degenerate . . . sequence(s)" '631 patent, claims 1, 12, 13, 15 '951 patent, claim 23 '127 patent, claim 13	A nucleotide sequence that is known or unknown in which every nucleotide position is unrestricted in its nucleotide variability
"semi-degenerate . . . sequence(s)" '631 patent, claims 1, 12, 13, 15 '951 patent, claim 23 '127 patent, claim 13	A nucleotide sequence that is known or unknown in which at least one, but not all, nucleotide positions are fixed or restricted in their nucleotide variability
"high accuracy sequence reads" '631 patent, claims 1, 16	Plain and ordinary meaning; not indefinite
"high accuracy consensus sequence read" '631 patent, claims 1, 4, 7, 16, 23	Plain and ordinary meaning; not indefinite
"fragment features" '631 patent, claims 16, 18	Plain and ordinary meaning; not indefinite
"DNA fragment-specific information" '127 patent, claim 22	Plain and ordinary meaning; not indefinite
"fragment ends" '631 patent, claim 1	Plain and ordinary meaning
"comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules" '221 patent, claim 3 '306 patent, claim 19	Plain and ordinary meaning

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 objections and responses to the objections are limited to ten (10) pages each. 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 Sincavage v. Barnhart*, 171 F. App'x 924, 925 n.1 (3d Cir. 2006); *Henderson v. Carlson*, 812 F.2d 874, 878-79 (3d Cir. 1987).

The parties are directed to the court's Standing Order For Objections Filed Under Fed. R. Civ. P. 72, dated March 7, 2022, a copy of which is available on the court's website, http://www.ded.uscourts.gov.

Dated: December 29, 2022

Sherry R. Fallon
UNITED STATES MAGISTRATE JUDGE