IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

LIFE TECHNOLOGIES CORPORATION; APPLIED BIOSYSTEMS, LLC; INSTITUTE FOR PROTEIN RESEARCH; ALEXANDER CHETVERIN; HELENA CHETVERINA; and WILLIAM HONE,	§	
	§	C.A. No. 09-706-RK
Plaintiffs/Counterclaim Defendants,	§	
v.	§	
ILLUMINA, INC. and SOLEXA, INC.,	§	
Defendants/Counterclaim Plaintiffs.	§	

PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

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LEGEND

The following citation conventions are used in this brief:

- D.I. # = Docket Item number
- JA## = page number in the Joint Appendix
- ’478 patent = U.S. Patent No. 5,616,478
- ’568 patent = U.S. Patent No. 6,001,568
- ’698 patent = U.S. Patent No. 5,958,698
- ’994 patent = U.S. Patent No. 6,831,994
- ’505 patent = U.S. Patent No. 6,654,505
- ’656 patent = U.S. Patent No. 7,232,656
- ’035 patent = U.S. Patent No. 7,598,035
- XX:YY = column number:line number(s) of referenced patent
- All emphases to citations in this brief have been added to the original quotes, except where indicated otherwise.

NATURE AND STAGE OF THE PROCEEDING

Life Technologies Corp. and Applied Biosystems, LLC (together, "Life"), the Institute for Protein Research, Alexander Chetverin, Helena Chetverina, and William Hone (together, "Plaintiffs") filed their complaint for infringement of U.S. Patent Nos. 5,616,478, 6,001,568, and 5,958,698 (together, the "Chetverin patents") against Illumina, Inc. and Solexa, Inc. (together, "Illumina") on September 21, 2009.[1] D.I. 1. Illumina answered and counterclaimed on October 13, accusing Life of infringing four Illumina patents, D.I. 7. On November 5, Plaintiffs answered Illumina's counterclaims and denied the allegations of patent infringement. D.I. 17.

Plaintiffs have also filed requests with the United States Patent and Trademark Office ("PTO") for reexamination of the four Illumina patents. The PTO has granted ***all*** of the requests and has issued office actions rejecting ***all*** asserted claims in ***all*** four of the patents. Because of the substantial inefficiencies in proceeding in parallel on the same invalidity issues in the PTO and before this Court (and because the claims will likely be cancelled or changed),[2] Plaintiffs have moved this Court to stay the litigation of Illumina's counterclaims pending final decisions in the reexamination proceedings. D.I. 49. Plaintiffs' stay motion is fully briefed and is awaiting decision. If the Court enters a stay, there will be no need for the Court to address claim construction disputes on the four Illumina patents (amounting to twelve disputed claim terms).

Fact discovery is ongoing, and there have been no depositions to date and no expert discovery. A claim construction hearing is scheduled for July 26, 2010. D.I. 41. This is Plaintiffs' opening claim construction brief.

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[1] Life is an exclusive licensee under the Chetverin patents for *in situ* sequencing by synthesis.

[2] At present, Illumina has responded to two of the PTO's office actions, and seeks to add 24 new claims to one patent and 36 to another, underscoring the near certainty that if any claims emerge from reexamination they will be different than those asserted here. *See* Exhs. B, C.

SUMMARY OF ARGUMENT AND GOVERNING LEGAL PRINCIPLES

Plaintiffs' claim construction positions (including where no construction is warranted) are driven by the plain language of the claims and the specifications of the patents-in-suit, in accord with the Federal Circuit's *en banc* decision in *Phillips v. AWH*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), and its progeny. Illumina's proffered claim constructions, in contrast, routinely ignore (and often contradict) the claim language and teachings of the patent specifications.

To begin, a claim term may not even warrant construction when its meaning is plain. *See, e.g., Phillips*, 415 F.3d at 1314. As discussed below, Illumina proposes numerous terms for construction that do not warrant construction; their meanings are plain. For terms that do need construction, *Phillips* governs. Claim construction begins with the words of the claims, as "the claims themselves provide substantial guidance as to the meaning of particular claim terms." *Id*. at 1314. Claim terms "are generally given their ordinary and customary meaning;" that is, the "meaning that the term would have to a person of ordinary skill in the art" at the time of the invention. *See id.* at 1312-13. Claims must be read in view of the specification, which "is the single best guide to the meaning of a disputed term." *Id.* at 1315 (internal citations and quotations omitted). The prosecution history is also relevant, but neither the specification nor the prosecution history should be used to read limitations into the claims. *See id.* at 1317.

Finally, although extrinsic evidence is "less significant than the intrinsic record in determining the legally operative meaning of claim language," *id.* at 1317, the Federal Circuit has recognized that "dictionaries and treatises can be useful in claim construction," as long as they do not contradict the intrinsic record. *Id.* at 1322-23. "Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention

will be, in the end, the correct construction." *Id.* at 1316.

STATEMENT OF FACTS[3]

I. Plaintiffs' Suit

The Chetverin patents, conceived and developed by the husband-and-wife team of Alexander Chetverin and Helena Chetverina, are directed to pioneering inventions in the art of nucleic acid amplification and detection. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are the most significant examples of nucleic acids, as the sequences of DNA and RNA provide the blueprints for life by dictating the structure, function and appearance of all the cells and tissues in an organism. DNA/RNA analysis is a core aspect of medical and genetic research and, because these nucleic acids are very small, the ability of scientists to amplify (or make multiple copies of) and detect individual DNA and RNA molecules is crucial to this research.

Prior to the invention, a number of different methods for amplifying nucleic acids were known, such as "polymerase chain reaction" (PCR), "viral RNA-directed RNA polymerase" amplification (VRP), and an "isothermal multienzyme" amplification reaction called "3SR." *See, e.g.*, JA7 ('478 patent) at 1:2-2:65. Each of these methods was typically performed in solution, and had the resulting disadvantage that the synthesized nucleic acid products of the amplification reaction were free to migrate throughout the solution. These methods resulted in products containing many non-identical nucleic acids, making the study of individual amplified nucleic acids difficult. The Chetverins solved that problem with their invention of methods and compositions for the formation and detection of colonies of single nucleic acids that are sequestered in separate zones. *See, e.g.*, JA3 at Fig. 1. This is accomplished by "entrapping" the

[3] For the Court's convenience, attached as Exhibit J is background material on molecular biology and sequencing (Public Broadcasting Service, Sequence for Yourself, http://www.pbs.org/wgbh/nova/genome/sequ_sans.html (last visited May 27, 2010)).

nucleic acids to be amplified such that the individual nucleic acids grow into colonies without interference from other non-identical nucleic acids. *See* JA9 at 5:36-42. To constrain the migration of the nucleic acids and their synthesized copies, the Chetverin method utilizes an "immobilized medium" to perform amplification, rather than the free-floating solutions that had been commonly used in the prior art. The Chetverin inventions are a significant development over the prior art and have materially advanced techniques of nucleic acid amplification and detection.

II. Illumina's Countersuit

The four Illumina patents that are the basis of its counterclaims relate generally to DNA sequencing but do not otherwise relate to the subject matter of the Chetverin patents.

(1) Two of the Illumina patents—U.S. Patent Nos. 6,831,994 and 6,654,505 (the "Bridgham patents")—share a common specification and generally relate to "an apparatus and system for simultaneously analyzing a plurality of analytes anchored to microparticles." JA1076 ('505 patent) at Abstract.[4] The Bridgham patents describe microscopic beads (microparticles) to which DNA or RNA fragments (analytes) are anchored. JA1071 at 19:61-20:25. In the patents, microparticles are arranged in a planar array inside a "flow chamber" and the system collects and records images of the optical signals generated by all of the analytes in the planar array. *See* JA1066. The patents claim to solve problems in the prior art relating to bead movement during processing by "tracking" the microparticles, and state that it would be desirable to have a system that "permitted the tracking and analysis of multiple analytes anchored to separate microparticles through a sequence of several processing … steps." *See* JA1062 at 1:57-63. The patents claim to meet this need with "an apparatus for simultaneously tracking the positions of individual

[4] For simplicity, all cites for the common specifications of the two Bridgham patents have been made just to the '505 patent.

microparticles in a population of microparticles" (*id*. at 2:13-15) by "periodically record[ing] optical characteristics of individual microparticles that provide a close approximation [of] microparticle centers." JA1065 at 8:51-54.

(2) The third asserted Illumina patent—U.S. Patent No. 7,232,656 (the "Balasubramanian patent")—is "directed at a method for analyzing genome wide variation in an individual." *See* JA1102 ('656 patent) at Abstract. (The genome is the complete DNA blueprint for an individual.) The invention is claimed to be accomplished by (1) randomly fragmenting an individual's genome, (2) "reading" the nucleotide sequence of all the fragments, and (3) aligning the read sequence with a known reference sequence to determine variations between the two. *Id.* The specification explains that the use of "single molecule arrays" is key to the invention: after the genome is fragmented, the unamplified fragments are attached to solid supports (such as beads) in a manner that makes it "possible to distinguish one molecule on the array from its neighboring molecules." JA1109 at 4:37-39. The specification distinguishes the invention from multi-molecule arrays of the prior art (arrays that comprise "distinct clusters of many molecules of the same type"), *id.* at 4:33-36, and emphasizes the advantages of single molecule arrays over multi-molecule (cluster) arrays. *See, e.g.,* JA1108-09 at 2:18-29; 3:20-3.

(3) The fourth asserted Illumina patent—U.S. Patent No. 7,598,035 (the "Macevicz Patent")—is entitled "Method and Compositions for Ordering Restriction Fragments" and "provides a method for constructing a high resolution physical map of a polynucleotide." JA1121 ('035 patent) at Abstract. This is accomplished by first digesting a piece of DNA with one or more "restriction enzymes," which recognize particular short DNA sequences and cut the DNA at or near those sequences. The fragments can be realigned using these sequences, thus providing a map of the original piece of DNA that includes at least partial sequence information.

See JA1127 at 2:7-9; 2:59-62. The use of restriction enzymes is crucial to the claimed invention because without them it would not be possible to use the sequence of the ends of fragments to align those fragments with one another. *See id*. The claimed invention utilizes vectors to amplify the fragments and prepare the DNA for sequencing and mapping. JA1129 at 6:50-55.

ARGUMENT

I. PLAINTIFFS' CHETVERIN PATENTS: DISPUTED CLAIM TERMS

The '478 patent, the parent of the Chetverin patents,[5] claims methods of exponential nucleic acid amplification to form detectable colonies of nucleic acids, the '698 patent is directed to methods of amplifying and detecting a nucleic acid sequence in colonies, and the '568 patent is directed to certain compositions for forming separate detectable colonies.[6] Sample claims with the disputed terms highlighted are included as Exhibit A hereto.

1. "Amplification system" ('478 patent, all claims; '698 patent, all claims; '568 patent, claim 16)

"Polymerase enzyme system" ('568 patent, claims 1, 2, 4, 10)

Term(s)[7]	Plaintiffs' Construction	Defendants' Construction
"amplification system" "polymerase enzyme system"	a set of components that together can amplify a nucleic acid	a set of components (including a buffer, a nucleic acid amplification enzyme, nucleotide substrates, and, where required, oligonucleotide primers) that together can amplify a nucleic acid

The parties agree that these claim terms are defined by their ability to perform nucleic acid amplification. Plaintiffs' construction embodies that meaning as "a set of components that together can amplify a nucleic acid." Defendants seek to limit this term by requiring that the claimed system include particular individual components. But Defendants' proposed limitation is contradicted by the claim language, specification, and prosecution history. Several dependent

[5] The '478 patent is referred to as the parent patent as it was the first of the family to issue.

[6] All three Chetverin patents share the same specification, apart from the claims. For simplicity, all cites for the common specifications of the Chetverin patents have been made just to the '478 patent. (JA1-20).

[7] Each Chetverin patent contains claims with at least one of these terms and the parties agree that they should be construed the same way.

claims specify particular amplification or polymerase enzyme systems to be used, indicating that the independent claims containing the claim terms at issue are broader and do not require the specific recitation of individual components. *See, e.g.*, JA18 ('478 patent) at claim 12 (claiming particular nucleotides) and claims 4, 5, 6 (claiming the use of VRP, 3SR, and PCR systems); JA38 ('698 patent) at claims 13, 14, 15 (same); JA57 ('568 patent) at claims 6, 7, 10 (same). Further, the specification refers generally to various examples of amplification or polymerase enzyme systems without requiring any specific components for use with the invention so long as the combination of components that is used can accomplish the necessary amplification. *See, e.g.*, JA8-9 ('478 patent) at 4:66-5:1 ("The method can employ any system of exponential amplification of nucleic acids in vitro, such as VRP reaction, PCR, or 3SR reaction."); JA8 at 4:52-54 ("The immobilized medium contains an amplification system comprising a cell-free enzyme system capable of exponentially amplifying the nucleic acids."); JA10 at 7:40-44 ("The immobilized medium according to our invention also contains the components of an amplification and/or an expression system comprising the components of a cell-free enzyme system capable of exponential amplification and/or of expression of nucleic acids, respectively.").

The prosecution history of the '478 patent shows that both the patentee and the PTO considered whether the claims should identify a particular set of components and concluded that they did not. The patentee explained during prosecution that "amplification systems are not the claimed invention, that a wide variety are disclosed, and that there is no teaching that the invention is limited to a particular system." *See* JA615 (Paper 22 at 7); *see also* JA574 (Paper 18 at 15) (explaining that the claimed invention is not about an amplification per se, but about a way to apply amplification techniques generally); *id*. ("Whatever exponential enzymatic nucleic acid

amplification is selected for use in applicants' method, the necessary components for that amplification system must be provided so that templates for that system will be amplified."). The PTO agreed that specific components need not be recited in the claims. *See* JA614 (Paper 22 at 6) ("Given the extensive teaching, Applicant maintains that individual components need not be recited. The Examiner accepted Applicant's explanation."). The intrinsic record shows that the claimed amplification and polymerase enzyme systems are defined by their function and not by any specific components. Although one of skill in the art would appreciate that amplification systems or polymerase enzyme systems will generally contain certain components, such as a buffer, enzyme, and substrates, the claims are neither so defined nor so limited. Illumina's proposed construction should be rejected.

2. "Aqueous liquid phase that includes a cell-free, enzymatic, exponential nucleic acid amplification system" ('478 patent, claims 1, 2, 6, 7, 11, 12; '698 patent, claims 17, 18, 20, 21, 23)

"Aqueous liquid phase that includes a cell-free nucleic acid polymerase enzyme system" ('568 patent, claims 1, 2, 4, 10)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"aqueous liquid phase that includes a cell-free, enzymatic, exponential nucleic acid amplification system" "aqueous liquid phase that includes a cell-free nucleic acid polymerase enzyme system"	*No construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* aqueous liquid portion that includes a set of components that together can perform cell-free, enzymatic, exponential amplification of a nucleic acid aqueous liquid portion that includes a cell-free nucleic acid polymerase enzyme system	a solution dissolved in water containing a buffer, a nucleic acid amplification enzyme, nucleotide substrates, and, where required, oligonucleotide primers

These claim terms do not require construction beyond the terms "amplification system" and "polymerase enzyme system," as discussed above. The claims recite an immobilized medium comprising two phases—an aqueous liquid phase that includes the claimed

amplification system or polymerase enzyme system, and a solid water-insoluble matrix phase. The claimed aqueous liquid phase is the liquid in the immobilized medium that includes a cell-free (without cells), enzymatic (with an enzyme), exponential nucleic acid (*e.g.*, DNA) "amplification system" or "polymerase enzyme system." No further construction is necessary.[8]

Defendants' request that the Court construe these terms is curious because it indicates their view that, outside of "amplification system" and "polymerase enzyme system," the other words in the terms at issue—"aqueous liquid phase," "includes," "cell-free," "exponential," and "nucleic acid"—are somehow unclear. Yet Defendants' proposed construction does not even seek to address the meaning of all of those words. These words are not unclear; they have ordinary and well-understood meanings such that no construction by the Court is needed.

Should the Court require construction of these terms, however, the proper constructions should be, respectively, "aqueous liquid portion that includes a set of components that together can perform cell-free, enzymatic, exponential amplification of a nucleic acid" and "aqueous liquid portion that includes a cell-free nucleic acid polymerase enzyme system." Contrary to Defendants' proposed construction, Plaintiffs' constructions account for all of the claim language and are consistent with the specification and the prosecution history. For example, the claims indicate that the aqueous liquid phase is the liquid portion of the immobilized medium. *See, e.g.*, JA18 ('478 patent) at claim 1 ("said [immobilized] medium including (i) an aqueous liquid phase and (i) a solid, water-insoluble matrix"); JA38 ('698 patent) at claim 17 (same); JA57 ('568

[8] *See Phillips*, 415 F.3d at 1314 ("[T]he ordinary meaning of claim language … may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words."); *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) ("Claim construction is a matter of resolution of disputed meanings and technical scope, to clarify and when necessary to explain what the patentee covered by the claims, for use in the determination of infringement. It is not an obligatory exercise in redundancy.").

patent) at claim 1 ("a preformed immobilized medium … comprising a) an aqueous liquid phase and b) a thin layer … of a solid, water-insoluble matrix"). Similarly, the specification describes the aqueous liquid phase as the liquid portion of the immobilized medium. *See* JA8 at 4:46-48 ("According to our invention, the immobilized medium for amplification of nucleic acids comprises a liquid phase entrapped within a solid matrix …."); JA10 at 7:52-54 ("The upper diagram [of Fig. 1] Shows segment 11 of an immobilized medium comprising solid matrix 12, and liquid phase 13."). The '478 patent prosecution history also confirms that the aqueous liquid phase is the liquid portion of the immobilized medium. *See* JA568 (Paper 18 at 27) ("Step (1)(a) recites that the medium includes 'an aqueous liquid phase.'").

Defendants' proposed construction is fatally flawed in that it reads out the express requirement in the claim that the aqueous liquid phase "includes a[n] … amplification system [or polymerase enzyme system]." Notably, Defendants' proposal fails to incorporate even their own proposed construction of "amplification system" and "polymerase enzyme system."[9] The claimed aqueous liquid phase must include a set of components that together can amplify a nucleic acid. Defendants further ignore the claim language by reading out of the claim terms "cell-free" and "exponential," contravening the principle that claims are to be construed by giving effect to all terms in the claim.[10] Defendants additionally seek to re-write the claim language "aqueous liquid phase" as "a solution dissolved in water." Defendants' substitute language is inconsistent with the claims and contradicted by the specification, which

[9] *See Fin Control Sys. Pty, Ltd. v. OAM, Inc.*, 265 F.3d 1311, 1318 (Fed. Cir. 2001) ("[T]he same terms appearing in different portions of the claims should be given the same meaning unless it is clear from the specification and prosecution history that the terms have different meanings at different portions of the claims.").

[10] *See, e.g.*, *Lantech, Inc. v. Keip Mach. Co.*, 32 F.3d 542, 547 (Fed. Cir. 1994) ("The district court erred as a matter of law by effectively reading out a specific and clearly stated limitation, and embracing an erroneous interpretation of the term conveyor.").

distinguishes between a solution and the liquid phase of the immobilized medium. JA9 at 6:47-50. The specification instead describes the aqueous liquid phase as simply a "liquid water-based phase." *Id.* at 6:53-55 ("An immobilized medium suitable for the reaction according to the invention comprises a liquid water-based phase entrapped within a solid matrix."). Defendants' proposed construction and the actual claim language are like two ships passing in the night.

Finally, contrary to Defendants' proposed construction, the intrinsic record establishes that the components of the amplification system included in the aqueous liquid phase ***do not*** have to be fully dissolved or even suspended in liquid. Dependent claim 8 of the '568 patent expressly requires an enzyme linked to the matrix rather than dissolved in water. *See* JA57. The '478 patent prosecution history explains that "[c]aim [1] requires that the enzymes be in the aqueous phase but ***does not require that the enzymes be totally free in solution*** in the aqueous phase. The specification teaches that enzymes ***may be linked to the matrix***." JA587 (Paper 18 at 28). Defendants' proposed construction should be rejected.

3. "Forming a liquid mixture of the sample and said amplification system" ('698 patent, claims 1-3, 6, 12, 15, 16)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"forming a liquid mixture of the sample and said amplification system"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* combining the sample and the amplification system together in a liquid	mixing the sample and every component of the amplification system into solution (i.e., not linked to the water-insoluble matrix)

Like the above term, this term requires no construction beyond "amplification system." Should the Court determine that construction is warranted, this term should be construed as "combining the sample and the amplification system together in a liquid," consistent with the plain meaning of the claim term.

Defendants' proposed construction impermissibly seeks to introduce an additional limitation that the sample and every component of the amplification system be in solution. This contradicts the teachings of the intrinsic record that allow for individual components of the amplification system to be linked to the matrix, as established above. *See, e.g.*, JA587 ('478 PH Paper 18 at 28) ("The specification teaches that enzymes may be linked to the matrix.").

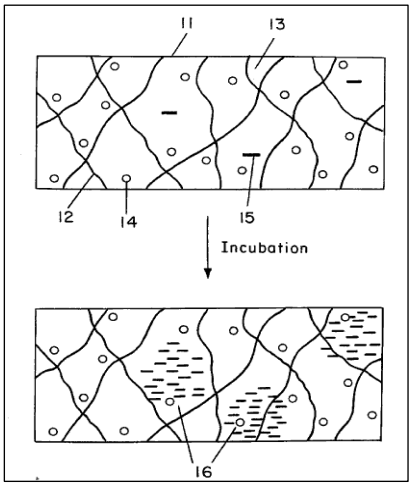
4. "Entrapping" (all claims)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"entrapping"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* keeping within limited zones	continuously holding substantially motionless and preventing any convection and intermixing

The claim term "entrapping" appears in each asserted claim of all three Chetverin patents. There is no need for the Court to construe this term because its meaning is readily apparent from the claim language, the specification, and the overall purposes of the invention. The specification explains that "[t]he present invention is based on our discovery that nucleic acid molecules can be, like microorganisms, grown as colonies in an immobilized medium." *See, e.g.*, JA8 at 4:43-45. Amplification of target nucleic acids in the prior art was commonly conducted in liquid reaction medium, *see* JA7 at 1:23-24, a process that was susceptible to cross-contamination by non-target nucleic acids, *see, e.g.*, JA8 at 3:34-38, 44-45. Due to the cross-contaminating amplification of non-target nucleic acids, "neither the true cloning (*i.e.*, obtaining the progeny of a single molecule), nor the detection of solitary molecules [were] achievable with these techniques." *See id.* at 3:58-61. The Chetverin invention solves this problem by providing methods and compositions for amplifying and detecting target nucleic acids that are formed as discrete "colonies," containing progeny of a single molecule, uncontaminated by other nucleic

acids. *See* JA9 at 5:5-9, 53:56. The invention accomplishes this by providing an "immobilized medium … compris[ing] a liquid phase entrapped within a solid matrix" such that target nucleic acids "become entrapped somewhere in the medium, and their exponential amplification results in a 'colony' within a limited zone surrounding the progenitor template." *See* JA8 at 4:46-66. The specification explains that "[e]ntrapment of nucleic acids in an immobilized medium according to the invention substantially prevents a competition between different templates, since their progeny is not allowed to spread all over the reaction volume." JA9 at 5:36-39. One of the purposes of the invention is to avoid the transfer of nucleic acid products from one zone to another during the amplification reaction. *See* JA10 at 8:36-39. In particular, this "allows individual nucleic acids to be amplified in bulk with the interference form background growth being largely suppressed." JA9 at 5:39-42.

The specification explains that "[a]fter incubating the immobilized medium for a period of time at a temperature regime allowing nucleic acids to be amplified, nucleic acid colonies 16 form at the locations where the parental nucleic acid templates have been entrapped (the lower diagram)." JA10 at 7:57-61. The patent teaches that "entrapping" means keeping the amplification reaction separate—*i.e.*, in separate zones—so that the formation of discrete colonies without cross-contamination can be accomplished. Accordingly, no construction of this term is necessary. Figure 1 of the patents (*see* JA3), shown at right, depicts an example of the entrapment of nucleic acid templates (15) with enzymes (14) in a liquid phase (13), and the resultant formation of discrete nucleic acid colonies, without contamination from other nucleic acids, confined to limited zones (16).



Should the Court deem construction necessary, however, this term should be construed as "keeping within limited zones," as the specification repeatedly states. The specification explains: "According to our invention, exponential amplification of nucleic acids and/or their expression (hereinafter referred to as a 'reaction') is carried out in an immobilized medium, rather than in solution as it is done in the prior art, in order to keep the templates and the reaction products within ***limited zones*** at fixed locations of the reaction volume." JA9 at 6:47-52. The specification further explains that the "liquid phase entrapped within a solid matrix" is entrapped in a manner such that "***different zones*** of the liquid phase" do not undergo convection or intermixing. *See* JA8 at 4:46-51; *see also* JA11 at 9:14-20 (immobilized medium "allows the contaminating nucleic acids to be amplified at, and their competition to the growth of the desired nucleic acids to be restricted to, ***limited zones*** of an immobilized medium where the contaminating templates were originally entrapped"); JA9 at 5:2-5 ("[D]ifferent colonies occupy ***separate zones*** within the immobilized medium, and this allows the respective clones to be observed and handled separately."). Accordingly, Plaintiffs' construction of "entrapping" as "keeping within limited zones" should be adopted.

Defendants' proposed construction—"continuously holding substantially motionless and preventing any convection and intermixing"—selectively plucks words from the specification and then injects others, such as "continuously" and "any," to deprive Plaintiffs of the full scope of the Chetverins' invention by effectively requiring that which is entrapped to remain completely motionless at all times. But the intrinsic record is contrary to Defendants' proposed restrictive construction, showing that the entrapped components can, in fact, move. For example, in one embodiment described in the specification, the amplification reaction is carried out in coated granules (capsules), which are continuously washed with a fresh substrate solution to

yield a higher reaction rate wherein the nucleotide substrates can permeate through the shells and in and out of the capsules. *See* JA11 at 9:54-10:18. Also, as explained during prosecution of the '478 patent, "although individual components, e.g., nucleotides, need not be completely entrapped in the matrix, the full system is, and amplification is done without mixing." JA587 (Paper 18 at 28). In addition, dependent claim 11 of the '478 patent specifies that the "immobilized medium comprises distributing said aqueous liquid phase in such solid matrix," *see* JA18, which would be foreclosed by Defendants' proposed limitations that the liquid phase be "continuously h[eld] substantially motionless." Plaintiffs' position thus should be adopted.

5. "Completely entrapping" ('478 patent, all claims; '698 patent, claims 17, 18, 20, 21, 23; '568 patent, all claims)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"completely entrapping"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* completely keeping within limited zones	entrapping all (*i.e.*, the entirety or whole) of [the thing listed after the term]

This term does not require construction. Just as the term "entrapping" requires no construction, neither does the term "completely entrapping," as one of skill in the art would understand the meaning of the term based on the plain language of the claims and the specification. Defendants' proposed construction does no more than proffer an alternate definition for the word "completely," without including its construction for "entrapping." Thus, the Court need not construe this term. Should the Court determine that this term requires construction, Plaintiffs propose defining this term as "completely keeping within limited zones," consistent with their construction of "entrapping," which is supported by the intrinsic record as discussed above for the term "entrapping."

6. "Thin Layer" ('698 patent, claims 1-3, 6, 12, 15, 16, 18; '568 patent, claims 1, 2, 4, 10)[11]

Term(s)	Plaintiffs' Construction	Defendants' Construction
"thin layer"	*No construction necessary.*	A layer having a thickness of at least 1 millionth of a meter

"Thin layer" does not require construction because many of the asserted claims already specify ranges of thickness while the others do not require further specificity.[12] Defendants' proposed construction violates several fundamental tenets of claim construction—they seek to read a limitation into the claim that is not required; they render the terms in certain claims superfluous or redundant; and they violate the doctrine of claim differentiation. First, several claims reciting this term already separately define a specific range that the thickness of the thin layer falls within. For example, independent claim 1 of the '568 patent (and claims 2 and 10, which depend from it) specifically recites a "thin layer, from 1 μm to 10 mm in thickness." JA57. Dependent claim 4 of '568 further recites that the thin layer "has a thickness in the range of 50 μm to 10 mm." *Id*. There is thus no need to construe that term to include a specific range of thickness—it is already defined in those claims. Defendants' proposed construction, which seeks to specify "a thickness of at least 1 millionth of a meter [*i.e.*, 1 μm]," would render redundant other terms in claims 1, 2, and 10 of the '568 patent that already specify that very same lower limit.

Similarly, claim 6 of the '698 patent expressly recites that the thin layer "has a thickness from 1 μm to 10 mm." JA38. But, significantly, independent claim 1 of the '698 patent from which claim 6 depends does ***not*** recite a specific numerical range for the claimed "thin layer."

[11] The joint claim chart submitted to the Court incorrectly lists the term, "thin layer," as appearing in all asserted claims of the '568 patent. D.I. 58.

[12] *See supra* n.9.

The same is true for dependent claim 18 of the '698 patent. Defendants' construction, which seeks to impose a numerical limitation on this term as used in all claims across all patents, should be rejected for (1) incorporating redundant language where a numerical range is specified (such as for the claims of the '568 patent),[13] and (2) importing limitations into claims containing no such limitation (*e.g.*, claims 1 and 18 of the '698 patent) in violation of various doctrines of claim construction, including the doctrine of claim differentiation in which "the presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the independent claim."[14] As the Federal Circuit has explained,[15] "[t]hat presumption is especially strong when the limitation in dispute is the only meaningful difference between an independent and dependent claim, and one party is urging that the limitation in the dependent claim should be read into the independent claim"—just as the only meaningful distinction between claims 1 and 6 of the '698 patent is that claim 6 further specifies a range of thickness of the thin layer, and Defendants are urging that this range be read into claim 1.

Indeed, Defendants' proposal to inject "1 millionth of a meter" as the lower thickness limit into the claims is contradicted by the claim language and by the specification. First, claim 16 of the '568 patent specifies a thickness of the matrix of 0.1 μm as a lower limit—a ten-fold lower limit than that which Defendants seek to import. Second, the specification expressly teaches that the thinner the layer, the better, "as this increases the resolving power of the method and reduces cost." *See* JA11 at 10:62-64. The specification additionally explains that "[t]he

[13] *See Stumbo v. Eastman Outdoors, Inc.*, 508 F.3d 1358, 1362 (Fed. Cir. 2007) (rejecting construction of a claim term that would render other language in the same claim redundant).

[14] *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004) (concluding that an independent claim lacking any reference to a requirement added by a dependent claim is properly construed as not requiring that limitation).

[15] *Sunrace Roots Enter. Co. v. SRAM Corp.*, 336 F.3d 1298, 1303 (Fed. Cir. 2003).

lower limit of the thickness depends on the mechanical strength of the solid matrix, on the possibility to prevent its drying during manipulation and during the reaction, and on the sensitivity of the method used for detecting the reaction products." *Id.* at 10:64-11:1. As the Federal Circuit has noted, "when a claim term is expressed in general descriptive words, [the Court] will not ordinarily limit the term to a numerical range that may appear in the written description or in other claims.[16] Accordingly, Defendants' efforts to import a numerical limitation into the term "thin layer" should be rejected. No construction is needed for this term.

7. "Incubating said immobilized medium" ('478 patent, claims 1, 3, 6, 7, 11, 12; '698 patent, claims 17, 18, 20, 21, 23)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"incubating said immobilized medium"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* maintaining the immobilized medium under conditions that promote the claimed reaction	maintaining all of the immobilized medium provided in step (a) under conditions that promote exponential amplification

This term does not warrant construction because its meaning is readily apparent. The parties agree that "incubating" means maintaining the claimed immobilized medium under conditions that promote a reaction, which is consistent with the common understanding of this term.[17] If the Court deems construction necessary, however, the proper construction is "maintaining the immobilized medium under conditions that promote the claimed reaction." This is consistent with the claim language.

[16] *Conoco, Inc. v. Energy & Environmental Int'l, L.C.*, 460 F.3d 1349, 1358 (Fed. Cir. 2006).

[17] *See* The American Heritage Dictionary of the English Language (3d ed. 1992) ("2. … b. To maintain (a chemical or biochemical system) under specific conditions in order to promote a particular reaction.") [Exh. D].

Defendants improperly seek to alter the claim language in more than one way. First, Defendants impose the requirement that what is incubated is "all of the immobilized medium provided in step (a)," suggesting that there can be no change in what is being incubated. There is no basis for limiting the claims in this manner. The specification describes examples in which individual components of the immobilized medium may change during incubation. *See, e.g.*, JA9 at 5:23-27 (describing the supplementation of new components in the claimed medium during an amplification reaction); JA12 at 11:48-53 (same); JA11 at 10:4-14 (describing an amplification reaction being carried in coated granules "by incubating them in substrate containing solution" wherein "[a] higher yield of the reaction can be obtained by continuously washing the coated granules with a fresh substrate solution"); *id.* at 10:30-39 ("To carry out the amplification reaction, the opposite side of the [solid matrix] is washed with a solution containing nucleotides.").

Defendants also seek to import the term "exponential" into the claim language. But that is not supported because the claim language does not require that the reaction that is promoted through incubation be exponential amplification. The particular reaction that the claimed act of incubating promotes is instead expressly recited as a separate term later in the same claim. *See* JA18 ('478 patent) at claim 1 ("incubating said immobilized medium … under conditions promoting synthesis of an exponentially amplified nucleic acid product by said amplification system from said at least one template"); JA38 ('698 patent) at claim 17 (same). In other words, the reaction being promoted by incubation is the synthesis of an exponentially amplified nucleic acid product, not necessarily exponential amplification itself. Defendants' construction thereby improperly renders other claim language redundant.[18]

[18] *See Stumbo*, 508 F.3d 1362.

8. "Incubating said trapped mixture" ('698 patent, claims 1-3, 6, 12, 15)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"incubating said trapped mixture"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* maintaining the trapped mixture under conditions that promote the claimed reaction	maintaining all of the trapped medium provided in step (b) under conditions that promote exponential amplification

This term does not require construction for the reasons discussed for the prior term. If construed, Defendants' proposed construction is incorrect for the same reasons as above. In addition, Defendants' substitution of the word "medium" for "mixture" does not add any clarity and the Court should thus decline to provide a construction.

9. "Wherein the average distance between the nearest solid surfaces is smaller than the distance which the synthesized nucleic acid product can migrate by diffusion during the reaction" ('698 patent, claims 1-3, 6, 12, 15)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"wherein the average distance between the nearest solid surfaces is smaller than the distance which the synthesized nucleic acid product can migrate by diffusion during the reaction"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* wherein the average distance between the nearest solid surfaces is sufficiently small to prevent synthesized nucleic acid products from migrating between zones during the reaction	wherein the average distance between the nearest solid surfaces is less than the distance that any nucleic acid product synthesized during the accused reaction can move (*i.e.*, from one location in the matrix to another) during that reaction

This term requires no construction. As described in the specification and discussed above, a purpose of the invention is the amplification and detection of nucleic acids as distinct colonies. This is achieved in part by limiting the amplified nucleic acid products from "spread[ing] all over the reaction volume" and thus preventing cross-contamination between colonies. JA9 at 5:36-39. This claim requirement aims to achieve that goal by requiring that the

average distance between the nearest solid surfaces of the matrix (*i.e.*, size of the pores in the matrix (*see id.* at 6:62-63)) be less than the distance at which the synthesized products can migrate by diffusion during exponential amplification (*see id.* at 6:64-67; 6:47-49). The matrix allows the creation of colonies of a single nucleic acid by physically constraining the migration of synthesized nucleic acid products such that amplification of the single nucleic acid occurs within a limited zone. *See id.* at 6:47-52 (explaining that reaction products are kept "within limited zones at fixed locations of the reaction volume"); JA8 at 4:61-64 (explaining that exponential amplification of entrapped nucleic acid molecules "results in a 'colony' within a limited zone surrounding the progenitor template."). One skilled in the art would be able to readily apply this term to achieve that goal and no construction is warranted.

If the Court concludes that construction is warranted, however, Plaintiffs' construction should be adopted because it defines the requirement according to its function for achieving the intended result of the invention: "wherein the average distance between the nearest solid surfaces is sufficiently small to prevent synthesized nucleic acid products from migrating between zones during the reaction." That is, solid surfaces entrap the liquid mixture of the sample and amplification system, holding in place the sample and amplification products so that nucleic acid colonies may form. *See* JA11 at 10:59-67 (explaining that colony size "depends mainly on the rate of nucleic acid diffusion."). Defendants' construction should be rejected because it ignores the claim requirement that accounts for "the distance which the synthesized nucleic acid product can migrate by diffusion during the reaction." Further, Defendants' construction is based on the distance that ***any*** synthesized nucleic acid product, not the specific synthesized nucleic acid product, can migrate as the claim expressly requires.

10. "Distributing in said aqueous liquid phase" ('478 patent, claims 1, 2, 6, 7, 11, 12; '698 patent, claims 17, 18, 20, 21, 23)

"Distributing in said amplification system" ('478 patent, claims 14, 15, 16)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"distributing in said aqueous liquid phase" "distributing in said amplification system"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* separating nucleic acid molecules in the aqueous liquid phase separating nucleic acid molecules in the amplification system	entirely dissolving in [the aqueous liquid phase/amplification system] (*i.e.*, not linking to the water-insoluble matrix)

No construction is needed for the terms "distributing in said aqueous liquid phase" and "distributing in said amplification system" beyond the construction of "amplification system." "Aqueous liquid phase" is readily understandable as discussed above, as is the word "distributing." There is thus no need for further construction.

Should the Court determine otherwise, however, Plaintiffs propose that these terms be construed as "separating nucleic acid molecules in the aqueous liquid phase" and "separating nucleic acid molecules in the amplification system," as supported by the claim language and the specification in view of the goals of the invention. A purpose of the invention is the formation of colonies of a single nucleic acid in immobilized media. *See, e.g.*, JA8 at 4:43-45. "Distributing" in this context plainly refers to including nucleic acid molecules in the aqueous liquid phase or amplification system in such a way so that the nucleic acid molecules are separate from each other. The claims build on this term by additionally requiring that this step of distributing results in the separation of individual templates, which allows for the formation of separate, detectable nucleic acid colonies. JA18 ('487 patent) at claim 1. "[T]he construction that stays true to the

claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction."[19]

Defendants' definition of "distributing" as "entirely dissolving" and "not linking to the water-insoluble matrix" does not comport with the plain meaning of the claim terms and is without support in the intrinsic record. Nothing in the claims, specification, or prosecution history requires that the method of distributing nucleic acid molecules in the aqueous liquid phase or amplification system be by dissolution. Instead, the specification discusses how nucleic acid molecules are introduced into the liquid phase of the immobilized medium more generally—simply "by including them into the enzyme and/or substrate solution prior to its immobilization," for example. *See* JA12 at 12:63-67. The specification describes enzymes and substrates as being in solution, but does not so describe nucleic acid molecules. Dissolving nucleic acid molecules entirely in solution is just not a requirement of the invention.

11. "A preformed immobilized medium" ('568 patent, claims 1, 2, 4, 10)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"a preformed immobilized medium"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* an immobilized medium that is formed prior to amplification	an immobilized medium that is formed prior to addition of a template for amplification

This term requires no construction because it is specifically defined in claim 1 of the '568 patent as comprising the specified liquid phase of item (a) and the thin layer of item (b) of the claim. No further construction is needed. If the Court deems further construction required, however, Plaintiffs' proposed construction should be adopted because it is consistent with the claim language that specifies that the claimed immobilized medium is formed prior to

[19] *See Renishaw PLC v. Marposs Societa per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

amplification of individual nucleic acid molecules, as "separate detectable colonies" are produced by "a cell-free enzymatic exponential amplification process" from this immobilized medium. *See* JA57 at claim 1.

Defendants' construction improperly seeks to limit the immobilized medium to one that is formed prior to any addition of a template for amplification, contrary to the intrinsic evidence in various respects. First, the claims as a whole indicate that nucleic acid molecules can be a part of the immobilized medium prior to amplification. Dependent claim 9, for example, recites an activatable reagent in the medium "for preventing nucleic acids from serving as templates for enzymatic amplification." JA57. If the nucleic acid molecules could only be added after the formation of the immobilized medium for amplification, there would be no need to include a reagent for preventing the nucleic acids from being amplified. Second, the claim language refers to the application of nucleic acid molecules to the immobilized medium, whereas the specification expressly distinguishes between nucleic acid molecules and templates. For example, in a 3SR amplification system, the specification explains that nucleic acid molecules that are introduced to the system give rise to, and are therefore distinct from, the actual templates for amplification. *See* JA7 at 2:33-65; *see also* JA577 ('478 PH Paper 18 at 18) ("The amplified product is synthesized directly from the distributed molecules by exponential amplification as in PCR with DNA molecules [], or indirectly from the distributed molecules by exponential amplification of a complimentary strand, as in PCR with RNA molecules [] or in VRP with DNA molecules."). Third, the specification teaches that "[n]ucleic acids intended for amplification … should be introduced into the liquid phase of a layer … prior to its immobilization." JA12 at 12:63:66

12. "Nucleotide substrate" ('568 patent, claim 16)

Term(s)	Plaintiffs' Construction	Defendants' Construction
"nucleotide substrate"	*No further construction necessary. Should the Court determine that construction is required, Plaintiffs propose:* a substance comprising a nucleotide on which an enzyme acts	nucleotides, nucleotide analogs, or similar structures used as the building blocks of a new nucleic acid strand. Nucleic acids, such as primers, are not nucleotide substrates

"Nucleotide substrate" is a readily-understandable term—a substance comprising a nucleotide on which an enzyme acts. No further construction is necessary. If construction is deemed appropriate, Plaintiffs' construction should be adopted. Defendants improperly seek to limit this term to exclude "primers," even though primers are "used as the building blocks of a new nucleic acid strand." Defendants' construction is contradicted by the claim language, which contains no such exclusion, and instead broadly refers to the entrapping of "nucleotide substrates" for amplification (which plainly could include primers or templates). This is consistent with an overall object of the invention—amplification of nucleic acids. Plaintiffs' construction encompasses the full scope of nucleotide substrates, as required by the claims and should be adopted over Defendants' unduly restrictive construction.

II. ILLUMINA'S PATENTS: DISPUTED CLAIM TERMS

A. THE BRIDGHAM PATENTS (NOS. 6,831,994 AND 6,654,505)

1. "Optical characteristic of each/said microparticle" ('994 patent, claim 1; '505 patent, claim 2)

Term	Life's Construction	Illumina's Construction
"optical characteristic of each microparticle" "optical characteristic of said microparticle"	an optical quality of the microparticle itself, not the attached analyte	an optical characteristic of the microparticle

The parties agree that the "optical characteristic" recited in the claims is a characteristic of a microparticle, just as the claim language states. Illumina, however, is unwilling to agree that an "optical characteristic" relates exclusively to the microparticle, and instead proposes a construction that leaves open the possibility that the "optical characteristic" may also relate to the analyte attached to the microparticle. Life's construction clarifies this ambiguity and makes express what is obvious from the claim language and specification: the optical characteristic is a quality of the microparticle and ***not*** the attached analyte. After all, the claim recites that the "optical characteristic" is "of each microparticle" and is used to "determine the approximate center of said microparticle." JA1101 ('994 patent) at 27:51-55; JA1075 ('505 patent) at 27:57-60.[20] The claims (and the specification) unquestionably assign "optical characteristics" exclusively to microparticles, not analytes, and the term should be construed accordingly.

Life's construction is also consistent with a stated purpose of the claimed invention—"track[ing] individual ***microparticles*** through multiple steps of a process" while avoiding

[20] This is in contrast with optical signals ***from*** the microparticles—the claims and the specification recite that those signals are used to classify analytes, *see* JA1076, JA1088, JA1090 ('994 patent) at Abstract, 2:48-51, 5:1-3, and the parties have agreed that the optical signals come ***from*** the analytes attached to the microparticles. D.I. 57, Exh. A.

"inappropriate interaction of ***microparticles*** and/or reagents." JA1088 ('994 patent) at 1:40-63. The tracking purpose of the invention is fulfilled by the claim requirement of "record[ing] at least one optical characteristic of each microparticle which can be used to determine the approximate center of said microparticle[s]." This claim requirement could not be met and the tracking purpose of the invention could not be satisfied by focusing on an attachment to the microparticle (the analyte), for that would not locate the center of the microparticle.

This can be illustrated by considering a hockey player (the microparticle) and the player's hockey stick (the analyte). If a spectator wants to pinpoint exactly where a hockey player is located, the focus should be on the player and not on the stick that the player is holding (and that extends outward and away from the player). The importance of looking at the player becomes more apparent when two or more players are near each other, competing for control of the puck. In such situations, the players' sticks often cross, and the spectator is unable to tell the players apart if the focus is on the sticks. This applies here—tracking individual microparticles (players) requires one to focus on the microparticles (players) themselves, not the analytes (hockey sticks). JA1088 at 1:40-51. Determining the center of the microparticle by focusing on the appended analyte (as Illumina's construction would allow) would not facilitate tracking microparticle movement as required. JA1091 at 8:48-50.

The specification is consistent with this construction, explaining repeatedly that optical characteristics of microparticles are used to track the microparticles:

> [a]n important feature … of the invention is the ability to keep track of individual microparticles [by] periodically record[ing] optical characteristics of individual microparticles that provide a close approximation [of] microparticle centers. Preferably, when trans-illumination, or "back lighting" of flow chamber (100) is possible, the optical characteristic is the focused back light from the microparticles…. In an epiillumination system, light from flow chamber (100), i.e. "top light (610)," is directed from a vertical direction onto microparticles (602) where it scatters from the top surface of the microparticles. In this

> configuration, the optical characteristic is the scatter center of the microparticle…. As with focused back lighting, the image of the scatter centers provides a convenient way to readily determine the approximate centers of the microparticles.

JA1091-1092 at 8:48-9:5; *see also* JA1085 (Figs. 6a, 6b). This passage is not an anomaly; the specification nowhere references an optical characteristic of an analyte.[21]

Indeed, the patent teaches that the analytes serve a different purpose than the microparticles. The patent claims to have two primary goals; the first is to track the movement of the microparticles, as discussed above, and the second is to collect and process the sequence of signals emitted by the analytes. The patent explains that optical ***signals*** relate to the analytes and states that the method used to record signals ***from analytes*** is fluorescence (or similar luminescent emission). *See* JA1092 at 10:28-39. The phrases "optical characteristic" and "optical signals" thus refer to two different measurements, and are used to accomplish two different purported goals: optical characteristics are used to determine the locations of microparticle centers and to track the microparticles; optical signals from analytes are used to determine the sequences of nucleotides on the DNA analytes. JA1095 at 15:1-61. The two phrases should, therefore, be construed to have different meanings.[22] JA1091 at 8:48-50. Life's construction recognizes the difference between the two phrases, is consistent with the claim language, respects a stated purpose of the invention, and should be adopted here.

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[21] When the specification consistently describes a term in one manner, broader interpretations of the term that are unsupported by the specification should be rejected. *See Pause Tech., LLC v. TiVo, Inc.*, 419 F.3d 1326, 1333 (Fed. Cir. 2005) ("Because this construction is driven by the use of [the term] in the context of the claim and is supported by the written description, a broader construction that lacks support in the intrinsic record must yield.").

[22] *Comaper Corp. v. Antec, Inc.*, 596 F.3d 1343, 1348 (Fed. Cir. 2010); *CAE Screenplates Inc. v. Heinrich Fiedler GmbH & Co.*, 224 F.3d 1308, 1317 (Fed. Cir. 2000) ("In the absence of any evidence to the contrary, we must presume that the use of these different terms in the claims connotes different meanings.").

2. "With sufficient resolution for individual microparticles to be distinguished" ('994 patent, claim 1)

Term	Life's Construction	Illumina's Construction
"with sufficient resolution for individual microparticles to be distinguished"	the image resolution is sufficient to distinguish each individual microparticle from every other microparticle	the image resolution is sufficient to distinguish individual microparticles

The dispute here is whether the claim requires that all or only some microparticles be distinguishable from one another. The patent requires that the resolution of the imaging device (and thus the images themselves) be sufficiently clear so that each individual microparticle can be distinguished from every other microparticle, and Life's construction honors this requirement. Illumina's proffered construction, in contrast, would require no more than the ability to distinguish between two single microparticles—meaning that the remaining particles in the image could be clustered together to appear as one large particle. This construction would defeat the purpose of the invention, contradict the specification, and thus should be rejected.

The claim language and the specification indicate that the image resolution for the claimed invention must be sharp enough to distinguish individual microparticles from one another. JA1090 ('994 patent) at 5:7-12; JA1101 at 28:44-45. And the specification demonstrates the necessity for each individual microparticle to be distinguishable from every other microparticle, as the objects of the invention are achieved with "[a] detection means for detecting a sequence of optical signals from ***each*** of the microparticles in the population."[23] JA1088 at 2:20-26. In order to determine the sequence of optical signals from ***each***

[23] The specification also acknowledges that interaction between (*i.e.*, clumping of) microparticles was a problem in the prior art. JA1088 ('994 patent) at 1:40-56 ("However, handling and manipulating large numbers of microparticles … gives rise to many difficulties, including … whether adjacent microparticles will interact, e.g. to degrade or obscure a signal or to inhibit reagent access, and the like.").

microparticle, it is necessary to distinguish ***each*** microparticle from every other microparticle. This is not merely a preferred embodiment; practicing the invention requires that the resolution be sufficiently powerful to distinguish each microparticle from every other microparticle.[24] Life's construction addresses this requirement and should be adopted.

3. "Signal tracking means effective to correlate the optical signals from each of the microparticles in each of the sequence of digital images with said center of said microparticle" ('994 patent, claim 1)

Term	Life's Construction	Illumina's Construction
"signal tracking means effective to correlate the optical signals from each of the microparticles in each of the sequence of digital images with said center of said microparticle"	This "means plus function" limitation requires the same or equivalent structure disclosed in the patent for performing the claimed function, which is to correlate the optical signals from each of the microparticles in each of the sequence of digital images with said center of said microparticle. The disclosed structure is a microprocessor running software that performs the process shown in Fig. 8.	This is a "means plus function" limitation subject to an analysis under 35 U.S.C. § 112, ¶6. The claimed function is: correlating the optical signals from microparticles in a sequence of digital images with the centers of those microparticles. The disclosed structure is: a data processor that runs software that assigns pixels of the fluorescent images of the microparticles to the microparticle centers.

The parties agree that this claim limitation is written in the form of a "means-plus-function" claim and thus must be construed in view of the requirements of 35 U.S.C. § 112 ¶ 6. "Claim construction of a means-plus-function limitation includes two steps. First, the court must determine the claimed function. Second, the court must identify the corresponding structure in the written description of the patent that performs the function."[25] "In order to qualify as corresponding, the structure must not only perform the claimed function, but the specification

[24] *See Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1369 (Fed. Cir. 2001) ("Notably, the 'objects of the invention are achieved by means of a panel-joining system having the features recited in the appended claims'…. Thus, the specification teaches that the invention as a whole, not merely a preferred embodiment, provides for play in the positioning of floor panels.").

[25] *Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 448 F.3d 1324, 1332 (Fed. Cir. 2006) (internal citation omitted).

must clearly associate the structure with performance of the function."[26]

For the first step, the parties do not dispute that the claimed function is "to correlate the optical signals from each of the microparticles in each of the sequence of digital images with said center of said microparticle." JA1101 ('994 patent) at 28:46-49. The dispute is over the scope of the corresponding structure. The parties agree that the structure is a processor that runs software, but disagree about what the software is designed to do. "In cases involving a computer-implemented invention in which the inventor has invoked means-plus-function claiming, [the Federal Circuit] has consistently required that the structure disclosed in the specification be more than simply a general purpose computer or microprocessor"—the patentee must disclose an algorithm or, at a minimum, a step-by-step process that performs the claimed function.[27] Language that simply describes the function to be performed is not sufficient.

The only disclosure in the specification that remotely resembles an algorithm is the system depicted in Figure 8. JA1087. That figure and the accompanying text in the specification demonstrate how optical signals are correlated with the centers of microparticles: after calibrating the focal plane, reagents are delivered via the fluidics controller and interact with the analytes attached to the microparticles. JA1092 at 9:32-61. The system first focuses on the plane that runs along the tops of the beads (806). It then focuses on the plane intersecting the hemispheres of the beads (step 808) and collects a fluorescent image (optical signals) (step 810). The system refocuses on the plane running along the top of the beads (step 814) and collects an image of the bead centers (step 816). The two images are then transferred to a data server (812),

[26] *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 296 F.3d 1106, 1113 (Fed. Cir. 2002).

[27] Where "the disclosed structure is a computer, or microprocessor, programmed to carry out an algorithm, the disclosed structure is not the general purpose computer, but rather the special purpose computer programmed to perform the disclosed algorithm." *Aristocrat Techs. Austl. Pty Ltd. v. Int'l Game Tech.*, 521 F.3d 1328, 1333 (Fed. Cir. 2008).

where the data processor (818) assigns (correlates) pixels of the fluorescent image to the microparticle centers. JA1087 at Fig. 8; JA1092 at 9:32-10:27; *id.* at 9:5-31 (describing how the pixels are assigned); JA1086 at Fig. 7. This is a means to achieve an outcome,[28] which is correlating the optical images with the microparticle centers.

Illumina claims that the disclosed algorithm assigns pixels of the fluorescent images to the microparticle centers. But this construction "simply describes the function to be performed, not the algorithm by which it is performed."[29] In a means-plus-function claim, "simply reciting 'software' without providing some detail about the means to accomplish the function is not enough," and Illumina's proposed construction is thus erroneous and should be rejected.[30]

4. "Tracking positions of the microparticles" ('505 patent, claim 1)

Term	Life's Construction	Illumina's Construction
"tracking positions of the microparticles"	following the movement of microparticles during a sequence of processing steps	This preamble term is not a substantive limitation on claim 1, and thus does not require construction. One of ordinary skill would understand this term to relate only to the intended use of the claimed invention, and in that regard, to relate to the "correlating" term in the body of the claim.

Though the specification describes the "tracking" function as a necessary aspect of the claimed invention, and though Illumina is specifically relying on the "tracking" language in the

[28] *See Aristocrat Techs.*, 521 F.3d at 1334.

[29] *Id.; see also Blackboard, Inc. v. Desire2Learn, Inc.*, 574 F.3d 1371 (Fed. Cir. 2009); *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1340-41 (Fed. Cir. 2008).

[30] *Finisar Corp.*, 523 F.3d at 1040-41. Not too that when a means-plus-function claim is not tied to a disclosure of an algorithm in the specification, the claim is indefinite under 35 U.S.C. § 112 ¶ 2. *Aristocrat*, 521 F.3d at 1337-38. Illumina's interpretation of this means-plus-function claim does not tie the claim to an algorithm, and the construction should thus be rejected because, in addition to the reasons explained above, adopting it would render the claim invalid.

pending reexamination of this patent to distinguish its claimed invention over prior art, Illumina asks this Court to hold that "tracking" is not a claim requirement because it appears in the preamble of the claim. Illumina's argument should be rejected. Where a term in the preamble of a claim states "a necessary and defining aspect of the invention"—here tracking positions of microparticles, *i.e.*, "following the movement of microparticles during a sequence of processing steps"—it is a substantive limitation of the claim. This is particularly true where, as here, a patentee relies on the preamble in an effort to distinguish the claimed invention over prior art.[31]

The tracking function is emphasized throughout the specification as a key aspect of the claimed invention, explaining that tracking microparticles as they move through a series of processing steps distinguishes the claimed invention over the prior art. For example:

> However, handling and manipulating large numbers of microparticles, e.g. tens to hundreds of thousands, for carrying out specific chemical and/or biochemical analyses gives rise to many difficulties, including whether sufficient signal is generated on individual microparticles for detection, how to track individual microparticles through multiple steps of a process, … and the like. It would be especially desirable if such system and apparatus permitted the tracking and analysis of multiple analytes anchored to separate particles through a sequence of several processing or analysis steps.

JA1062 ('505 patent) at 1:40-64. The Summary of the Invention recites that the claimed invention is intended to satisfy the need for such tracking, stating: "Accordingly, objects of our invention include, but are not limited to … providing an apparatus for simultaneously tracking the positions of individual microparticles in a population of microparticles disposed in a flow

[31] *See On Demand Mach. Corp. v. Ingram Indus.*, 442 F.3d 1331, 1343 (Fed. Cir. 2006); *see also Poly-America L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309-10 (Fed. Cir. 2004) (when the preamble "recites additional structure or steps underscored as important by the specification, the preamble may operate as a claim limitation." (internal quotations omitted)); *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008); *Vizio, Inc. v. TVP Tech., Ltd.*, __ F.3d __, 2010 WL 2079769 at **8-10 (Fed. Cir. 2010). *See also Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 952-53 (Fed. Cir. 2006) ("When limitations in body of patent claim rely upon and derive antecedent basis from claim preamble, then preamble may act as necessary component of claimed invention.").

chamber as a closely packed planar array…." *Id.* at 1:66-2:19. The specification further explains: "An important feature of detection means (114) of the invention is the ability to keep track of individual microparticles though multiple process steps and/or cycles." JA1065 at 8:48-50. "[T]he patentee here has clearly indicated via the specification and the prosecution history that the invention provides, as an essential feature, [tracking positions of the microparticles]. It is therefore appropriate to construe the claims so as to ensure that they, too, require that feature."[32]

Indeed, Illumina relies on the importance of the tracking function in the pending reexamination of this patent in an effort to distinguish the claimed invention over the prior art, stating to the PTO: "These groups of [prior art] references do not contain disclosures directed to the difficulties inherent in 'tracking positions of the microparticles during a sequence of processing steps' as provided by claim 1 of the '505 patent." *See* Exh. B at 11; *see also id.* at 14 (distinguishing a prior art reference that, in Illumina's view, does not contain the substantive limitation of "tracking positions of microparticles during a sequence of processing steps"); 35 (same). A preamble term is a claim limitation that limits the scope of the claims where, as here, "the written description and ***applicant's statements during the prosecution emphasize this feature of the invention***."[33]

The claim requirement of "tracking positions of the microparticles" is thus a substantive claim limitation and is appropriate for construction. The proper construction as proposed by Life is "following the movement of microparticles during a sequence of processing steps." The passages of the specification, cited above, support this construction. And the purpose of the

[32] *MBO Labs., Inc.*, 474 F.3d at 1330.

[33] *Computer Docking Station Corp.*, 519 F.3d at 1375.

tracking step—monitoring movement—is also acknowledged in the specification's statement that "more movement of microparticles within a planar array increases the computational and measurement burden of tracking positions of microparticles by image processing software." JA1064 at 5:44-50. In other words, when the particles move, the invention must track that movement, even if such tracking burdens the system. Life's construction is consistent with the above and should be adopted.[34] Illumina has not proposed a construction of this term.

5. "Processing the plurality of digital images, wherein said processing includes correlating the optical signals generated at each microparticle with its corresponding image in each of the plurality of digital images" ('505 patent, claim 1)

Term	Life's Construction	Illumina's Construction
"processing the plurality of digital images, wherein said processing includes correlating the optical signals generated at each microparticle with its corresponding image in each of the plurality of digital images"	analyzing the digital images so as to match the light signal that comes from each microparticle during each process step with the images showing the different positions of the microparticle during the sequence of processing steps	processing the digital images so as to match the light that comes from each microparticle in one image with the light that comes from that microparticle in a second image

The parties agree that the "correlating" requirement of this claim should be construed as matching the light signal (*i.e.,* optical signal) of the claim with something; the parties disagree on what that "something" is. Life's construction—that the invention requires that the light signal from one image be matched with the position of the microparticle shown in a second image—should be adopted because it is supported by the claim language and the specification. Illumina,

[34] Dictionary definitions of "tracking" are also consistent. *See, e.g.,* Merriam Webster 519 (2005) ("track" is "to observe the moving path of") [Exh. E]; Am. Heritage Dictionary 1896 (Houghton-Mifflin Co. 3d ed. 1992) ("5. To observe or monitor the course of (aircraft, for example), as by radar") [Exh. D]. Courts may rely "on dictionary definitions when construing claim terms, so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1322-23 (Fed. Cir. 2005).

on the other hand, contends that the light signal from one image must be matched with the signal from a second image. This proposal should be rejected as unsupported by the specification.

The claim language central to the parties dispute is "correlating the optical signals generated at each microparticle with ***its*** corresponding image." This claim language plainly recites the requirement that the optical signals must be matched with the image of each microparticle, not a later image of the optical signals. Had the latter been required, the claim would have recited, "correlating the optical signals generated at each microparticle with ***their*** corresponding image." This is an instance where the ordinary meaning of the claim language is readily apparent, and "claim construction in such cases involves little more than application of the widely accepted meaning of commonly understood words."[35]

This ordinary meaning is supported by the specification, which explains that the correlating step involves determining the position of microparticles and then assigning (*i.e.*, correlating) pixels to the microparticles that ultimately represent the optical signals emitted from the analytes attached to the microparticles. *See* JA1061-1071 ('505 patent) at 8:48-9:31; 10:3-20; 18:60-19:6; 19:38-20:15; Fig. 8. This "key feature" of the invention is consistently described as correlating the optical signals with the positions of the microparticles, not as correlating one image of the optical signals with a second image of the optical signals.[36] JA1062 at Abstract. Nothing in the specification suggests that the correlating requirement involves matching one

[35] *Phillips,* 415 F.3d at 1314.

[36] Illumina has implicitly adopted Life's construction in the pending reexamination of the '505 patent. Exh. B at 39 (describing the DiMilla reference and suggesting that determining the center and position of microparticles is part of the "correlating" step).

image of the optical signals with another.[37] Life's construction, on the other hand, is supported by the plain language of the claim and the specification and should be adopted.

Illumina's proposed construction would also render the claim invalid under section 112 of the Patent Act for lack of written description and enablement because there is no support in the specification for the proposed matching of "the light that comes from each microparticle in one image with the light that comes from that microparticle in a second image."[38] This is another reason for rejecting Illumina's proposed construction and adopting Life's.

B. THE BALASUBRAMANIAN PATENT (NO. 7,232,656)

6. "Generating sequence reads" (claims 1, 7)

Term	Life's Construction	Illumina's Construction
"generating sequence reads"	determining the identity and order of at least two nucleotide bases	determining the identity of at least two nucleotide bases

The parties agree that "generating sequence reads" requires the identification of at least two nucleotide bases.[39] The parties disagree, however, whether the term also requires one to determine the order of those bases. Life's proposed construction requires that the order of at least two nucleotide bases be determined; Illumina's proposed construction contains no such requirement. Life's proposed construction is correct because it is based on the plain language of

[37] A patentee is "not entitled to a claim construction divorced from the context of the written description and prosecution history." *Old Town Canoe, Inc. v. Confluence Holdings Corp.*, 448 F.3d 1309, 1318 (Fed. Cir. 2006).

[38] *See* 35 U.S.C. § 112 ¶ 1.

[39] There is ample support for this requirement, including in the Abstract: "The method comprises randomly fragmenting the individual's genome and generating sequence reads of multiple bases on all fragments of the individual's genome, aligning the sequence reads generated with a known genomic reference sequence, and analyzing variations between the sequence reads derived from the individual's genome and the known genomic reference sequence." JA1102 ('656 patent).

the claims, the purpose of the invention and common sense. The purpose of the claim requirement of "generating sequence reads of multiple bases on all fragments of said genome" is to gain information about the "sequence," a word which, by its plain meaning, connotes the order of at least two nucleotide bases. A sequence is defined as "a following of one thing after another; succession," and DNA sequencing is the "[d]etermination of the ***order*** of nucleotides in a DNA molecule or DNA fragment by DNA sequencing techniques, e.g., Maxam-Gilbert's method or Sanger's method."[40] Necessarily, "generating sequence reads" means determining the order of the nucleotides in the sequence. This construction involves "little more than the application of the widely accepted meaning of commonly understood words."[41]

The specification confirms this plain meaning, as all methods of sequencing described therein require some sort of order determination. For example, the specification explains:

> When the arrays are composed of polynucleotides they may be used in conventional techniques for obtaining genetic sequence information. Many of these techniques rely on the stepwise identification of suitably labeled nucleotides, referred to in U.S. Patent No. 5,634,413 as 'single base' sequencing methods….

JA1112 at 9:6-11. The other embodiments also require that both the identity ***and*** the order of the nucleotide bases be determined, even if the identified nucleotides do not appear side-by-side. For example the specification explains:

> Identifying the nucleotides at selected positions in the genome may be carried out by contacting the array sequentially with each of the bases A, T, G, and C, under conditions that permit the polymerase reaction to proceed, and monitoring the incorporation of a base at selected positions in the complementary sequence…. Template DNA (genomic fragments) can be contacted with each of the bases A, T, and G, added sequentially or together, so that the complementary strand is extended up to a position that requires C…. the addition of C is followed by

[40] Am. Heritage Dictionary 1646 (Houghton-Mifflin Co. 3d ed. 1992) [Exh. D]; Concise Dictionary of Biomedicine and Molecular Biology 319 (1996) [Exh. F].

[41] *Phillips*, 415 F.3d at 1314.

monitoring the next base incorporation (using a labeled base).

JA1113 at 11:49-12:24. There is no reference in the specification to any sequencing procedure that determines only the identity of the nucleotide bases and not the order. There is a reason for this: the invention ultimately aims to align a sequence read with a known reference sequence. JA1102 at Abstract; JA1111 at 8:24-30; JA1118-19 at claims 1, 7; *see also* JA1721 (explaining that the invention is meant to detect variations on the level of individual nucleotide sequences). By definition, the alignment of two texts requires knowing the order of the letters or words in the texts. It follows, then, that a sequence read cannot be aligned if the order of the nucleotide bases is unknown. Illumina's construction therefore is inconsistent with the claim as a whole, the specification, and with the plain meaning of "sequence." Life's construction is consistent with each of the foregoing and should be adopted.[42]

[42] *Pause Tech.*, 419 F.3d at 1333 ("Because this construction is driven by the use of [the term] in the context of the claim and is supported by the written description, a broader construction that lacks support in the intrinsic record must yield.").

7. "An array of polynucleotide molecules" (claim 3);

8. "Which molecules can be individually resolved by optical microscopy" (claim 3);

9. "Arraying the fragments such that different fragments can be individually resolved by optical microscopy" (claim 7)

Term	Life's Construction	Illumina's Construction
"an array of polynucleotide molecules"	an array of single DNA fragments, as opposed to clusters of many DNA fragments of the same type	an arrangement of different types of DNA fragments
"which molecules can be individually resolved by optical microscopy"	each DNA molecule in the array can be distinguished from every other molecule by optical microscopy	wherein the polynucleotides having different sequences can be distinguished from each other using a microscope
"arraying the fragments such that different fragments can be individually resolved by optical microscopy"	separating single DNA fragments (as opposed to clusters of DNA fragments) on a support so that each fragment can be distinguished from every other fragment by optical microscopy	arranging the fragments so that the fragments having different sequences can be distinguished from each other using a microscope.

These disputed terms all relate to the "arraying" and subsequent resolution (*i.e.*, viewing) of DNA fragments and, though separate terms, can generally be treated together in terms of the analysis that underlies the proper construction for each. The context of the terms in claim 3 of the '656 patent is that the genomic DNA fragments "are immobilized onto the surface of a solid support to form an array of polynucleotide molecules capable of interrogation and which molecules can be individually resolved by optical microscopy." JA1118. Fig. 2 of the patent, above, illustrates an individual molecule (14) immobilized (via microsphere 11) to a solid support. *See* JA1104.

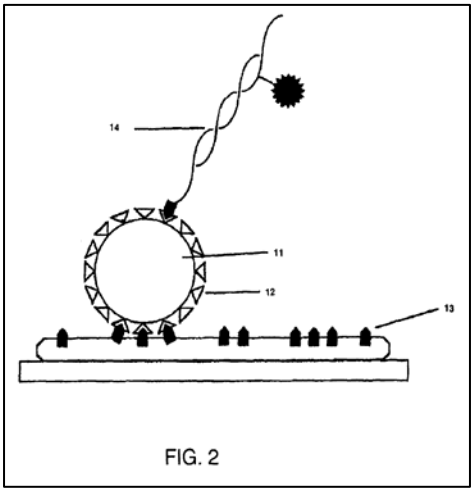

FIG. 2

Claim 7 similarly requires "arraying the genome fragments such that different fragments

can be individually resolved by optical microscopy." JA1119. The purpose of the claimed "arraying" of genomic fragments is to view the fragments individually. JA1109 at 4:8-13. There appears to be no dispute that the claimed arraying and resolution process requires some separation of DNA fragments, but the parties dispute the extent of separation and distinction required. Life's construction, consistent with the express definitions and numerous examples in the specification, requires that the DNA fragments in the array be separated from one another so that each fragment can be distinguished from every other fragment. The patent describes this as a single molecule array; this is expressed in the claim requirement that the fragments be "individually resolved." JA1118-19 at 22:56-61 (claim 3), 23:10-21 (claim 7).

The specification unambiguously and expressly defines arrays to be single molecule arrays, not cluster arrays: "The terms 'arrayed polynucleotides' and 'polynucleotide arrays' are used herein to define a plurality of single molecules that are characterized by comprising a polynucleotide." JA1109 at 4:51-54. The specification further explains that "[t]he term 'single molecule' is used herein to distinguish from high density multi-molecule arrays in the prior art, which may comprise distinct clusters of many molecules of the same type." *Id.* at 4:33-36. Finally, the specification defines "[t]he term 'individually resolved' [] to indicate that, when visualized, it is possible to distinguish one molecule on the array from its neighboring molecules." *Id.* at 4:37-39. Consistent with the specification and claim language, Life construes "individually resolved" to mean that "each DNA molecule in the array can be distinguished from every other molecule by optical microscopy."

Illumina, in contrast, seeks to contradict this intrinsic evidence, proposing a construction whereby the fragments may be arrayed so that fragments sharing the same sequence are clustered together; that is, all that is required is that ***clusters*** of fragments having different sequences be

distinguishable.[43] But such a construction contradicts the claim language and the uniform teaching of the specification that the invention entails single molecule arrays, not cluster arrays:

- **3:13-23**: "The arrays of the present invention comprise what are effectively single molecules. This has many important benefits for the study of the molecules and their interaction with other biological molecules. In particular, fluorescence events occurring on each molecule can be detected using an optical microscope linked to a sensitive detector, resulting in a distinct signal for each molecule. When used in a multi-step analysis of a population of single molecules, the phasing problems that are encountered using high density (multi-molecule) arrays of the prior art, can be reduced or removed."

- **4:09-13**: "According to the present invention, the single molecules immobilized onto the surface of a solid support should be capable of being resolved by optical means. This means that within the resolvable area of the particular imaging device used, there must be one or more distinct images each representing one molecule."

- **9:41-46**: "Because sequencing is performed at the single molecule level, the sequencing can be carried out on different polynucleotide sequences at one time without the necessity for separation of the different sample fragments prior to sequencing. This sequencing also avoids the phasing problems associated with prior art methods."

- **1:33-45** (describing the arrays in the prior art): "Typically, these arrays may be described as 'many molecule' arrays, as distinct regions are formed on the solid support comprising a high density of one specific type of polynucleotide;" **2:18-29** (describing problems with prior art arrays): "the use of high-density arrays in a multi-step analysis procedure can lead to problems with phasing…. This problem is recognized in the sequencing procedure described in U.S. Patent No. 5,302,509."

- **4:33-36**: "The term 'single molecule' is used herein to distinguish from high density multi-molecule arrays in the prior art, which may comprise distinct clusters of many molecules of the same type."

- **4:66-5:2**: "These high density arrays [of the present invention] are in contrast to other arrays which may be described in the art as 'high density' but which are not necessarily as high and/or which do not allow single molecule resolution."

- **4:37-39**: "The term 'individually resolved' is used herein to indicate that, when visualized, it is possible to distinguish one molecule on the array from its neighboring molecules."

[43] It is unclear how these clusters would be formed under Illumina's construction. Cluster arrays are generated by amplification, but during prosecution the patentee emphasized that the arrayed fragments are ***not*** selectively amplified. JA1720 (9/28/2006 Amendment at 10).

- **5:54-57**: "Single molecules may be arrayed by immobilization to the surface of a solid support. This may be carried out by any known technique, provided that suitable conditions are used to ensure adequate separation of the molecules."

JA1108-12. These statements in the specification are exemplary; indeed, the specification includes no less than seventeen different references to individually resolvable, single molecule arrays, leaving no doubt that the invention is what is described—individually resolvable single molecule arrays. The patentee explicitly defined its arrays as single-molecule, and expressly disclaimed multi-molecule (cluster) arrays. Where a patentee defines a term, as here, that definition governs.[44] And when the specification shows that the invention does not include a particular feature—here, cluster arrays—"that feature is deemed to be outside of the reach of the claims of the patent."[45] Life's constructions align with the definitions and descriptions in the specification; Illumina's do not and should therefore be rejected.[46]

C. THE MACEVICZ PATENT (NO. 7,598,035)

10. "Population of polynucleotide fragments" (claims 1, 3)

Term	Life's Construction	Illumina's Construction
"population of polynucleotide fragments"	the collection of every fragment that is made when DNA is digested by a restriction enzyme	a collection of polynucleotide fragments

The title of this patent is "Method and Compositions for Ordering Restriction Fragments," and the patent repeatedly defines "population[s] of polynucleotide fragments" as

[44] *Phillips*, 415 F.3d at 1316.

[45] *Id.; Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1319 (Fed. Cir. 2006).

[46] Illumina's proposal that fragments of the same type need not be distinguishable from one another is not only unsupported, but is expressly contradicted by at least one embodiment in the specification. JA1109 ('656 patent) at 4:27-32 ("In some applications all the molecules in the single array will be the same, and may be used to interrogate molecules that are largely distinct. In other applications, the molecules on the array may all, or substantially all, be different, e.g. less than 50%, preferably less than 30% of the molecules will be the same.").

collections of every polynucleotide fragment generated from digestion with a restriction enzyme.[47] The specification demonstrates that restriction enzyme digestion of polynucleotides is at the core of the invention, and Life's construction properly makes that express. Illumina, however, seeks to broaden the term in a manner that lacks intrinsic support and is contradicted by the object of the invention. Moreover, if adopted, Illumina's construction would likely render the patent invalid for lack of written description and enablement in violation of 35 U.S.C. § 112; this fact further supports the Court's adoption of Life's construction.

First, the requirement of "every fragment" in Life's construction is based on claim 1, which requires the use of "***each*** fragment of a population of polynucleotide fragments, wherein ***each*** said fragment is in a vector," and on claim 3, which requires "inserting ***each*** of said polynucleotide fragments from said population into a vector." JA1118. In a recent filing with the PTO related to the pending reexamination on this patent, Illumina confirmed the requirement that each and every fragment be used, explaining that claims 1 and 3 of the patent "are directed to providing a number of vectors, which all together contain each of the polynucleotide framents from a population of polynucleotides." Exh. C at 14 (emphasis in original).

Second, the fragments must be generated by a restriction enzyme digest. Indeed, the specification repeatedly explains that the starting point for the claimed invention is digestion of a polynucleotide ***with a restriction enzyme***. The reason is that such enzymes provide known and predictable information as to the DNA sequence surrounding the cleavage sites, and that information is used to "map" the fragments. Without this information, such mapping would be impossible. The specification states:

[47] A restriction enzyme is an enzyme that recognizes a particular DNA sequence (usually 4-8 bases in length) and cuts the DNA at or near the sequence. *See* Tom Strachan and Andrew P. Read, Human Molecular Genetics at 4.2.2 (2d ed. 1999), *available at* http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hmg [Exh. G].

> In accordance with the invention, a polynucleotide is separately digested with different combinations of restriction endonucleases and the ends of the restriction fragments are sequenced so that pairs of sequences from each fragment are produced. A physical map of the polynucleotide is constructed by ordering the pairs of sequences by matching the identical sequences among such pairs resulting from all of the [restriction] digestions.

JA1127 at 2:30-37. This passage does not stand alone. A comprehensive review of the specification leaves no doubt that the invention to be practiced requires the use of ***restriction fragments***:

- **1:14-18**: "This invention relates … to a method of providing high resolution physical maps by sequence analysis of concatenations of segments of restriction fragments ends."
- **2:7-9**: "Another object of my invention is to provide a method of ordering restriction fragments from multiple enzyme digests by aligning matching sequences of their ends."
- **2:25-50**: My invention achieves these and other objects by providing methods and materials for determining the nucleotide sequences of both ends of restriction fragments obtained from multiple enzymatic digests of a target polynucleotide…."
- **2:59-62**: "This invention provides a means for generating a high density physical map of target polynucleotides based on the positions of the restriction sites of predetermined restriction endonucleases."
- **4:12-15**: "In accordance with the present invention, segments of nucleotides at each end of restriction fragments produced from multiple digestions of a polynucleotide are sequenced and used to arrange the fragments in a physical map."

JA1127-28. There is indeed no reference in the specification to fragments generated by any mechanism other than restriction enzyme digestion.[48] This is not a situation where a party is

[48] The specification describes an embodiment where the sequences of the ends of cDNA molecules, not polynucleotide fragments, are determined. Illumina may argue that this teaches against limiting populations of fragments to those generated by restriction enzyme digests. But cDNA is never referred to as a fragment in the specification, and therefore this embodiment falls outside of the claims. *See 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 … 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."). Illumina has confirmed this distinction in the pending reexamination of this patent. *See* Exh. C at 40-41 ("Velculescu does not disclose or even remotely suggest the formation of a

attempting to read a limitation into claims that could support a broader reading; this is an instance where the proposed limitation is consistently described in the specification as ***the*** invention, not merely a preferred embodiment.[49] Thus, because Life's proposed construction is "driven by the use of [the term] in the context of the claim and is supported by the written description, a broader construction that lacks support in the intrinsic record must yield."[50]

11. "Vector" (Claims 1, 3, 5)

Term	Life's Construction	Illumina's Construction
"vector"	a self-replicating nucleic acid molecule which may be employed to introduce a nucleic acid sequence or gene into a cell; such nucleic acid molecules are designated as vectors and may be in the form of a plasmid, hybrid plasmid, cosmid, viral vector, bacteriophage vector, etc.	a nucleic acid molecule which may be employed to introduce a nucleic acid sequence or gene into a cell.

The specification does not expressly define a "vector" for purposes of these claims, but the specification does indicate that a vector must both be self-replicating and be able to be used to introduce a nucleic acid sequence into a cell. Life's construction is based on these requirements; Illumina's proposed construction ignores the requirement that the vector be self-replicating. Life's construction should be adopted.

VECTOR, PER SE (E.G., PLASMID, HYBRID PLASMID, COSMID, VIRAL VECTOR, BACTERIOPHAGE VECTOR, ETC.):
This subclass is indented under the class definition. Subject matter directed to self-replicating nucleic acid molecules which may be employed to introduce a nucleic acid sequence or gene into a cell; such nucleic acid molecules are designated as vectors and may be in the form of a plasmid, hybrid plasmid, cosmid, viral vector, bacteriophage vector, etc.

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vector, which contains a *pair* of *oligonucleotide end segments*, derived from opposite ends of the *same* polynucleotide *fragment*. The constructs described in Velculescu only have only [sic] a *single tag sequence* derived from any given *cDNA molecule.*") (emphasis in original).

[49] *Honeywell Int'l, Inc.*, 452 F.3d at 1318 ("On at least four occasions, the written description refers to the fuel filter as 'this invention' or 'the present invention.'").

[50] *Pause Tech.*, 419 F.3d at 1333.

The specification discloses preferred vectors pUC19, λ-based phages, or like vectors, which are capable of both self-replication and introducing nucleic acid sequences into cells.[51] These examples in the specification are consistent with the PTO's definition of "vectors" as "self-replicating nucleic acid molecules which may be employed to introduce a nucleic acid sequence or gene into a cell." This definition is reproduced above.[52]

The definition employed by the PTO is in the very art unit in which this patent was examined and should be deemed to have particular weight here. Moreover, technical dictionary definitions agree that a vector must be self-replicating.[53] There is nothing in the specification indicating a definition of "vector" contrary to the definition provided by the PTO. Life's construction embraces the widely-accepted definition of vector and should be adopted here.[54]

12. "Ligating together the cleaved ends produced by said removing" (Claim 1); "Ligating the pair of segments together" (Claim 5)

Term	Life's Construction	Illumina's Construction
"ligating together the cleaved ends produced by said removing" "ligating the pair of segments together"	For a piece of DNA that was cut by a restriction enzyme, connecting one of the cut ends directly to the other cut end.	Connecting the cut ends

The first issue presented by this term is whether the DNA fragments must come from a fragment cut by a restriction enzyme. The answer is yes, as explained above. The second issue,

[51] *See supra* n.47 at 4.3.2, 4.10 (Exh. G).

[52] USPTO Classification Definitions for Chemistry: Molecular Biology and Microbiology, *available at* http://www.uspto.gov/web/patents/classification/uspc435/defs435.htm (last accessed May 27, 2010) at 320.1; *see also* Exh. I.

[53] *See, e.g.,* Concise Dictionary of Biomedicine and Molecular Biology 952 (1996) (defining vector as a "plasmid or viral DNA molecule into which another DNA molecule can be inserted without disruption of the ability of the molecule to replicate itself") [Exh. F].

[54] *See, e.g., Erbe Elektromedizin GmbH v. Int'l Trade Comm'n*, 566 F.3d 1028, 1038 (Fed. Cir. 2009); *Old Town Canoe Co.*, 448 F.3d at 1316-17.

and the one that is in dispute for this term, is whether the requirement of "ligating together the cleaved ends" or "ligating the pair of segments together" requires that the ligation (connection) be directly between the cleaved fragments of DNA. The answer again is yes: the claim language and specification indicate that the "ligating" requirement of the patent involves the connection—ligation—of two fragments that were cut apart by a restriction enzyme. *See, e.g.*, JA1128-30 ('035 patent) at 4:18-23 ("Excised segments from the same fragment are ***ligated*** together to form a pair of segments."); 5:28-30 ("The vector is then recircularized by ligating the two ends together, thereby forming a pair of segments."); 8:4-7 ("The fragments comprising the vector and ends (i.e. segments) of the restriction fragment insert are isolated, e.g. by gel electrophoresis, blunted (316) and recircularized (320).")). Life's construction is consistent with these disclosures—ligating means that "for a piece of DNA that was cut by a restriction enzyme, connecting one of the cut ends directly to the other cut end."

Illumina seeks to avoid that limitation and preserve its ability to argue that (1) the ligating requirement can be met independent of the restriction enzyme digestion and that (2) two ends can be connected together, either directly ***or*** via a piece of linking DNA. These are attempts to reach outside the scope of the invention and are not supported by the specification or the prosecution history,[55] which both reject the notion that a piece of linking DNA can be inserted between the two cut ends and still constitute ligation of those two ends.[56]

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[55] In an amendment submitted during the prosecution of parent application No. 10/706,118, the patentee stated: "It is the applicant's view that two sequences that are separated by sixteen nucleotides … would not be considered 'ligated together.'" Exh. H at 6.

[56] In its papers in the pending reexamination proceedings on this patent, Illumina appears to concede that ligation means "directly connected." *See* Exh. C at 11 ("These segments, which remain connected by the linearized vector, may be ligated directly together, generally after treatment to blunt end the cleaved ends of the segments…, thereby forming a 'linked pair' of segments derived from the same fragment in a single vector."); *id.* at 14 ("The linearized vector formed in Claim 3 may be re-circularized via ligation, such that the cleaved ends of the two

CONCLUSION

For the aforementioned reasons, Plaintiffs respectfully request that the Court adopt their proffered constructions of the disputed claim terms.

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paired segments are ligated directly together (i.e., are linked directly to each other)."); *id.* at 26 ("The insertion of a replacement nucleotide sequence between the cleaved ends is not the same as the ligation, recited in present Claim 1, of the cleaved ends of the two fragment segments, which remain attached to the vector after the type IIs restriction endonuclease cleavages.").

CERTIFICATE OF SERVICE

I hereby certify that on May 27, 2010 I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing to:

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