UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

VERINATA HEALTH, INC., et al.,

Plaintiffs,

v.

ARIOSA DIAGNOSTICS, INC,

Defendant.

Case No. 12-cv-05501-SI
Consolidated Case: 14-cv-1921-SI

CLAIM CONSTRUCTION ORDER RE: US PATENT NO. 7,955,794

Re: Dkt. No. 176

On December 16, 2014, the Court heard argument on the parties' proposed claim constructions. Having considered the arguments of the parties and the papers submitted, the Court construes the disputed terms as follows.

BACKGROUND

I. Procedural History

This dispute began in 2011, when Ariosa[1] filed a declaratory relief action against Sequenom, seeking a declaration that Ariosa's "Harmony Test" does not infringe any claims of U.S. Patent No. 6,258,540 ("the '540 patent"). *Aria Diagnostics, Inc. v. Sequenom, Inc.*, C 11-6391-SI (filed Dec. 19, 2011). Sequenom filed a counterclaim against Ariosa, asserting infringement of Sequenom's '540 patent. Subsequently, two other companies, Natera and Verinata, also filed declaratory judgment actions in this Court seeking judgments that their products do not infringe Sequenom's '540 patent and asserting that the '540 patent is invalid. *See Natera Inc. v. Sequenom, Inc.*, C 12-0132-SI (filed Jan. 6, 2012) (regarding Natera's "Non-Invasive Paternity Test"); *Verinata Health, Inc. v. Sequenom, Inc. (Verinata I)*, C 12-0865-SI

[1] Formerly known as Aria Diagnostics, Inc.

(filed Feb. 22, 2012) (regarding Verinata's "Verifi Prenatal Test"). Sequenom then filed counterclaims alleging that Natera, DNA Diagnostics Center, Verinata, and Stanford are infringing the '540 patent. *See id.* On October 30, 2013, this Court held the '540 patent to be invalid. Sequenom has appealed this ruling to the Federal Circuit, and that appeal is pending. C 11-cv-6391 SI, Docket No. 254.

In *Verinata I,* Verinata and Stanford also alleged that Sequenom is infringing U.S. Patent Nos. 7,888,017 ("the '017 patent"), 8,008,018 ("the '018 patent"), and 8,195,415 ("the '415 patent"). In addition, Verinata and Stanford filed a case alleging that Ariosa and LabCorp are infringing U.S. Patent Nos. 8,296,076 ("the '076 patent") and 8,318,430 ("the '430 patent"). *See Verinata Health, Inc. v. Ariosa Diagnostics, Inc. (Verinata II)*, C 12-5501-SI (filed Oct. 25, 2012). Finally, Illumina[1] filed a case alleging that Ariosa is infringing U.S. Patent No. 7,955,794 ("the '794 patent"). *See Illumina, Inc. v. Ariosa Diagnostics, Inc.*, C 14-1921-SI (filed April 25, 2014). This final action was consolidated with *Verinata II.*

II. Factual Background

These patents involve methods to conduct non-invasive prenatal DNA testing. Fetal DNA testing can aid sex determination, blood typing and other genotyping, and detection of pre-eclampsia in the mother. It can also detect fetal aneuploidy, which is a disorder in which the fetus has an abnormal number of chromosomes, instead of the normal 23 pairs. Common aneuploidy disorders include Down syndrome (a third copy, or "trisomy," of chromosome 21), Edwards syndrome (a third copy of chromosome 18), and Patau syndrome (a third copy of chromosome 13).

Prior to these patents, testing fetal DNA required invasive techniques that took samples from the fetus or placenta. However, invasive prenatal testing presented risks to both the fetus and the mother. Scientists began researching various techniques to make these prenatal diagnoses non-

[1] In January of 2013, Illumina acquired Verinata. ..

invasively. Initially, non-invasive research had focused on detecting fetal cells that had passed through the amniotic sac into the mother's bloodstream. The fetal cells then had to be separated from the much more common maternal cells. This process of isolating intact fetal cells was labor-intensive and produced unreliable results.

The '540 patent followed the discovery in 1996-1997 by Drs. Lo and Wainscoat that fetal DNA is detectable in maternal serum or plasma samples in extra-cellular or cell-free form. According to Sequenom, prior non-invasive research had focused on detecting fetal cells because the presence of cell-free fetal DNA was not known. Evans Decl. ¶ 40. Therefore, the significance of the discovery by Drs. Lo and Wainscoat was that the process of isolating fetal cells was not necessary because fetal DNA was present outside of cells, as "extracellular" or "cell-free DNA" suspended together with the mother's DNA in the maternal bloodstream. This was a more efficient and reliable method then previous non-invasive techniques.

A decade later, Drs. Quake and Fan at Stanford further advanced the science in non-invasive prenatal testing using molecular counting techniques. Previously, researchers had believed that because aneuploidies do not present a mutational change in the DNA sequence (but are merely a change in the number of chromosomes), they would need to distinguish fetal DNA from maternal DNA in order to diagnose fetal aneuploidy non-invasively. The Stanford researchers used advanced DNA sequencing techniques, such as digital polymerase chain reaction ("PCR") and massive parallel sequencing. They discovered a method to diagnose fetal aneuploidy through their molecular counting techniques, without needing to distinguish the maternal DNA from the fetal DNA. Stanford and Verinata claim that these techniques are much more efficient and effective than those utilized previously. They further refined their method by teaching how to correct for sequence tag density variances, how to selectively analyze specific DNA sequences, and how to generate a library from a pool of multiple samples, all in order to increase the accuracy and efficiency of the prenatal tests. The '017, '018, and '415 patents reflect some of the

discoveries.

The ’794 patent, which is the subject of this Claim Construction Order, is not confined to prenatal DNA testing. Titled "Multiplex Nucleic Acid Reactions," "the invention is directed to a variety of multiplexing methods used to amplify and/or genotype a variety of samples simultaneously." The ’794 Patent, Abstract.

LEGAL STANDARD

Claim construction is a matter of law. *Markman v. Westview Instr., Inc.*, 517 U.S. 370, 372 (1996). Terms contained in claims are "generally given their ordinary and customary meaning." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* at 1312. In determining the proper construction of a claim, a court begins with the intrinsic evidence of record, consisting of the claim language, the patent specification, and, if in evidence, the prosecution history. *Id.* at 1313; *see also Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "The appropriate starting point . . . is always with the language of the asserted claim itself." *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998); *see also Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir. 1997).

Accordingly, although claims speak to those skilled in the art, claim terms are construed in light of their ordinary and accustomed meaning, unless examination of the specification, prosecution history, and other claims indicates that the inventor intended otherwise. *See Electro Medical Systems, S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1053 (Fed. Cir. 1994). The written description can provide guidance as to the meaning of the claims, thereby dictating the manner in which the claims are to be construed, even if the guidance is not provided in explicit definitional format. *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337, 1344 (Fed. Cir. 2001). In other words, the specification may define claim terms "by implication" such that the meaning may be "found in or ascertained by a reading of the patent

documents." *Vitronics*, 90 F.3d at 1584 n.6.

In addition, the claims must be read in view of the specification. *Markman*, 52 F.3d at 978. Although claims are interpreted in light of the specification, this "does not mean that everything expressed in the specification must be read into all the claims." *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 957 (Fed. Cir. 1983). For instance, limitations from a preferred embodiment described in the specification generally should not be read into the claim language. *See Comark*, 156 F.3d at 1187. However, it is a fundamental rule that "claims must be construed so as to be consistent with the specification." *Phillips*, 415 F.3d at 1316. Therefore, if the specification reveals an intentional disclaimer or disavowal of claim scope, the claims must be read consistently with that limitation. *Id.*

Finally, the Court may consider the prosecution history of the patent, if in evidence. *Markman*, 52 F.3d at 980. The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution. *See Southwall Technologies, Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995). In most situations, analysis of this intrinsic evidence alone will resolve claim construction disputes. *See Vitronics*, 90 F.3d at 1583. Courts should not rely on extrinsic evidence in claim construction to contradict the meaning of claims discernable from examination of the claims, the written description, and the prosecution history. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583). However, it is entirely appropriate "for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to from the patent file is not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical field." *Id.* Extrinsic evidence "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317. All extrinsic evidence should be evaluated in light of the intrinsic evidence. *Id.* at 1319.

DISCUSSION

The '794 patent is "directed to a variety of multiplexing methods used to amplify and/or

genotype simultaneously." The '794 Patent, Abstract. The invention allows for the detection of over 100 different target sequences by introducing probes with complementary sequences into a sample and observing whether hybridization occurs. The parties dispute the construction of two terms: (a) "modified probes" and (b) "wherein said different modified probes are amplified and forming different amplicons." Relevant for the purposes of this motion, Claim 1 of the '794 patent claims the following:

> 1. A multiplex method for determining whether a sample contains at least 100 different target sequences, comprising:
>
> a) providing a sample which may contain at least 100 different single-stranded target sequences attached to a first solid support;
>
> b) contacting said target sequences with a probe set comprising more than 100 different single-stranded probes, wherein each of said more than 100 different probes comprises:
>
> i) a first universal priming site, wherein each of said more than 100 different probes has identical universal priming sites, and
>
> ii) a target specific domain, such that different double-stranded hybridization complexes are formed, each of the different hybridization complexes comprising one of said more than 100 different single-stranded probes and one of the different single-stranded target sequences from the sample;
>
> c) removing unhybridized probes;
>
> d) contacting said probes of the hybridization complexes with a first enzyme and forming different **modified probes**;
>
> e) contacting said **modified probes** with:
>
> i) at least a first primer that hybridizes to said universal priming site;
>
> ii) NTPs; and
>
> iii) an extension enzyme; **wherein said different modified probes are amplified and forming different amplicons**;
>
> f) immobilizing said different amplicons to a second solid support, and
>
> g) detecting said different amplicons immobilized to said second solid support, thereby determining whether the sample contains at least 100 different target sequences.

Claim 1 is the '794 patent's only independent claim.

A. "modified probe"

Claim Term	Illumina's Proposed Construction	Ariosa's Proposed Construction
"modified probe"	"modified polynucleotide that hybridizes to a target sequence"	"enzymatically altered nucleic acid fragments, each of which contains a universal priming site and a region complementary to a specific target sequence"

First, the parties disagree regarding whether a modified probe is always the result of enzymatic alteration. Claim 1(d) describes: "contacting said probes of the hybridization complexes with a first enzyme and forming different modified probes." Illumina first points to dependent claims 9 and 13, to show that probes in Claim 1 may be modified by non-enzymatic means.

> 9. The method of claim 1, wherein step (b) further comprises hybridizing said target sequences with a plurality of other probes and step (d) further comprises ligating said other probes to said probes.
>
> 13. The method of claim 9, wherein each of said target sequences comprises a detection position, each of said probes comprises an interrogation position, and said first enzyme modifies said probes if there is substantial complementarity between the bases at said interrogation position and said detection position.

The '794 Patent 69:39-42, 70:7-12.

Neither of these claims supports Illumina's contention. Claim 9 states only that step 1(d) "further comprises" ligation, not that it has eliminated the introduction of enzymes. Claim 13 specifically describes the use of enzymes to modify the probes. Nonetheless Illumina contends that "[s]ince claim 13 applies to the modification disclosed in claim 1, step (d), modification in 1(d) can be accomplished by using an enzyme, as required by claim 13, or by other means, as disclosed more broadly by claim 1." Docket No. 171-4, Pl. Brf. at 9. This argument ignores the fact that claim 1(d) itself requires the use of "a first enzyme" to modify the probes. A person skilled in the art would understand claim 1(d) to describe enzymatic modification, while claims 9

and 13 provide for specific variations wherein enzymatic modification occurs. Illumina's reliance on embodiments in the specification is similarly misplaced.

Next, the parties dispute whether the definition of "modified probe" must include the presence of a universal priming site. On this point, Illumina's argument appears internally inconsistent. Illumina concedes that claims 1(b)(i)(the probes comprise, inter alia, "a first universal priming site") and 1(e)(i) (contacting modified probes with a primer that hybridizes to "said universal priming site") require that a universal priming site be present in both the modified and unmodified probes, but argues that modified probes should not be construed to have universal priming sites because it would be redundant of the claim language. Pl. Brf. at 10. However, Illumina also argues that including a universal priming site as part of the definition would improperly import a limitation from the specification. Pl. Brf. at 11; Docket No. 176-4, Pl. Rep. at 3 ("Thus, the specification states that to the extent probes [include] priming sites, they need not be 'universal priming sites.'"). This latter argument does not square with the plain language of the claims.[2]

Next, the parties dispute whether a modified probe "hybridizes" to a target sequence, or merely has a "region complementary" to a target sequence. Here, the parties seem to have substantial agreement on what the definition should conceptually convey, but rather disagree on the best rhetorical mode of conveyance. Both parties acknowledge that (1) an unmodified probe must possess a threshold level of complimentarity to hybridize, but need not be perfectly complementary, (2) an unmodified probe may never hybridize at all, (3) a modified probe does not necessarily remain hybridized at all times throughout the multiplexing process, but that (4) a

[2] At argument, the Court asked Illumina if a preferred embodiment involves cleaving the universal priming site from the modified probe during the amplification stage. The '794 Patent 33:51-34:33. However, Illumina was unable to confirm whether that was the case. The Court finds that to the extent the embodiment provides for amplification without the use of a universal priming site, it is unclaimed.

modified probe must at some point hybridize to a target sequence.[3]

Finally, Ariosa has agreed to Illumina's proposed term "polynucleotide" in lieu of its proposed term, "nucleic acid fragments." Docket No. 175, Def. Resp. at 13 nt. 3.

For the reasons stated above, the Court construes "modified probe" to mean: "an enzymatically altered polynucleotide which contains a universal priming site and is capable of substantially hybridizing to a target sequence."

B. "wherein said different modified probes are amplified and forming different amplicons"

Claim Term	Illumina's Proposed Construction	Ariosa's Proposed Construction
"wherein said different modified probes are amplified and forming different amplicons"	"wherein the different modified probes are amplified to yield amplicons different in sequence from the modified probes"	"wherein said different modified probes are copied to form PCR amplification products of each of the different modified probes."

First, the parties disagree regarding whether the word "copied" should be substituted for the word "amplified." Illumina argues that amplification encompasses an array of processes broader than mere copying, including for example using RNA to create a complementary strand. Pl. Brf. 13-14. Illumina further points out that amplification often involves copying only a portion of a template sequence, *Id.* at 13. Ariosa points the Court to numerous citations in the specification which employ the term copying in the context of amplification, and argues that copying is the "essence" of amplification. Def. Resp. at 20. Nonetheless, Ariosa acknowledges that "amplification can involve *more* than simple copying." *Id.* (emphasis in original). The Court agrees that amplification can involve more than copying, and that Ariosa's proposed definition therefore unduly circumscribes what is a more nuanced and expansive concept – regardless of whether copying is the essence of amplification or not. However, Illumina's proposed construction

[3] In its brief, Ariosa argues that "a probe will not hybridize to its target sequence unless there is substantial complementarity." Def. Resp. at 3-4. However, at argument, Ariosa claimed that a probe which has only a minimal level of complementarity may "incorrectly" hybridize.

merely parrots the language of the claim, without explaining it, and therefore falls short of "ensur[ing] that the jury fully understands the court's claim construction rulings and what the patentee covered by the claims." *Power-One, Inc. v. Artesyn Technologies, Inc.*, 599 F.3d 1343, 1348 (Fed. Cir. 2010), *quoting Sulzer Textil A.G. v. Picanol N.V.*, 358 F.3d 1356, 1366 (Fed.Cir.2004).

Next, the parties dispute whether all amplicons are the product of the PCR technique. Ariosa argues that while the specification discloses other methods for amplification (i.e. SDA, NASBA, LCR), these methods are unclaimed because they do not include the three steps outlined in claim 1(e) and because the specification only refers to the products of PCR amplification as "amplicons." Def. Resp. at 21-22. However, it is clear that the specification refers to the products of other methods of amplification as "amplicons." *See e.g.* '794 Patent 32:56-57. Further, it appears that, at a minimum, the LCR method reflects the three steps outlined in claim 1(e). *See id.* 31:45-49, 37:34-43.[4]

Finally the parties disagree over the meaning of the term "different" when used to modify "amplicons." Illumina suggests that "different" means that the amplicons are different in sequence from the modified probes, while Ariosa interprets the term to mean that the amplicons are different from one another. Illumina argues that "if the amplicons are required to be different from one another, additional rounds of amplification would fall outside the claim." Pl. Brf. at 16. Conversely, Ariosa remarks that amplicons "are different from one another because the target sequences to which they […] correspond are different from one another." Def. Resp. at 24. To an extent, the parties' divergent proposals arise out of the same disagreement regarding whether an amplicon is a copy. As discussed above, while an amplicon is not necessarily a copy of the modified probe, the amplification process itself involves replicating the amplicons so that they

[4] At argument, Ariosa conceded that amplicons need not be the product of PCR.

may be more readily detected. Therefore, while a sample may have millions of identical amplicons, each type of amplicon corresponds to a unique modified probe, and each type of modified probe is unique, and thus different from the other types of modified probes. Therefore "different" means that each *type* of amplicon is different, and that this difference arises out of the uniqueness of the types of modified probes which they amplify.

For the reasons stated above, the Court construes "wherein said different modified probes are amplified and forming different amplicons" to mean: "wherein the different modified probes are replicated, in whole or in part, to yield amplification products of each of the different modified probes."

CONCLUSION

For the foregoing reasons and for good cause shown, the Court adopts the constructions set forth above.

IT IS SO ORDERED.

Dated: December 17, 2014

SUSAN ILLSTON
United States District Judge