



Patent Nos. 6,797,470 (“the ‘470 patent”), 7,166,434 (“the ‘434 patent”), 7,312,039 (“the ‘039 patent”), 7,332,285 (“the ‘285 patent”), and 7,429,453 (“the ‘453 patent”).<sup>3</sup> The remaining asserted claims are: claim 4 of the ‘470 patent; claims 1, 2, and 18 of the ‘917 patent; claim 5 of the ‘434 patent; claim 5 of the ‘039 patent; claim 3 of the ‘285 patent; claim 10 of the ‘453 patent; claims 1 and 2 of the ‘746 patent; claims 1, 2, 4, 5, 7, 8, 13, 15, and 26 of the ‘233 patent; claims 18 and 19 of the ‘521 patent; claims 1, 2, 3, 5, 13, and 18 of the ‘016 patent; and claims 1, 2, and 3 of the ‘928 patent.<sup>4</sup>

A *Markman* hearing was held on February 22, 2016. The court’s construction of disputed claim terms is set forth below.

## II. CLAIM CONSTRUCTION

The asserted patents cover instruments and methods for determining whether a certain DNA sequence is present in a sample. The Abstract of the Array Patent family recites:

The present invention describes a method for identifying one or more of a plurality of sequences differing by one or more single base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences. The method includes a ligation phase, a capture phase, and a detection phase. The ligation phase utilizes a ligation detection reaction between one oligonucleotide probe, which has a target sequence-specific portion, and a second oligonucleotide probe, having a target sequence-specific portion and a detectable label. After the ligation phase, the capture phase is carried out by hybridizing the ligated oligonucleotide probes to a solid support with an array of immobilized capture oligonucleotides at least some of which are complementary to the addressable array-specific portion. Following completion of the capture

---

patent.

<sup>3</sup> *Id.* at 1 n.2. The specifications of the LCR-PCR Patent family are identical in substance, and citations to the common specification are generally made to the ‘470 patent.

<sup>4</sup> *Id.* at 1 n.3.

phase, a detection phase is carried out to detect the labels of ligated oligonucleotide probes hybridized to the solid support. The ligation phase can be preceded by an amplifications process. The present invention also relates to a kit for practicing this method, a method of forming arrays on solid supports, and the supports themselves.<sup>5</sup>

The Abstract of the LDR-PCR Patent family recites:

The present invention relates to the detection of nucleic acid sequence differences using coupled ligase detection reaction and polymerase chain reaction. One aspect of the present invention involves use of a ligase detection reaction coupled to a polymerase chain reaction. Another aspect of the present invention relates to the use of a primary polymerase chain reaction coupled to a secondary polymerase chain reaction coupled to a ligase detection reaction. A third aspect of the present invention involves a primary polymerase chain reaction coupled to a secondary polymerase chain reaction. Such coupling of the ligase detection reaction and the polymerase chain reaction permits multiplex detection of nucleic acid sequence differences.<sup>6</sup>

The parties agree to the construction of the following claim terms.

“Oligonucleotide probe set(s)” means “oligonucleotide sequences that hybridize to a target sequence in a ligase detection reaction.”

“Primer-specific portion” means “portion of an oligonucleotide capable of hybridizing to a nucleotide sequence used to initiate PCR amplification.”

“Ligation product sequence(s)” and “ligation product(s)” mean “oligonucleotide sequence(s) resulting from a ligase detection reaction.”

“Composite oligonucleotides” means “an oligonucleotide having to or more portions.”

Based on the parties’ agreement as to the meaning of those terms, the court adopts the parties’ proposed constructions.

---

<sup>5</sup> ‘917 patent, Abstract.

<sup>6</sup> ‘470 patent, Abstract.

The meanings of the following claim terms are in dispute.

1. “solid support”

Representative claim 1 of the ‘917 patent recites:

1. A device comprising:

a *solid support* having an array of positions each suitable for attachment of an oligonucleotide probe;

a linker suitable for coupling an oligonucleotide probe to the solid support at each of the array positions; and

an array of capture oligonucleotide probes on the solid support at the array positions, said capture oligonucleotide probes each having greater than sixteen nucleotides and able to bind to complementary nucleic acids at uniform hybridization conditions, wherein each capture oligonucleotide probe of the array differs in sequence from its adjacent capture oligonucleotide probe, when aligned to each other by at least 25% of the nucleotides.<sup>7</sup>

Plaintiffs’ proposed construction is: “solid-phase substrate.”

Defendant’s proposed construction is: “a single unitary substrate.”

The parties agree the construction of “solid support” includes “substrate,” but disagree whether the substrate comprises one or more components or structures (plaintiffs) or just a “single unitary” structure (defendant).<sup>8</sup>

Plaintiffs state the specification provides for beads or slides to be used individually or together as supports and describes coupling oligonucleotides to a solid support via another solid support.<sup>9</sup> They argue, therefore, that a combination of supports is within the scope of the claims.<sup>10</sup> Defendant maintains a person of ordinary

---

<sup>7</sup> ‘917 patent, claim 1 (emphasis added).

<sup>8</sup> D.I. 419 at 32.

<sup>9</sup> *Id.* at 34.

<sup>10</sup> *Id.*

skill in the art reading the intrinsic evidence, including the prosecution history, would understand the claims do not cover the use of intermediate supports coupling the oligonucleotide to the solid support.<sup>11</sup> The court agrees with defendant that the “solid support” is “a single unitary substrate.”

In support of their position, plaintiffs rely on the specification’s statement that “[t]he solid support can be made from a wide variety of materials. The substrate may be biological, nonbiological, organic, inorganic, or a *combination of any of these*, existing as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, discs, membranes, etc.”<sup>12</sup> As defendant explained during the *Markman* hearing, however, the “combined” reference is to composite materials, for instance a slide coated with a polymer, which is nevertheless a unitary structure like a piece of plywood is a unitary structure.<sup>13</sup> The specification describes such composite: “[p]olymer-coated slides were tested for their capture capacity of addressable oligonucleotide probes following different procedures for immobilization of capture oligonucleotides.”<sup>14</sup> Those “polymer-coated slides” are a unitary structure.

Plaintiffs also rely on the specification’s statement that:

Yet another aspect of the present invention relates to an array of oligonucleotides on a solid support per se. The *solid support* has an array of positions each suitable for attachment of an oligonucleotide. A *linker or support* (which can be non-hydrolyzable), suitable for coupling an oligonucleotide to the solid support, is attached to the solid support at

---

<sup>11</sup> *Id.*

<sup>12</sup> ‘917 patent, 22:1-6 (emphasis added).

<sup>13</sup> *Markman* Tr. at 65:6-19; see also D.I. 419 at 40 n.12.

<sup>14</sup> ‘917 patent, 51:15-17; see also ‘917 patent, 22:34-35 (“Surfaces on the solid substrate will usually, though not always, be composed of the same material as the substrate.”).

each of the array positions.<sup>15</sup>

That passage indicates the “linker” or “support” for coupling an oligonucleotide to the “solid support” are distinct, separate, structures; not that “support” is a species of “linker” as plaintiffs suggest.<sup>16</sup> The specification thus contemplates use of a linker *or* a support to couple an oligonucleotide to the solid support. That use of an intervening support structure, however, was foreclosed during prosecution. The patentees originally attempted to claim either a linker or a support for oligonucleotide coupling. During prosecution, claim 120 of the application leading to the ‘917 patent claimed “a linker *or support* for coupling an oligonucleotide to the solid support attached to the solid support at each of the array positions.”<sup>17</sup> The examiner rejected that claim as indefinite, stating:

Claim 120 is indefinite by reciting “a linker or support suitable for coupling an oligonucleotide probe to the solid support . . .”, it is not clear what does applicants [sic] mean by support suitable for coupling to the solid support. Does applicants mean the oligonucleotide is coupled to the solid support by using a different support[?] Applicants are requested to amend the claim.<sup>18</sup>

In response to that rejection, the patentees amended the claims to remove the words “or support” from the limitation clarifying that the oligonucleotides are coupled to the solid support using only a “linker”<sup>19</sup> and stated to the patent office “[t]he rejection of

---

<sup>15</sup> ‘917 patent, 6:37-43 (emphasis added).

<sup>16</sup> Elsewhere in the specification, “supports” and “linkers” are also distinguished. See, e.g., ‘917 patent, 26:13-18 (“DNA oligonucleotides can be synthesized and terminated with a residue of the amino acid tryptophan, and conjugated efficiently to *supports* that have been modified by tris(alkoxy)benzyl ester (hypersensitive acid labile (‘HAL’)) or tris(alkoxy)benzylamide (‘PAL’) *linkers*.”) (emphasis added).

<sup>17</sup> D.I. 421 at A1548 (emphasis added).

<sup>18</sup> *Id.* at A1399-1400.

<sup>19</sup> *Id.* at 1416.

claims 120-125, 128, and 136-137 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments.”<sup>20</sup> The court agrees with defendant that, in addition to reviewing the specification, the amendment removing “or support” in response to the examiner’s question of whether the original language of application claim 120 was meant to indicate an oligonucleotide was coupled to the solid support by using a different support, a person of ordinary skill in the art would understand that a “solid support” means a single unitary object without any intermediate supports.<sup>21</sup>

The court adopts defendant’s proposed construction that “solid support” means “a single unitary substrate.”

2. “array of positions”

Representative claim 1 of the ‘928 patent recites:

1. An instrument comprising:

a solid support comprising at least 25 types of capture oligonucleotides immobilized on the solid support at an *array of positions*, wherein each type of capture oligonucleotide is greater than 16 oligonucleotides and differs in nucleotide sequence, when aligned to another type of capture oligonucleotide on an adjacent position of said solid support, by at least 25%;

---

<sup>20</sup> *Id.* at 1424.

<sup>21</sup> *See, e.g., Tr. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1363 (Fed. Cir. 2016) (“Our case law does not require explicit redefinition or disavowal. *See, e.g. Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1330 (Fed. Cir. 2012) (‘This clear expression need not be *in haec verba* but may be inferred from clear limiting descriptions of the invention in the specification or prosecution history.’).”); *Schindler Elevator Corp. v. Otis Elevator Co.*, 593 F.3d 1275, 1285 (Fed. Cir. 2010) (“[A]n amendment that clearly narrows the scope of a claim, such as by the addition of a new claim limitation, constitutes a disclaimer of any claim interpretation that would effectively eliminate the limitation or that would otherwise recapture the claim’s original scope.”).

one or more nucleic acid molecules hybridized to complementary portions of the one or more capture oligonucleotides on said solid support, wherein the capture oligonucleotides hybridize to the complementary portions of the nucleic acid molecules under uniform hybridization conditions; and

an imager configured to detect the hybridized nucleic acid molecules.<sup>22</sup>

Plaintiffs' proposed construction is: "arrangement of positions"

Defendant's proposed construction is: "positions organized in known locations."

The parties disagree whether the positions of the array can be either random or pre-defined (plaintiffs) or must be pre-defined (defendant).<sup>23</sup>

Plaintiffs contend defendant's proposed construction improperly imposes a temporal requirement on the "array of positions," i.e. that the positions of each oligonucleotide be known before they are attached to the solid support.<sup>24</sup> They maintain nothing in the patent requires the oligonucleotides to be placed at a pre-determined location rather than at a location determined after the solid support is manufactured.<sup>25</sup>

In briefing, plaintiffs also maintained that "Illumina correctly states that, by having discrete locations for attachment on the array, a spacial relationship can be observed between the oligonucleotides attached to the solid support," but reiterated "the specific identity and position of the oligonucleotides at each discrete spot can be determined before or after the oligonucleotides are attached to the array."<sup>26</sup> At the *Markman* hearing they stated there was no dispute that when an array is used one must know

---

<sup>22</sup> '928 patent, claim 1 (emphasis added).

<sup>23</sup> D.I. 419 at 42.

<sup>24</sup> *Id.* at 46.

<sup>25</sup> *Id.*

<sup>26</sup> *Id.* at 48.



which oligonucleotide is where on the array.<sup>27</sup>

At the hearing, defendant explained its proposed construction did not require the positions be pre-determined, just that those positions are known.<sup>28</sup> It also stated its construction was not about how the arrays are manufactured.<sup>29</sup>

Because the parties agree that when the arrays are used the positions of the oligonucleotides must be known, and with defendant's representation that its construction does not set a temporal limit (does not require pre-determination of oligonucleotide positions) or relate to how the solid supports are manufactured, the court adopts defendant's proposed construction of "array of positions" to mean "positions organized in known locations."

### 3. Claim Terms Related to the Connection of Oligonucleotides to the Solid Support

This group of terms relate to oligonucleotides being connected to a solid support.<sup>30</sup>

#### a. "linker"

Representative claim 1 of the '917 patent recites:

---

<sup>27</sup> *Markman* Tr. at 71:15-17 ("There's no dispute that when you use the array, you have to know which oligonucleotide is where."); 72:3-4 ("So there's no dispute that when you use the array you have to know which one is there."); 72:15-17 ("They have to be known before you use them, but they don't have to be known before you put them on the array."); 75:17-20 ("In fact, before any of those arrays are used, they determine where the positions are. It's just not a known location ahead of time . . .").

<sup>28</sup> *Markman* Tr. at 73:21-22 ("We're not saying pre-determined our proposal is known."); 74:10-14 ("So we're not asking the Court to construe it to be pre-determined, but they do have to be known, fixed locations as an array of positions because that's how the whole patent makes sense.").

<sup>29</sup> *Markman* Tr. at 74:23-75:2 ("We're not talking about how it's manufactured. We're talking about the idea of known locations").

<sup>30</sup> D.I. 419 at 51.

1. A device comprising:

a solid support having an array of positions each suitable for attachment of an oligonucleotide probe;

a *linker* suitable for coupling an oligonucleotide probe to the solid support and attachment to the solid support at each of the array positions; and

an array of capture oligonucleotide probes on the solid support at the array positions, said capture oligonucleotide probes each having greater than sixteen nucleotides and able to bind to complementary nucleic acids at uniform hybridization conditions, wherein each capture oligonucleotide probe of the array differs in sequence from its adjacent capture oligonucleotide probe, when aligned to each other by at least 25% of the nucleotides.<sup>31</sup>

Representative claim 15 of the '233 patent recites:

15. The device according to claim 7, wherein a *linker* couples the capture oligonucleotides to the solid support.<sup>32</sup>

Plaintiffs' proposed construction is: "feature that connects an oligonucleotide to a solid support."

Defendant's proposed construction is: "a molecule that covalently binds an oligonucleotide to the solid support without an intervening support."

Defendant states the critical difference in the parties' proposed constructions is whether a "linker" is a chemical molecule (defendant) or a "feature" which would allow a linker to be something else, such as an intervening solid structure, like a bead, between the oligonucleotide and the solid support (plaintiffs).<sup>33</sup>

Defendant's proposed construction defines a linker as "a molecule that *covalently*

---

<sup>31</sup> '917 patent, claim 1 (emphasis added).

<sup>32</sup> '233 patent, claim 15 (emphasis added).

<sup>33</sup> D.I. 419 at 53.

binds an oligonucleotide to the solid support without an intervening support.”<sup>34</sup> Plaintiffs note the specification discloses linkers that result in both covalent and non-covalent interactions. The specification describes covalent linkages when stating “linker molecules can be attached to the substrate via carbon–carbon bonds . . . or, preferably, by siloxane bonds” or as parts of a polymer on the substrate.<sup>35</sup> It also discloses non-covalent linkages in “alternative embodiments” where “the linker molecules are absorbed to the surface of the substrate.”<sup>36</sup> Plaintiffs argue their construction provides for linkers that result in both covalent and non-covalent interactions.<sup>37</sup> They state that construction also embraces intervening structures for connecting oligonucleotides to solid supports.<sup>38</sup>

The court has determined in its construction of the term “solid support,” above, that the claims do not cover intervening structures, like an additional support, for connecting oligonucleotides to solid supports. As plaintiffs’ proposed constructions for “linker” and the other terms in this group would cover intervening structures, the court rejects those proposed constructions. The court now addresses plaintiffs’ additional criticisms of defendant’s proposed constructions.

In addition to the purportedly improper exclusion of non-covalent connections, the disclosed absorption of the linker molecules to the surface of the substrate, plaintiffs argue defendant improperly limits the claimed linkers to “linker molecules.” That

---

<sup>34</sup> Emphasis added.

<sup>35</sup> ‘917 patent, 25:44-52.

<sup>36</sup> ‘917 patent, 25:52-54. Defendant acknowledges that absorption is different from covalent bonding and hybridization. D.I. 419 at 57 n.20.

<sup>37</sup> D.I. 419 at 51.

<sup>38</sup> *Id.*

criticism is based on plaintiffs' contention that in addition to linker molecules which can only be attached to a solid support through "chemical" linkers, plaintiffs assert attachment may be made through an "intervening solid structure." The court has rejected that argument.<sup>39</sup> Because there is no other description in the patent of linkers other than linker molecules attached to the support through chemical bonds, the court adopts defendant's proposed constructions for linker and the other terms in this group. The court modifies defendant's proposed constructions for "linker" and "attached" to reflect the possibility of absorption in light of the specification's recitation that "[i]n alternative embodiments, the linker molecules are absorbed to the surface of the substrate."<sup>40</sup>

The court adopts defendant's proposed construction of "linker," as modified, to mean "a molecule that covalently binds an oligonucleotide to the solid support, or is absorbed thereto, without an intervening structure."

b. "immobilized"

Plaintiffs' proposed construction is: "restricted in mobility."

---

<sup>39</sup> In further support of their contention that linkers can be either solid or chemical, plaintiffs cite the statement in the specification that the inventors contemplated "great flexibility in . . . attachment [of oligonucleotides] to solid supports." D.I. 419 at 51, 58 (quoting '917 patent, 43:12-14). As defendant points out, however, the entire passage refers not to flexibility in designing a linker as a solid support, but rather to flexibility in manufacturing oligonucleotides either on or off the support, and then subsequently attaching them to the solid support. The full passage reads: "The present invention also affords great flexibility in the synthesis of oligonucleotides and their attachment to solid supports. *Oligonucleotides can be synthesized off of the solid support and then attached to unique surfaces on the support.* Segments of multimers or oligonucleotides, which do not require intermediate backbone protection (e.g., PNA), can be synthesized and linked onto the solid support." '917 patent, 43:12-18 (emphasis added).

<sup>40</sup> '917 patent, 26:52-54.

Defendant's proposed construction is: "covalently bound or bound via hybridization."

Court's construction: "covalently bound or bound via hybridization."

c. "attached"

Plaintiffs' proposed construction is: "connected."

Defendant's proposed construction is: "covalently bound."

Court's construction: "covalently bound or absorbed."

d. "suitable for attachment"

Plaintiffs' proposed construction is: "capable of being connected."

Defendant's proposed construction is: "functionalized to permit covalent bonding."

Court's construction: "functionalized to permit covalent bonding."

e. "coupled to"

Plaintiffs' proposed construction is: "connected to."

Defendant's proposed construction is: "covalently bound or bound via hybridization."

Court's construction: "covalently bound or bound via hybridization."

4. "capture oligonucleotide probes" / "capture oligonucleotide(s)" / "capturing said one or more amplification product to a solid support"

Representative claim 1 of the '917 patent recites:

1. A device comprising:

a solid support having an array of positions each suitable for attachment of an oligonucleotide probe;

a linker suitable for coupling an oligonucleotide probe to the solid support

at each of the array positions; and

an array of *capture oligonucleotide probes* on the solid support at the array positions, said *capture oligonucleotide probes* each having greater than sixteen nucleotides and able to bind to complementary nucleic acids at uniform hybridization conditions, wherein each *capture oligonucleotide probe* of the array differs in sequence from its adjacent *capture oligonucleotide probe*, when aligned to each other by at least 25% of the nucleotides.<sup>41</sup>

Representative claim 1 of the '746 patent recites:

1. A method comprising:

providing an array of a plurality of *capture oligonucleotides* wherein each type of *capture oligonucleotide* is greater than 16 nucleotides and differs in nucleotide sequence, when aligned to another type of *capture oligonucleotide*, by at least 25%, wherein said *capture oligonucleotides* are coupled to a support;

providing a sample comprising a plurality of target oligonucleotides, each target oligonucleotide comprising (i) an addressable array-specific portion, (ii) a further nucleotide sequence, and (iii) a detectable reporter label;

contacting the sample comprising the plurality of target oligonucleotides with the array of *capture oligonucleotides* under uniform hybridization conditions effective to hybridize the addressable array-specific portion of each target oligonucleotide to its complementary *capture oligonucleotide*; and

detecting the reporter labels of one or more of the plurality of target oligonucleotides hybridized to their complementary *capture oligonucleotides* on the solid support.<sup>42</sup>

a. "capture oligonucleotide probes" / "capture oligonucleotide(s)"

Plaintiffs' proposed construction is: "oligonucleotide capable of hybridizing to a complementary nucleic acid."

Defendant's proposed construction is: "oligonucleotide [probe] which has no

---

<sup>41</sup> '917 patent, claim 1 (emphasis added).

<sup>42</sup> '746 patent, claim 1 (emphasis added).

homology to a target sequence and is complementary to the addressable array specific portion of an oligonucleotide containing an addressable array specific portion and a target specific portion.”

The parties disagree whether the capture oligonucleotide (probe) can be any sequence capable of hybridizing to a complementary nucleic acid (plaintiff) or must be a sequence that lacks homology<sup>43</sup> to a target sequence and only hybridizes to a specific portion of an oligonucleotide of the array (defendant).<sup>44</sup>

The Federal Circuit recently reiterated “[t]he only meaning that matters in claim construction is the meaning in the context of the patent.”<sup>45</sup> “[W]hen the scope of the invention is clearly stated in the specification, and is described as the advantage and distinction of the invention it is not necessary to disavow explicitly a different scope.”<sup>46</sup>

Plaintiffs argue the claim language supports their construction because the term “homology” is never used in any of the claims and not all of the asserted claims include the requirement that the capture oligonucleotide hybridizes to the addressable array-specific portion of the target oligonucleotide.

That none of the asserted claims recite the term “homology” is not determinative

---

<sup>43</sup> “Homology” refers to the level of similarity between two nucleotide sequences. D.I. 419 at 66 n.22.

<sup>44</sup> *Id.* at 64.

<sup>45</sup> *Tr. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1363 (Fed. Cir. 2016) (citation omitted); *see also Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001) (“The claims are directed to the invention that is described in the specification; they do not have meaning removed from the context from which they arose.”).

<sup>46</sup> *Columbia Univ.*, 811 F.3d at 1364 (alteration in original) (quoting *On Demand Mach. Corp. v. Ingram Indus., Inc.*, 442 F.3d 1331, 1340 (Fed. Cir. 2006)).

as the claims “must be read in view of the specification, of which they are a part.”<sup>47</sup>

“[T]he specification is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term.”<sup>48</sup>

Plaintiffs also state Illumina’s proposed construction requiring the “oligonucleotide [probe] . . . [to be] complementary to the addressable array specific portion of an oligonucleotide containing an addressable array specific portion and a target specific portion” might be appropriate if all the asserted claims included such limitations, as does representative claim 1 of the ‘746 patent.<sup>49</sup> All asserted claims, however, do not recite those limitations. For instance, representative claim 1 of the ‘917 patent does not require the oligonucleotide probe to have those limitations and asserted claim 18 of ‘917 patent, depending from claim 1, merely requires the “capture oligonucleotide probes” need only “hybridize” to other oligonucleotides.<sup>50</sup> Similarly, claim 1 of the ‘233 patent recites the “capture oligonucleotide” hybridizes to any “nucleic acid molecule” that has “a complementary nucleotide sequence.”<sup>51</sup> The differences in the recited limitations of the claims plaintiffs cite are also not determinative. To the extent plaintiffs basing their argument on the doctrine of claim differentiation, that doctrine is not a “hard and fast rule of construction” and “cannot broaden claims beyond their correct scope,

---

<sup>47</sup> *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (*en banc*) (citation and internal quotation marks omitted).

<sup>48</sup> *Id.* (citation and internal quotation marks omitted).

<sup>49</sup> D.I. 419 at 64-65.

<sup>50</sup> ‘917 patent, claim 18 (“The device according to claim 1, wherein the array is reusable for repeatedly hybridizing oligonucleotides to the array of capture oligonucleotides probes on the solid support.”).

<sup>51</sup> ‘233 patent, claim 1 (“[E]ach capture oligonucleotide of the collection hybridizes to a nucleic acid molecule comprising a complementary nucleotide sequence under uniform hybridization conditions.”).



determined in light of the specification and the prosecution history and any relevant extrinsic evidence.”<sup>52</sup> Whether or not plaintiffs are basing their argument on that doctrine:

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.<sup>53</sup>

The intrinsic record demonstrates the claimed invention was an addressable, or universal, array and was meant to improve on prior detection techniques using hybridization arrays where false positive and false negative results could occur due to cross-hybridization. The ‘917 patent is titled “Detection of Nucleic Acid Sequence Differences Using the Ligase Detection Reaction with Addressable Arrays,” and the specification states “[t]he array of the present invention will be universal, making it useful for detection of cancer mutations, inherited (germline) mutations, and infectious diseases.”<sup>54</sup> During prosecution, the applicants touted the advantage of the claimed invention over prior art hybridization arrays. “In a direct hybridization array, the capture probes, which are covalently linked to the array surface, are complementary to

---

<sup>52</sup> *Seachange Int’l, Inc. v. C-COR Inc.*, 413 F.3d 1361, 1369 (Fed. Cir. 2005) (citation omitted); *see also Atlas IP, LLC v. Medtronic, Inc.*, 809 F.3d 599, 606-07 (Fed. Cir. 2015) (“[W]e have been cautious in assessing the force of claim differentiation in particular settings, recognizing that patentees often use different language to capture the same invention, discounting it where it is invoked based on independent claims rather than the relation of an independent and dependent claim, and not permitting it to override the strong evidence of meaning supplied by the specification.”).

<sup>53</sup> *Phillips*, 415 F.3d at 1316 (emphasis added) (citation omitted).

<sup>54</sup> ‘917 patent, 43:7-9.

sequences within the gene or target nucleotides to be interrogated.”<sup>55</sup>

The present invention is directed to the use of an array designed to overcome the problems associated with false positive and false negative results generated by direct hybridization arrays when using LDR. An addressable array uses capture probes that are *de novo* sequences separate and distinct from the nucleic sequences of interest.<sup>56</sup>

The applicants repeatedly distinguished their addressable arrays from prior art hybridization arrays that they viewed as unsatisfactory.

I am presenting this declaration to demonstrate how the efforts of others in the art to develop a hybridization array-based detection assay to meet this need[, accurate detection of cancer related mutations,] have failed, and continue to fail, and how the method of my present application has overcome these failures and successfully resolved this unmet and long-felt need.<sup>57</sup>

Chee teaches arrays of nucleic acid probes on biological chips that are useful for determining whether a target nucleic acid is identical to or different from a specific reference nucleic acid sequence. The array contains probes that are exactly complementary to the reference sequence, as well as probes that differ by one or more bases from the exactly complementary sequence. *The Chee array is exemplary of the direct hybridization arrays discussed in paragraphs 8-9 above and subject to the constraints of these arrays as discussed in paragraphs 10-22.*<sup>58</sup>

The implications of Pozhitkov's and Naiser's findings are that *direct hybridization methods which attempt to simultaneously discriminate and detect nucleic acid sequence variations are inadequate because of the unpredictable cross-hybridization between target sequence and mismatched or perfect match probe sequences.*<sup>59</sup>

---

<sup>55</sup> D.I. 421 at A1758 ('981 FH 10/31/07 Gerry Decl. at ¶ 27 ("10/31/07 Gerry Decl.")). Dr. Norman Gerry was a Post-Doctoral Research Associate in Francis Barany's Laboratory from September 1996 until June 2001 and submitted a declaration as an "expert" during prosecution of the '981 patent. *Id.* at A1751 (10/31/07 Gerry Decl. at ¶ 3). Dr. Francis Barany is a named inventor of the patents-in-suit.

<sup>56</sup> *Id.* at A1761 (10/31/07 Gerry Decl. at ¶ 31).

<sup>57</sup> *Id.* at A1616-17 ('981 FH 2/25/10 Barany Decl. at ¶ 5 ("2/25/10 Barany Decl.")).

<sup>58</sup> *Id.* at A1627 (2/25/10 Barany Decl. at ¶ 25) (emphasis added).

<sup>59</sup> *Id.* at A1625 (2/25/10 Barany Decl. at ¶ 22) (emphasis added); see also *id.* at A1754 (10/31/07 Gerry Decl. at ¶ 11) ("Therefore, it is logical that Barany contemplated

The applicants again touted the superiority of the claimed invention over hybridization arrays.

*The present invention teaches a method of identifying one or more sequences, differing by one or more single base changes, insertions, deletions, or translocations, in a sample containing a plurality of target nucleotide sequence that avoids all of the aforementioned problems associated with typical hybridization arrays (i.e., target-capture probe cross-hybridization and false-positive/negative signal generation).*<sup>60</sup>

Plaintiffs' proposed construction of the "capture oligonucleotides" terms is "oligonucleotide capable of hybridizing to a complementary nucleic acid." They characterize that construction as meaning "the capture oligonucleotide (probe) can be *any sequence* capable of hybridizing to a complementary nucleic acid."<sup>61</sup> That construction would cover hybridization arrays that were repeatedly distinguished during prosecution as *not* being what was described and claimed in the Array Patent family. Consequently, plaintiffs' proposed construction is rejected. The court will next determine whether defendant's construction requiring no homology and complementarity is supported by the intrinsic evidence.

The intrinsic evidence, and extrinsic evidence in the form of deposition testimony

---

using the target DNA sequence itself to capture the target sequence (i.e. direct hybridization) as describe by others.") (distinguishing prior art Barany reference); *id.* at A1757 (10/31/07 Gerry Decl. at ¶ 22) ("This embodiment of Bouma, in which an immobilized hybridization probe having sequence complementarity to the target sequence directs the capture and detection of the target, is characteristic of a direct hybridization array.") (distinguishing prior art Bouma reference); *id.* at A1758 (10/31/07 Gerry Decl. at ¶ 25) ("Like Bouma, the terminal sorting embodiment of Chetverin is similar to a direct hybridization array where hybridization of the target sequence to an immobilized probe occurs via a target specific sequence.") (distinguishing prior art Chetverin reference).

<sup>60</sup> *Id.* at A1630 (2/25/10 Barany Decl. at ¶ 30) (emphasis added).

<sup>61</sup> D.I. 419 at 64 (emphasis added).

of named inventor Dr. George Barany, support defendant's argument that the capture oligonucleotides have no homology to a target sequence. The '917 patent specification states:

The 1,000 different addresses can be unique capture oligonucleotide sequences (e.g., 24-mer) linked covalently to the target-specific sequence (e.g., approximately 20- to 25-mer) of a LDR oligonucleotide probe. *A capture oligonucleotide sequence does not have any homology to either the target sequence or to other sequences on genomes which may be present in the sample.* This oligonucleotide probe is then captured by its addressable array-specific portion, a sequence complementary to the capture oligonucleotide on the addressable solid support array.<sup>62</sup>

That there be no homology was made clear during the prosecution of the '917 patent family. Dr. Barany stated "array hybridization is carried out using divergent capture probe sequences that are not homologous to the target sequence being detected or any other known genomic sequence."<sup>63</sup> Dr. Gerry also noted "[a]n addressable array uses capture probes that are *de novo* sequences separate and distinct from the nucleic acid sequences of interest."<sup>64</sup>

Finally, Dr. Barany testified it was the inventors' goal to design around the problems associated with hybridization arrays.

Q. What do you mean by "minimal sequence homology with the natural genome"?

A. So one of the problems is—of hybridization technologies before our invention of the universal arrays was that the—the detection step

---

<sup>62</sup> '917 patent, 20:62-21:4 (emphasis added).

<sup>63</sup> D.I. 421 at A1630 (2/25/10 Barany Decl. at ¶ 30).

<sup>64</sup> *Id.* at A1761 (10/31/07 Gerry Decl. at ¶ 31); *see also id.* at A1760 (10/31/07 Gerry Decl. at ¶ 29) ("Sequence homology between the capture probes and likewise between the target sequences can jeopardize the specificity of target/probe hybridization and lead to the generation of both false positive and false negative results as illustrated in Figure 3 below.").

was—was closely coupled to the—biological questions being asked. So—so you had—had something on the array and you had something complementary that had—may or may not have the mutation. It was supposed to hybridize. And—so it was very easy for—for you to get false positives and false negatives because it was non-orthogonal. You were testing something that had tremendous sequence homology with the natural genome. And so mistakes were happening all the time, and so this is what we—we got around with—with the—with our invention.<sup>65</sup>

The court determines, therefore, that the scope of the invention is limited to capture oligonucleotides having no homology to a target sequence.

The court also determines the intrinsic record supports defendant’s construction requiring the capture oligonucleotide to be “complementary to the addressable array specific portion of an oligonucleotide.” In the Summary of the Invention, the ‘917 patent specification states:

*The present invention relates to a method for identifying one or more of a plurality of sequences differing by one or more single base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences. The method includes a ligation phase, a capture phase, and a detection phase. . . . The next phase of the process is the capture phase. This phase involves providing a solid support with capture oligonucleotides immobilized at particular sites. The capture oligonucleotides are complementary to the addressable array-specific portions. The mixture, after being subjected to the ligation phase, is contacted with the solid support under conditions effective to hybridize the addressable array-specific portions to the capture oligonucleotides in a base-specific manner. As a result, the addressable array-specific portions are captured on the solid support at the site with the complementary capture oligonucleotides.*<sup>66</sup>

---

<sup>65</sup> D.I. 422 at A2040-41 (G. Barany Tr. at 86:11-87:4).

<sup>66</sup> ‘917 patent, 5:32-37, 6:3-13 (emphasis added); see also ‘917 patent, 9:4-9, 9:44-46 (same language in Detailed Description of the Invention and Drawings). Plaintiffs cites the Abstract describing the invention as including “a solid support with an array of immobilized capture oligonucleotides *at least some of which* are complementary to the addressable array-specific portion” of an oligonucleotide as demonstrating that in some arrays not all of the capture oligonucleotides comprise a portion complementary

According to defendant, this statement describes the invention as a whole and thus carries particular weight.<sup>67</sup>

The prosecution history also supports defendant's proposed construction. During prosecution of the '917 patent family, Dr. Barany represented to the PTO that "[t]hese claims further require that the capture probes have nucleotide sequence complementary to the addressable array specific portions of the oligonucleotide probes."<sup>68</sup> Dr. Gerry likewise explained "[t]he addressable array-specific portion of a ligation product is complementary to a capture oligonucleotide immobilized on a solid support."<sup>69</sup>

---

to an addressable array-specific portion of an oligonucleotide. D.I. 419 at 65 (quoting '917 patent, Abstract) (emphasis added by plaintiff). Plaintiffs do not site corresponding language in the specification and, nevertheless, the court must determine "what the inventors actually invented and intended to envelop with the claim." *Phillips*, 415 F.3d at 1316.

<sup>67</sup> D.I. 419 at 69 (citing *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007) ("When a patent thus describes the features of the 'present invention' as a whole, this description limits the scope of the invention."); see also *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 864 (Fed. Cir. 2004) ("Although a statement's location is not 'determinative,' the location can signal the likelihood that the statement will support a limiting definition of a claim term. Statements that describe the invention as a whole, rather than statements that describe only preferred embodiments, are more likely to support a limiting definition of a claim term."); *Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1348 (Fed. Cir. 2004) ("Those statements, some of which are found in the 'Summary of the Invention' portion of the specification, are not limited to describing a preferred embodiment, but more broadly describe the overall inventions of all three patents."), *cert. denied*, 543 U.S. 521 (2004).

<sup>68</sup> D.I. 421 at 1639-40 ('981 FH 7/15/09 Pre-Appeal Brief Request for Review at 1-2); see also *id.* at 1640 (explaining that the capture oligonucleotides are "oligonucleotides designed to bind to the addressable array specific portions on the oligonucleotide probes which are designed to ligate together."); *id.* at A1327-38 ('527 App. FH 5/14/07 Barany Decl. at ¶ 19 ("5/14/07 Barany Decl.)) ("[E]ach ligation product of the LDR process is provided with an addressable array-specific portion which is selectively captured by a complementary capture probe at a particular location on the solid support.").

<sup>69</sup> *Id.* at A1753 (10/31/07 Gerry Decl. at ¶ 8).

The court concludes that the “capture oligonucleotides” are limited to those “complementary to the addressable array specific portion of an oligonucleotide containing an addressable array specific portion and a target specific portion.” The court determines, therefore, that defendant’s proposed constructions are consistent with the terms’ “meaning in the context of the patent” and supported by the prosecution history and the specification’s description of the “advantage and distinction of the invention” over the prior art. Defendant’s proposed construction thus reflects “what the inventors actually invented.”<sup>70</sup> The court adopts defendant’s proposed construction that “capture oligonucleotide probes” and “capture oligonucleotide” mean “oligonucleotide [probe] which has no homology to a target sequence and is complementary to the addressable array specific portion of an oligonucleotide containing an addressable array specific portion and a target specific portion.”

b. “capturing said one or more amplification products to a solid support”

---

<sup>70</sup> In reaching that conclusion, the court rejects plaintiffs’ assertion that defendant’s proposed construction improperly imports limitations from particular embodiments. “Although . . . the claims are not limited to the preferred embodiment of the invention, neither do the claims enlarge what is patented beyond what the inventor has described as the invention.” *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001) (internal citation omitted); see also *Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1347 (Fed. Cir. 1998) (relying on “global comments made to distinguish the applicants’ ‘claimed invention’ from the prior art” during the prosecution of the patent in construing a claim term). Plaintiffs also criticize the intrinsic evidence relied upon by defendant as relating to descriptions of LDR methods which should not be imported as necessary features of every capture oligonucleotide. D.I. 419 at 75-76. The court agrees with the argument defendant made at the *Markman* hearing, that during prosecution the applicants were distinguishing the nature of the array of the invention from the prior art hybridization arrays by arguing the claimed universal/addressable arrays had certain fundamental features. *Markman* Tr. at 132:18-134:1.

Representative claim 10 of the '453 patent recites:

10. A method for identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences comprising:

producing one or more ligation products from a reaction mixture, wherein said reaction mixture comprises:

a ligase;

one or more target nucleotide sequences; and

one or more oligonucleotide probe sets, each probe set including (a) a first oligonucleotide probe comprising a first target-specific portion capable of hybridizing to a corresponding target nucleotide sequence and (b) a second oligonucleotide probe comprising a second target-specific portion capable of hybridizing to said corresponding target nucleotide sequence, wherein a ligation product comprising the first and the second target-specific portions is capable of being produced after the first and the second target-specific portions are hybridized to said corresponding target nucleotide sequence, but is not produced when the first and the second target-specific portions are hybridized with one or more mismatches to a nucleotide sequence present in said reaction mixture, wherein each of said one or more ligation products comprises a ligated sequence which includes (1) the first target-specific portion of the first oligonucleotide probe in a corresponding probe set and (2) the second target-specific portion of the second oligonucleotide probe in said corresponding probe set, or complements thereof;

subjecting said one or more ligation products to one or more polymerase chain reaction cycles to produce one or more amplification products, each amplification product comprising (1) the ligated sequence of a corresponding ligation product from which said amplification product is amplified, (2) a reporter label, and (3) an addressable array-specific portion, wherein said reporter label and said addressable array-specific portion distinguish said amplification product from other amplification products that comprise other ligated sequences or complements thereof;

*capturing said one or more amplification products to a solid support, and*

detecting the reporter labels and the identities of the addressable array-specific portions in said captured amplification products to indicate the presence of one or more target nucleotide sequences in said reaction



mixture.<sup>71</sup>

Plaintiffs' proposed construction is: "hybridizing the one or more amplification products to an oligonucleotide immobilized on a solid support."

Defendant's proposed construction is: "hybridizing the amplification products to capture oligonucleotides attached on the solid support."

The parties agree that "capture" means the amplification product hybridizes to an oligonucleotide on a solid support.<sup>72</sup> According to defendant, the parties' disagreement over this term is whether the amplification products may hybridize to any oligonucleotide on the solid support, as plaintiffs contend, or whether those products must be hybridized to capture oligonucleotides.<sup>73</sup> The court agrees with defendant.

The specification of the '917 patent is incorporated by reference in the '453 specification: "use of a solid support with an array of capture oligonucleotides is fully disclosed in the pending provisional U.S. Patent Application Ser. No. 60/011,359 [resulting in the '917 patent], which is hereby incorporated by reference."<sup>74</sup> Therefore, the "capturing" of claim 10 of the '453 patent is accomplished according to the understanding of the meaning of "capture" as it modifies "oligonucleotide" in the '917 patent. The court determined that "capture oligonucleotides" have specific characteristics because the applicants argued those characteristics distinguished their universal array from hybridization arrays. The '453 patent incorporated those

---

<sup>71</sup> '453 patent, claim 1 (emphasis added).

<sup>72</sup> D.I. 419 at 76.

<sup>73</sup> *Id.* at 67. "Amplification products" are the same as LDR-PCR products. *Id.* at 67 n.24.

<sup>74</sup> '453 patent, 35:53-56.

characteristics. The court adopts defendant’s proposed construction of “capturing said one or more amplification products to a solid support” to mean “hybridizing the amplification products to capture oligonucleotides attached on the solid support.”

5. Claim Terms Related to Hybridization of Oligonucleotides to Their Complementary Sequences

These terms are considered together because they all relate to the hybridization of oligonucleotides—or portions of oligonucleotides—with each other.<sup>75</sup>

- a. “each [type of] capture oligonucleotide hybridizes to a nucleic acid molecule comprising a complementary nucleotide sequence” / “the capture oligonucleotides hybridize to complementary portions of the target nucleic acid molecules”

Representative claim 1 of the ‘233 patent recites:

1. A collection of capture oligonucleotides, wherein each type of capture oligonucleotide of the collection has greater than sixteen nucleotides and comprises a nucleotide sequence that differs from the nucleotide sequence of other types of capture oligonucleotides by at least 25% when aligned, and wherein *each [type of] capture oligonucleotide* of the collection *hybridizes to a nucleic acid molecule comprising a complementary nucleotide sequence* under uniform hybridization conditions.<sup>76</sup>

Representative claim 7 of the ‘233 patent recites:

7. A device comprising:

a solid support having an array of positions each suitable for attachment of a capture oligonucleotide;

an array of capture oligonucleotides on the solid support at the array of positions, wherein each type of capture oligonucleotide on the solid support comprises a nucleotide sequence that is greater than sixteen nucleotides with a nucleotide sequence that differs from the nucleotide sequence of other types of capture oligonucleotides on the solid support

---

<sup>75</sup> D.I. 419 at 82.

<sup>76</sup> ‘233 patent, claim 1 (emphasis added).

by at least 25% when aligned; and

one or more target nucleic acid molecules hybridized to complementary portions of the capture oligonucleotides on the solid support, wherein *the capture oligonucleotides hybridize to the complementary portions of the target nucleic acid molecules* under uniform hybridization conditions.<sup>77</sup>

Plaintiffs' proposed construction is: "each capture oligonucleotide hybridizes to an oligonucleotide containing a complementary nucleotide sequence."

Defendant's proposed construction is: "each capture oligonucleotide hybridizes to an oligonucleotide containing a complement to the entire capture oligonucleotide sequence."

The parties dispute whether the terms allow an oligonucleotide and its complementary sequence to be partially hybridized with or without complete complementarity (plaintiffs) or, instead, require that the oligonucleotide be hybridized to the entire capture sequence (defendant).<sup>78</sup>

Plaintiffs base their arguments with respect to this term (and the others in this group of terms) on the doctrine of claim differentiation. 35 U.S.C. § 112, ¶ 4 states "a claim in dependent form shall contain a reference" to the claim from which it depends "and then specify a further limitation of the subject matter claimed."<sup>79</sup> Under the doctrine of claim differentiation, a dependent claim that adds a limitation gives rise to the presumption that the claim from which it depends is not so restricted.<sup>80</sup> As noted above, "[w]hile the doctrine of claim differentiation is not a hard and fast rule of construction, it

---

<sup>77</sup> '233 patent, claim 7 (emphasis added).

<sup>78</sup> D.I. 419 at 82.

<sup>79</sup> 35 U.S.C. § 112, ¶ 4.

<sup>80</sup> *SunRace Roots Enter. Co., LTD v. Sram Corp.*, 336 F.3d 1298, 1303 (Fed. Cir. 2003).

does create a presumption that each claim in the patent has a different scope.”<sup>81</sup> “This presumption is especially strong where ‘there is a dispute over whether a limitation found in a dependent claim should be read into an independent claim, and that limitation is the only meaningful difference between the two claims.’”<sup>82</sup>

Claim 1 of the ‘746 patent, one of the selected claims, sets forth a method that includes the step of contacting a sample with:

the array of capture oligonucleotides under uniform hybridization conditions effective to hybridize the addressable array-specific portion of each target oligonucleotide to its complementary capture oligonucleotide . . . .<sup>83</sup>

Dependent claim 4 of the ‘746 patent requires capture oligonucleotides with complete complementarity to a portion of the target oligonucleotides:

The method according to claim 1, wherein the addressable array-specific portions of the target oligonucleotides hybridize to their complementary capture nucleotides *with complete complementarity*.<sup>84</sup>

Similarly, claim 5 of the ‘746 patent includes a step of contacting a sample with:

the collection of capture oligonucleotides under uniform hybridization conditions effective to hybridize the address-specific portion of each target oligonucleotide to its complementary capture oligonucleotide . . . .<sup>85</sup>

---

<sup>81</sup> *Comark Commc’ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998).

<sup>82</sup> *Ecolab Inc. v. Paraclipse, Inc.*, 285 F.3d 1362, 1375 (Fed. Cir. 2002) (quoting *Intermatic Inc. v. Lamson & Sessions Co.*, 273 F.3d 1355, 1364 (Fed. Cir. 2001)); see also *Comark*, 156 F.3d at 1187 (“There is presumed to be a difference in meaning and scope when different words or phrases are used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that difference between claims is significant.”) (quoting *Tandon Corp. v. United States Int’l Trade Comm’n*, 831 F.2d 1017, 1023 (Fed. Cir. 1987)).

<sup>83</sup> ‘746 patent, claim 1.

<sup>84</sup> ‘746 patent, claim 4 (emphasis added).

<sup>85</sup> ‘746 patent, claim 5.

Dependent claim 8 of the '746 patent likewise requires capture oligonucleotides with complete complementarity to a portion of the target oligonucleotides:

The method according to claim 5, wherein the address-specific portions of the target oligonucleotides hybridize to the complementary capture oligonucleotides *with complete complementarity*.<sup>86</sup>

Thus, claims 1 and 5 require target oligonucleotides to “hybridize the addressable array-specific portion of each target oligonucleotide to its complementary capture oligonucleotide.” Claims 4 and 8 add that the hybridization be “with complete complementarity.” That additional requirement is the only meaningful difference added by dependent claims 4 and 8. To include the “complete complementarity” requirement to claims not reciting that requirement would render those dependent claims superfluous. The court therefore rejects defendant’s proposed constructions for each of the terms in this group and adopts plaintiffs’ proposed constructions for those terms.<sup>87</sup> The court defines “each [type of] capture oligonucleotide hybridizes to a nucleic acid molecule comprising a complementary nucleotide sequence” / “the capture oligonucleotides hybridize to complementary portions of the target nucleic acid

---

<sup>86</sup> '746 patent, claim 8 (emphasis added).

<sup>87</sup> The court is not persuaded by defendant’s argument that plaintiffs’ constructions must be rejected because those constructions would defeat the purpose of the '917 patent family: to prevent cross-hybridization of an addressable array specific portion to the wrong oligonucleotide. D.I. 419 at 84. One of the citations defendant directs the court to suggests some cross-hybridization can occur with the claimed inventions: “Capture specific probe sequences designed to differ by 25% or more to *minimize* cross-hybridization.” *Id.* at 85 (quoting D.I. 421 at A1358) (emphasis added). Minimization of cross-hybridization with universal arrays was, indeed, a major advance touted by the patentees over prior art hybridization arrays. Here, however, the court determines defendant’s arguments do not overcome the presumption created by the doctrine of claim differentiation that dependent claims adding only a single meaningful difference from the claims from which they depend have a different meaning than those independent claims.

molecules” to mean “each capture oligonucleotide hybridizes to an oligonucleotide containing a complementary nucleotide sequence.”

- b. “one or more target nucleic acid molecules hybridized [to complementary portions of the capture oligonucleotides on the solid support]”

Plaintiffs’ proposed construction is: “one or more nucleic acid molecules are hybridized to one or more complementary nucleic acid molecules on a solid support.”

Defendant’s proposed construction is: “one or more nucleic acid molecules are hybridized [to complementary portions of the capture oligonucleotides on the solid support].”

Court’s construction: “one or more nucleic acid molecules are hybridized to one or more complementary nucleic acid molecules on a solid support.”

- c. “each type of capture oligonucleotide . . . hybridizes to its complement”

Plaintiffs’ proposed construction is: “at least a portion of each capture oligonucleotide hybridizes to its complement.”

Defendant’s proposed construction is: “each type of capture oligonucleotide hybridizes to an oligonucleotide containing a complement to the entire capture oligonucleotide sequence.”

Court’s construction: “at least a portion of each capture oligonucleotide hybridizes to its complement.”

- d. “wherein the zip code portion of each of the composite oligonucleotides . . . hybridizes to its complement”

Plaintiffs’ proposed construction is: “wherein an address portion of each of the composite oligonucleotides, or a portion thereof, hybridizes to its complement.”

Defendant’s proposed construction is: “wherein the zip code portion of each of

the composite oligonucleotides hybridizes to an oligonucleotide containing a complement to the entire zip code portion.”

Court’s construction: “wherein an address portion of each of the composite oligonucleotides, or a portion thereof, hybridizes to its complement.”

- e. “the capture oligonucleotides hybridize to the complementary portions of the nucleic acid molecules”

Plaintiffs’ proposed construction is: “at least a portion of each capture oligonucleotide hybridizes to a complementary portion of a nucleic acid molecule.”

Defendant’s proposed construction is: “each capture oligonucleotide hybridizes to one or more oligonucleotides containing a complement to the entire capture oligonucleotide sequence.”

Court’s construction: “at least a portion of each capture oligonucleotide hybridizes to a complementary portion of a nucleic acid molecule.”

#### 6. Claim Terms that Relate to Differences between Oligonucleotide Sequences

The following terms are considered together because they relate to differences in sequence between oligonucleotides or portions of oligonucleotides. The parties disagree whether the each limitation is satisfied when one oligonucleotide differs in sequence from “its adjacent” sequence, “another” sequence, “another type of” sequence, or “other types of sequences” by at least 25% (plaintiff) or whether all of these limitations mean the same thing by requiring an oligonucleotide sequence to be at least 25% different from “every” other oligonucleotide sequence (defendant).<sup>88</sup>

The court agrees with defendant that the intrinsic record supports its proposed

---

<sup>88</sup> D.I. 419 at 93.

constructions. For instance, each claim of the '233 patents requires “*each type of capture oligonucleotide . . . differs from the nucleotide sequence of other types of oligonucleotides*” by at least 25%.<sup>89</sup> Claim 1 of the '746 patent requires that “*each type of capture oligonucleotide . . . differs in nucleotide sequence when aligned to another type of capture oligonucleotide, by at least 25%.*”<sup>90</sup> This language leads to the conclusion that each capture oligonucleotide differs from every other type of capture oligonucleotide, not just one other type as plaintiffs’ construction allows. Claim 1 of the '917 patent requires that “each capture oligonucleotide probe of the array differs in sequence from *its* adjacent capture oligonucleotide, when aligned to each other by at least 25% of the nucleotides.”<sup>91</sup> Plaintiffs argue that because the '917 patent uses the singular form, the limitation is satisfied when the capture oligonucleotide differs in sequence from “just one other oligonucleotide sequence.”<sup>92</sup> As a general rule of construction, however, use of the singular form includes the plural form.<sup>93</sup> Therefore, that singular form does not require the interpretation put forth by plaintiffs.

The specification also supports defendant’s position. As discussed above, the patentees sought to avoid the problem of cross-hybridization experienced in prior art arrays. To accomplish this, “[*e*]ach of the capture oligonucleotides have substantial

---

<sup>89</sup> *Id.* at 96 (quoting '233 patent, claims 4, 7) (emphasis added by defendant).

<sup>90</sup> *Id.* (quoting '746 patent, claim 1) (emphasis added by defendant).

<sup>91</sup> '917 patent, claim 1 (emphasis added).

<sup>92</sup> D.I. 419 at 94.

<sup>93</sup> See, e.g., *TiVo, Inc. v. EchoStar Commc’ns Corp.*, 516 F.3d 1290, 1303 (Fed. Cir. 2008) (“As a general rule, the words ‘a’ or ‘an’ in a patent claim carry the meaning of ‘one or more.’”); *01 Communique Lab., Inc. v. LogMeln, Inc.*, 687 F.3d 1292, 1297 (Fed. Cir. 2012) (“The patent’s use of words such as ‘a,’ ‘its,’ and ‘the’ in the claim is insufficient to limit the meaning of ‘locator server computer’ to a single physical computer.”).



sequence differences *to minimize any chances of cross-reactivity.*<sup>94</sup> The specification also explains that:

Since each address is designed by alternating tetramer addition in three rows and three columns, a given address will differ by at least three tetramers from its neighbor. Since *each tetramer differs from every other tetramer by at least 2 bases, a given address will differ from another address by at least 6 bases.* However, in practice *most addresses will differ from most other addresses by considerably more bases.*<sup>95</sup>

Since *each 24-mer differs from its neighbor by three tetramers and each tetramer differs from another by at least 2 bases, then each 24mer differs from another by at least 6 bases (i.e., 25% of the nucleotides differ).* Thus, a wrong address would have 6 mismatches in just 24 bases and, therefore, would not be captured at the wrong address, especially under 75-80° C.<sup>96</sup>

During prosecution, the applicants told the PTO the capture oligonucleotides were substantially different from each other.

The plurality of capture oligonucleotides immobilized on a solid are *designed to differ substantially from each other in their nucleotide sequence, yet all have the same or similar melting temperature. This design strategy drastically minimizes any chance of cross-hybridization leading to false-positive signals,* while allowing for simultaneous capture of a plurality ligation products, by their addressable sequence, under uniform hybridization conditions across the array.<sup>97</sup>

In explaining the claimed invention, Dr. Gerry told the PTO:

An addressable array uses capture probes that are *de novo sequences separate and distinct from the nucleic acid sequences of interest. . . . Because the addresses are de novo sequences, they can be designed to have as little homology to each other or to any other genomic sequence as possible,* while having very similar thermodynamic properties (e.g.,

---

<sup>94</sup> '917 patent, 35:41-43 (emphasis added). During prosecution, Dr. Barany told the PTO "[c]apture probe sequences [are] designed to differ by 25% or more to minimize cross-hybridization." D.I. 421 at A1358.

<sup>95</sup> '917 patent, 36:63-37:3 (emphasis added).

<sup>96</sup> '917 patent, 37:63-38:2 (emphasis added).

<sup>97</sup> D.I. 421 at A1176 (emphasis added).

melting temperature). *This combination results in high stringency hybridization across the array with no cross hybridization.*<sup>98</sup>

Finally, named inventor Dr. Robert Hammer testified that the capture oligonucleotides all needed to be different.

Q. And in order to avoid cross hybridization, you wanted to design *each zip code sequence* to be *different from every other zip code sequence on the array, right?*

A. *Yeah, whatever the—whatever the detection scheme, the idea was to make it so they wouldn't cross react with the other, you know, positions on the array.*<sup>99</sup>

Because the intrinsic records supports defendant's proposed constructions, the court adopts those construction for the terms in this group.

- a. "each capture oligonucleotide probe of the array differs in sequence from its adjacent capture oligonucleotide probe, when aligned to each other by at least 25%"

Plaintiffs' proposed construction is: "each capture oligonucleotide probe of the array differs in sequence from an adjacent capture oligonucleotide probe, when aligned, by at least 25% in nucleotide sequence."

Defendant's proposed construction is: "each capture oligonucleotide probe [of the array] differs in sequence from every adjacent capture oligonucleotide probe, when aligned, by at least 25% in nucleotide sequence."

Court's construction: "each capture oligonucleotide probe [of the array] differs in sequence from every adjacent capture oligonucleotide probe, when aligned, by at least

---

<sup>98</sup> *Id.* at A1761 (emphasis added); see also *id.* at 1760 ("Sequence homology between the capture probes and likewise between the target sequences can jeopardize the specificity of target/probe hybridization and lead to the generation of both false positive and false negative results as illustrated in Figure 3 below.") (emphasis added).

<sup>99</sup> D.I. 422 at A2046-47 (emphasis added).

25% in nucleotide sequence.”

- b. “each type of capture oligonucleotide . . . differs in nucleotide sequence, when aligned to another type of capture oligonucleotide that is located on an adjacent position of said solid support, by at least 25%”

Plaintiffs’ proposed construction is: “each capture oligonucleotide probe of the array differs in sequence from an adjacent capture oligonucleotide probe, when aligned, by at least 25% in nucleotide sequence.”

Defendant’s proposed construction is: “each capture oligonucleotide probe [of the array] differs in sequence from every adjacent capture oligonucleotide probe, when aligned, by at least 25% in nucleotide sequence.”

Court’s construction: “each capture oligonucleotide probe [of the array] differs in sequence from every adjacent capture oligonucleotide probe, when aligned, by at least 25% in nucleotide sequence.”

- c. “each type of capture oligonucleotide . . . differs in nucleotide sequence, when aligned to another type of capture oligonucleotide, by at least 25%” / “each type of capture oligonucleotide . . . differs by at least 25% in nucleotide sequence, when aligned to another type of capture oligonucleotide”

Plaintiffs’ proposed construction is: “each type of capture oligonucleotide probe of the array differs in sequence from another type of capture oligonucleotide probe, when aligned, by at least 25% in nucleotide sequence.”

Defendant’s proposed construction is: “each type of capture oligonucleotide differs by at least 25% in nucleotide sequence, when aligned, to every other type of capture oligonucleotide.”

Court’s construction: “each type of capture oligonucleotide differs by at least 25% in nucleotide sequence, when aligned, to every other type of capture

oligonucleotide.”

- d. “each type of capture oligonucleotide . . . comprises a nucleotide sequence that differs from the nucleotide sequence of other types of capture oligonucleotides in the collection by at least 25% when aligned” / “each type of capture oligonucleotide . . . comprising nucleotide sequence that differs from the nucleotide sequence of other types of capture oligonucleotide of the collection by at least 25% when aligned” / “each type of capture nucleotide . . . with a nucleotide sequence that differs from the nucleotide sequence of other types of capture oligonucleotides on the solid support by at least 25% when aligned”

Plaintiffs’ proposed construction is: “each type of capture oligonucleotide probe differs in sequence from other types of capture oligonucleotide probes, when aligned, by at least 25% in nucleotide sequence.”

Defendant’s proposed construction is: “each type of capture oligonucleotide . . . differs by at least 25% in nucleotide sequence, when aligned, to every other type of capture oligonucleotide.”

Court’s construction: “each type of capture oligonucleotide . . . differs by at least 25% in nucleotide sequence, when aligned, to every other type of capture oligonucleotide.”

7. “uniform hybridization conditions”

Representative claim 1 of the ‘917 patent recites:

1. A device comprising:

a solid support having an array of positions each suitable for attachment of an oligonucleotide probe;

a linker suitable for coupling an oligonucleotide probe to the solid support at each of the array positions; and

an array of capture oligonucleotide probes on the solid support at the array positions, said capture oligonucleotide probes each having greater than sixteen nucleotides and able to bind to complementary nucleic acids

at *uniform hybridization conditions*, wherein each capture oligonucleotide probe of the array differs in sequence from its adjacent capture oligonucleotide probe, when aligned to each other by at least 25% of the nucleotides.<sup>100</sup>

Plaintiffs' proposed construction is: "common conditions at which different oligonucleotides are capable of hybridizing to complementary nucleic acids."

Defendant contends this term is indefinite.

"Because a patent is presumed to be valid, the evidentiary burden to show facts supporting a conclusion of invalidity is one of clear and convincing evidence."<sup>101</sup>

Section 112 ¶ 2 provides: "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention."<sup>102</sup> "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention."<sup>103</sup> "[A] claim must be 'sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent.'"<sup>104</sup> The parties disagree as to whether the specification meets these requirements.

The specification states that prior art arrays required hybridization conditions optimized for each nucleotide sequence of interest: "existing methods in the prior art

---

<sup>100</sup> '917 patent, claim 1 (emphasis added).

<sup>101</sup> *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1345 (Fed. Cir. 2007) (citing *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1338-39 (Fed. Cir. 2003)).

<sup>102</sup> 35 U.S.C. § 112 ¶ 2.

<sup>103</sup> *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

<sup>104</sup> *Ancora Techs., Inc. v. Apple, Inc.*, 744 F.3d 732, 737 (Fed. Cir. 2014) (quoting *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1249 (Fed. Cir. 2008)).

relying on allele-specific PCR, differential hybridization, or sequencing-by-hybridization methods must have hybridization conditions optimized for each new sequence being analyzed. When attempting to detect multiple mutations simultaneously, it becomes difficult or impossible to optimize hybridization conditions.”<sup>105</sup>

The claimed universal array addressed that difficulty by selecting array sequences that enabled hybridization of a plurality of oligonucleotides to occur under common conditions: “the present invention is a general method for high specificity detection of correct signal, independent of the target sequence, and under uniform conditions.”<sup>106</sup>

Plaintiffs state the specification discloses exemplary common hybridization conditions in which oligonucleotides of the array hybridize to complementary sequences in solution.<sup>107</sup> For instance, in Example 3, capture oligonucleotides were hybridized with their complements under identical conditions.<sup>108</sup> Plaintiffs maintain from those and other disclosures, a person of ordinary skill in the art would understand that “uniform hybridization conditions” means “common conditions at which different oligonucleotides are capable of hybridizing to complementary nucleic acids” and fully appreciate the “scope of the invention with reasonable certainty.”<sup>109</sup>

Defendant argues the scope of the invention is not reasonably certain. It contends the specification provides no guidance as to when hybridization conditions

---

<sup>105</sup> ‘917 patent, 42:60-66.

<sup>106</sup> ‘917 patent, 42:67-43:2.

<sup>107</sup> D.I. 419 at 111.

<sup>108</sup> *Id.* (citing ‘917 patent 47:30-48:25; 48:24-25 (“Hybridizations were performed for 15 min[utes] at 70C”)).

<sup>109</sup> *Id.*

must be uniform, i.e. can the hybridization conditions vary over time?<sup>110</sup> Likewise, the specification does not describe which hybridization conditions must be uniform.<sup>111</sup>

According to defendant, without knowing those parameters, it is impossible to understand the bounds of the claims in order to avoid infringement.<sup>112</sup>

In light of the purpose of the claimed invention, the court agrees with plaintiffs that defendant's argument is mis-focused. The purpose of the invention was to overcome the difficulty in the prior art of detecting multiple sequences simultaneously. The prior art required optimization of conditions for each different oligonucleotide sequence being analyzed. Because of that requirement, "attempting to detect *multiple mutations simultaneously*, . . . becomes difficult or impossible to optimize hybridization conditions."<sup>113</sup> The claimed invention sought to detect multiple, sometimes thousands, of sequences on the same array and, using zip codes, accomplished that goal whereby all of the oligonucleotides are exposed to the same conditions, i.e., different conditions did not have to be optimized for each sequence. Put another way, the multiple oligonucleotides are detected in a hybridization solution having uniform, or common, conditions.<sup>114</sup> If some of those conditions, e.g. temperature, vary during the reaction, each different oligonucleotide is still exposed to the same common condition.

The court, therefore, determines defendant has not shown by clear and convincing evidence that this term is indefinite and adopts plaintiffs' construction of

---

<sup>110</sup> *Id.* at 113, 116-17.

<sup>111</sup> *Id.*

<sup>112</sup> *Id.* at 113-14.

<sup>113</sup> '917 patent, 42:64-66 (emphasis added).

<sup>114</sup> *See, e.g.*, '917 patent, 42

“uniform hybridization conditions” as meaning “common conditions at which different oligonucleotides are capable of hybridizing to complementary nucleic acids.”

8. “addressable array-specific portion” / “address-specific portion” / “zip code portion”

Representative claim 1 of the ‘746 patent recites:

1. A method comprising:

providing an array of a plurality of capture oligonucleotides wherein each type of capture oligonucleotide is greater than 16 nucleotides and differs in nucleotide sequence, when aligned to another type of capture oligonucleotide, by at least 25%, wherein said capture oligonucleotides are coupled to a support;

providing a sample comprising a plurality of target oligonucleotides, each target oligonucleotide comprising (i) an *addressable array-specific portion*, (ii) a further nucleotide sequence, and (iii) a detectable reporter label;

contacting the sample comprising the plurality of target oligonucleotides with the array of capture oligonucleotides under uniform hybridization conditions effective to hybridize the addressable array-specific portion of each target oligonucleotide to its complementary capture oligonucleotide; and

detecting the reporter labels of one or more of the plurality of target oligonucleotides hybridized to their complementary capture oligonucleotides on the solid support.<sup>115</sup>

Representative claim 18 of the ‘521 patent recites:

18. A kit for identifying one or more of a plurality of target nucleotide sequences in a sample comprising:

a ligase;

a plurality of oligonucleotide probe sets, each set characterized by (a) a first oligonucleotide probe, having a target-specific portion and an *address-specific portion* and (b) a second oligonucleotide probe, having a target-specific portion; and

---

<sup>115</sup> ‘746 patent, claim 1 (emphasis added).



a collection of capture oligonucleotide wherein each type of capture oligonucleotide in the collection comprises a nucleotide sequence complementary to an address-specific portion, wherein the *address-specific portion* is comprised of a nucleotide sequence which is distinct from that of the target-specific portions, and wherein each type of capture oligonucleotide in the collection hybridizes to its complement under uniform hybridization conditions but differs by at least 25% in nucleotide sequence, when aligned to another type of capture oligonucleotide in the collection.<sup>116</sup>

Representative claim 1 of the '016 patent recites:

1. An apparatus comprising:

a solid support having an array of positions;

composite oligonucleotides coupled to the solid support at the array of positions, each of said composite oligonucleotides characterized by having a target-specific portion and a *zip code portion*, wherein the *zip code portion* of each of the composite oligonucleotides comprises a nucleotide sequence of greater than sixteen nucleotides that differs for each different target-specific portion and hybridizes to its complement under uniform hybridization conditions, wherein the nucleotide sequence of one *zip code portion* differs from the nucleotide sequence of another *zip code portion*, when aligned with each other, by at least 25% of the nucleotides; and

one or more detectable labels coupled to at least one of the composite oligonucleotide, thereby facilitating detection of the composite oligonucleotide and its *zip code portion*.<sup>117</sup>

The following terms relate to portions of the oligonucleotide sequences in the Array Patents. The parties agree these terms are directed to the portion of the composite oligonucleotide that hybridizes to the complementary capture oligonucleotide on the array.<sup>118</sup> Parties disagree as to whether the terms should be construed to prohibit the recited "portions" of oligonucleotides from hybridizing to naturally occurring

---

<sup>116</sup> '521 patent, claim 18 (emphasis added).

<sup>117</sup> '016 patent, claim 1 (emphasis added).

<sup>118</sup> D.I. 419 at 119.

nucleic acids and other oligonucleotides of the array (defendant) or not (plaintiff).<sup>119</sup> Plaintiffs contend nothing in the claims or specification supports defendant's proposed prohibition.<sup>120</sup> Defendant argues this prohibition follows from the fundamental objective stated in the specification: to prevent cross-hybridization.<sup>121</sup> The parties each reference their arguments concerning the "capture oligonucleotide probe" / "capture oligonucleotide(s)" terms as being applicable here.<sup>122</sup> Plaintiffs also state defendant's proposed constructions are also based on its purportedly incorrect arguments with respect to the "25% difference" terms.<sup>123</sup>

According to the specification, "[t]he capture oligonucleotides are *complementary* to the addressable array-specific portions"<sup>124</sup> and "[t]his oligonucleotide probe is then

---

<sup>119</sup> *Id.* at 118.

<sup>120</sup> *Id.*

<sup>121</sup> *Id.* at 119-20.

<sup>122</sup> *Id.* at 119 (*Plaintiffs' analysis above for "capture oligonucleotide probe" and "capture oligonucleotide(s) applies with equal force here."*) (emphasis added); *id.* at 120 ("[T]he lack of homology to the target or other natural DNA, and to other oligonucleotides located on the array, is fundamental to the claimed invention and *is characteristic of the "capture oligonucleotides" as described in the specification*") (emphasis added); *id.* at 122 (Like it did for the "capture oligonucleotide" terms above, Illumina is trying to further limit these claim elements to require the absence of hybridization to naturally occurring nucleic acids to other oligonucleotides on an array. . . . *Illumina generally relies on the same incorrect arguments it made to support its construction of the capture oligonucleotide terms. . . . For the same reasons already explained, there is no reason to restrict the "address" terms as Illumina proposes.*") (emphasis added); *id.* at 123 ("As described in [defendant's arguments with respect to the 'capture oligonucleotide' terms and '25% difference' terms] . . . the patentees were concerned with the problems associated with cross-hybridization, and the patents are directed to methods and technologies designed to eliminate such problems. *The arguments made in those sections apply with equal force here.*") (emphasis added).

<sup>123</sup> *Id.* at 123 ("Illumina's argument that there must be no hybridization to other oligonucleotides on the array is another attempt to require *every* oligonucleotide on the array to be different from every other. But that is incorrect, *as described above in the context of the "25% difference" terms.*") (emphasis added).

<sup>124</sup> '917 patent, 6:5-7 (emphasis added).

captured by its addressable array-specific portion, a sequence *complementary* to the capture oligonucleotide on the addressable solid support array.”<sup>125</sup> The addressable array-specific portion is complementary to the capture oligonucleotide. Because the parties each rely on their arguments concerning the “capture oligonucleotide” terms and the “25% difference” terms with respect to these terms, and the court adopted defendant’s proposed construction of those groups of terms, the court adopts defendant’s construction of these terms for the reasons explained in those sections.

a. “addressable array-specific portion”

Plaintiffs’ proposed construction is: “a portion of oligonucleotide that hybridizes to a complementary oligonucleotide, or portion thereof, at a particular location on an array.”

Defendant’s proposed construction is: “portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on the array.”

Court’s construction: “portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on the array.”

b. “address-specific portion”

Plaintiffs’ proposed construction is: “a portion of oligonucleotide that hybridizes to a complementary oligonucleotide, or portion thereof, at a particular location on an

---

<sup>125</sup> ‘917 patent, 27:1-4 (emphasis added).

array.”

Defendant’s proposed construction is: “portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on an array.”

Court’s construction: “portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on an array.”

c. “zip code portion”

Plaintiffs’ proposed construction is: “a portion of oligonucleotide that hybridizes on an array to a complementary oligonucleotide.”

Defendant’s proposed construction is: “portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on an array.”

Court’s construction: “portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on an array.”

9. “unique nucleotide sequence” / “unique nucleotide sequence portions”

Representative claim 4 of the ‘470 patent recites:

4. A method according to claim 1, wherein the oligonucleotide probes in each set are configured so that the sequence of the ligation product sequence from each oligonucleotide probe set is unique and can be distinguished from other nucleic acids in the polymerase chain reaction mixture, said method further comprising:

providing a solid support with different capture oligonucleotides immobilized at different particular sites, wherein the capture oligonucleotides have nucleotide sequences complementary to the *unique nucleotide sequences* of given probe sets;

contacting the polymerase chain reaction mixture, after said subjecting it to one or more polymerase chain reaction cycles with the solid support under conditions effective to hybridize the extension product to the capture oligonucleotide in a base-specific manner, wherein said detecting indicates the presence of extension products captured using the *unique nucleotide sequence portions* to identify one or more target nucleotide sequences in the sample.<sup>126</sup>

Plaintiffs' proposed construction is: "a sequence that is different for each locus."

Defendant's proposed construction is: "portion(s) of a ligation product that hybridizes to a complementary address sequence on an addressable array that does not exist in ligation products resulting from any other target sequence."

The parties dispute whether every ligation product has to have a portion that hybridizes to the array and is different from every other ligation product (defendant) or whether such a portion need only be different for each locus analyzed (plaintiffs).<sup>127</sup>

The parties competing constructions differ based upon whether the claims cover the embodiments illustrated in Figures 13B and 13C of the '917 patent, as plaintiffs contend, or are limited to covering only the Figure 13B embodiment, as defendant contends.

With respect to Figure 13B, on which defendant relies, the specification recites:

*FIGS. 13A-B shows two LDR primers that are designed to discriminate wild type and mutant p53 by containing the discriminating base C or T at the 3' end. In the presence of the correct target DNA and Tth ligase, the discriminating probe is covalently attached to a common downstream*

---

<sup>126</sup> '470 patent, claim 4 (emphasis added).

<sup>127</sup> D.I. 419 at 124.

oligonucleotide. The downstream oligonucleotide is fluorescently labeled. *The discriminating oligonucleotides are distinguished by the presence of unique addressable array-specific portions, Z1 and Z2, at each of their 5' ends.*<sup>128</sup>

With respect to Figure 13C, which plaintiffs rely on, the specification recites:

FIG. 13C shows the discriminating signals may be quantified using a fluorescent imager. This format uses a *unique address* where oligonucleotide probes are distinguished by having different fluorescent groups, F1 and F2, on their 5' end. *Either oligonucleotide probe may be ligated to a common downstream oligonucleotide probe containing an addressable array-specific portion Z1 on its 3' end.* In this format, both wild type and mutant LDR products are captured at the same address on the array, and are distinguished by their different fluorescence. This format allows for a more efficient use of the array and may be preferred when trying to detect hundreds of potential germline mutations.<sup>129</sup>

Defendant acknowledges that Figure 13C is described as allowing a capture probe to have more than one corresponding type of assay product. It maintains that while the independent claims of the asserted '470 patent family cover both embodiments, the asserted dependent claims, through their use of the term "unique," cover only the embodiment depicted in Figure 13B.<sup>130</sup> The court disagrees with defendant. Each embodiment describes a "unique" address or portion. The court declines to exclude the Figure 13C embodiment from the construction of these terms and adopts plaintiffs proposed construction of "unique nucleotide sequence" and "unique nucleotide sequence portions" to mean "a sequence that is different for each locus."

10. "ligase detection reaction" / "ligase detection reaction cycles" / "suitable for ligation together"

---

<sup>128</sup> '917 patent, 21:28-37 (emphasis added).

<sup>129</sup> '917 patent, 21:56-67 (emphasis added).

<sup>130</sup> D.I. 419 at 128.

Representative claim 1 of the '285 patent recites:

1. A method for identifying one or more different target nucleotide sequences comprising:

providing a sample potentially containing one or more target nucleotide sequences comprising sequence differences;

performing a *ligase detection reaction* to form a ligation product comprising a first target specific portion complementary to the target nucleotide sequence and a second target specific portion complementary to the target nucleotide sequence, wherein the ligation product further comprises a 5' upstream primer-specific portion and a 3' downstream primer-specific portion, wherein the first target specific portion and the second target specific portion are located between the 3' downstream primer-specific portion and the 5' upstream primer specific portion;

providing an oligonucleotide primer set comprising (a) an upstream primer containing the same sequence as the 5' upstream primer-specific portion of the ligation product sequence and (b) a downstream primer complementary to the 3' downstream primer-specific portion of the ligation product sequence;

performing a polymerase chain reaction to form extension products comprising the ligation product sequence and/or complements thereof; and

detecting the extension products to identify one or more target nucleotide sequences in the sample.<sup>131</sup>

Representative claim 1 of the '470 patent recites:

1. A method for identifying one or more different target nucleotide sequences comprising:

providing a sample potentially containing one or more target nucleotide sequences comprising sequence differences;

providing one or more oligonucleotide probe sets, each set comprising (a) a first oligonucleotide probe comprising a target-specific portion and a 5' upstream primer-specific portion and (b) a second oligonucleotide probe

---

<sup>131</sup> '285 patent, claims 1 (emphasis added).

comprising a target-specific portion and 3' downstream primer-specific portions, wherein the first and second oligonucleotide probes in each particular set are *suitable for ligation together* when hybridized on a corresponding target nucleotide sequence, but have a mismatch which interferes with such ligation when first and second oligonucleotide are hybridized to any other nucleotide sequence present in the sample;

providing a ligase;

blending the sample, the one or more oligonucleotide probe sets, and the ligase to form a ligase detection reaction mixture;

subjecting the ligase detection reaction mixture to one or more *ligase detection reaction cycles* to form a ligation product sequence comprising (a) the 5' upstream primer specific portion, (b) the target-specific portions, and (c) the 3' downstream primer-specific portion, when the respective target nucleotide sequence of the corresponding oligonucleotide probe set is present in the sample;

providing one or a plurality of oligonucleotide primer sets, each comprising (a) an upstream primer containing the same sequence as the 5' upstream primer-specific portion of the ligation product sequence and (b) a downstream primer complementary to the 3' downstream primer-specific portion of the ligation product sequence;

providing a polymerase;

blending the ligase detection reaction mixture with the one or a plurality of oligonucleotide primer sets, and the polymerase to form a polymerase chain reaction mixture;

subjecting the polymerase chain reaction mixture to one or more polymerase chain reaction cycles to form extension products comprising the ligation product sequence and/or complements thereof; and

detecting the extension products to identify one or more target nucleotide sequences in the sample.<sup>132</sup>

a. "ligase detection reaction"

Plaintiffs' proposed construction is: "reaction capable of forming a ligation

---

<sup>132</sup> '470 patent, claim 1 (emphasis added).



product that can be detected.”

Defendant’s proposed construction is: “reaction which detects the presence of target nucleotide sequence in a sample by using a ligase and one or more sets of two oligonucleotide probes in which the ligase joins the two oligonucleotide probes only if they are hybridized at adjacent positions on a target nucleotide sequence.”

b. “suitable for ligation together”

Plaintiffs’ proposed construction is: “capable of forming a ligation product.”

Defendant’s proposed construction is: “able to be ligated together only when hybridized adjacent to one another on the target nucleotide sequence.”

c. “ligase detection cycles”

Plaintiffs’ proposed construction is: “cycles comprising at least the following steps: denaturation, hybridization, and ligation, with the denaturation step occurring at the beginning or the end.”

Defendant’s proposed construction is: “ligase detection reaction comprising: (1) denaturation; (2) hybridization of the oligonucleotide probe set; and (3) ligation of adjacently hybridized oligonucleotide probe sets.”

The Parties have two disputes about these terms. First, is whether a ligation detection reaction requires that the oligonucleotides must hybridize adjacent or abutting each other (defendant) or do not have to (plaintiff).<sup>133</sup> The second dispute relates to whether a “ligase detection cycle” requires a denaturation step to be at the beginning of the cycle (defendant) or whether it can be at the end, after the oligonucleotide probes

---

<sup>133</sup> D.I. 419 at 132.

are hybridized and (some) are ligated (plaintiff).<sup>134</sup>

Beginning with the first dispute, plaintiffs primarily rely a claim differentiation argument.

Claim 1 of the '039 patent recites:

1. A method for identifying a target nucleotide sequence comprising:

forming a ligation product on a target nucleotide sequence in a *ligation detection reaction mixture*, wherein the ligation product comprises an upstream primer portion and a downstream primer portion, wherein the upstream primer portion and the downstream primer portion are not complementary with the target nucleotide sequence;

amplifying the ligation product to form an amplified ligation product in a polymerase chain reaction (PCR) mixture, wherein the PCR mixture comprises an upstream primer and a downstream primer; and

detecting the amplified ligation product to identify the target nucleotide sequence.<sup>135</sup>

Claim 2 of the '039 patent depends from claim 1 and recites:

2. The method according to claim 1 wherein the ligation detection reaction mixture comprises *adjacently hybridizing* ligation probes.<sup>136</sup>

Because claim 2 adds the “adjacently hybridizing” requirement, plaintiffs maintain it would be improper to impose that requirement on claims not explicitly requiring adjacency.<sup>137</sup> However, “[i]t is axiomatic that the claim construction process entails more than viewing the claim language in isolation. Claim language must always be read

---

<sup>134</sup> *Id.* at 134.

<sup>135</sup> '039 patent, claim 1 (emphasis added).

<sup>136</sup> '039 patent, claim 2 (emphasis added). Plaintiffs also note, independent claim 10 of the '453 patent recites that a ligation product is formed after oligonucleotides “are hybridized to said corresponding target nucleotide sequence,” without requiring adjacency, while independent claim 11 requires the ligation product be formed by ligation probes “*hybridized adjacent* to one another.” D.I. 419 at 134.

<sup>137</sup> D.I. 419 at 133.

in view of the written description and any presumption created by the doctrine of claim differentiation will be overcome by a contrary construction dictated by the written description or prosecution history.”<sup>138</sup>

The court determines that in this case the presumption is overcome. The ‘470 specification incorporates by reference the definition of “ligase detection reaction” in the disclosure of Barany’s prior art patent application WO 91/17239. The specification states “[t]he ligase detection reaction is described generally in WO 9[1]/17239 to Barany et al. . . . , the disclosures of which are hereby incorporated by reference.”<sup>139</sup> That application recites:

In order to avoid any misunderstandings as to what is being referenced, and to provide the reader with a clear understanding of what is being described, the following definitions will be used: . . . . “Ligase detection reaction (LDR)” refers to the use of *two adjacent oligonucleotides* for the detection of specific sequences with the aid of a thermophilic ligase with linear product amplification.<sup>140</sup>

When the specification “reveal[s] a special definition given to a claim term by the patentee . . . the inventor’s lexicography governs.”<sup>141</sup> This includes definitions included in documents incorporated by reference.<sup>142</sup>

---

<sup>138</sup> *Retractable Techs., Inc v. Becton, Dickinson & Co.*, 663 F.3d 1296, 1305 (Fed. Cir. 2011) (citations and internal quotation marks omitted).

<sup>139</sup> ‘470 patent, 32:13-20.

<sup>140</sup> D.I. 422 at A2191, A2196 (emphasis added).

<sup>141</sup> *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (*en banc*).

<sup>142</sup> *See Cook Biotech Inc. v. Acell, Inc.*, 460 F.3d 1365, 1376 (Fed. Cir. 2006) (construing a term based on the specification of a prior art patent incorporated by reference); *see also id.* (“Incorporation by reference provides a method for integrating material from various documents into a host document . . . by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein.”) (quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)).

The specification consistently and exclusively describes the ligase detection reaction of the invention as requiring adjacent hybridization:

A second aspect of *the present invention* relates to a method for identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences. . . . In the ligase detection reaction phase one or more oligonucleotide probe sets are provided. . . . The oligonucleotide probes in a particular set are *suitable for ligation together when hybridized adjacent* to one another on a corresponding target nucleotide sequence. However, there is a *mismatch which interferes with such ligation when they are hybridized to any other nucleotide sequence present in the sample*. . . . The ligase detection reaction mixture is subjected to one or more ligase detection reaction cycles. These cycles include a denaturation treatment and a hybridization treatment. . . . The hybridization treatment causes the oligonucleotide probe sets to *hybridize at adjacent positions* . . . . Once hybridized, the oligonucleotide probe sets ligate to one another to form a ligation product sequence.<sup>143</sup>

Figure 16 of the '470 patent illustrates successful ligation where the oligonucleotide probes are adjacently hybridized and unsuccessful ligation where there is a gap between the hybridized probes.<sup>144</sup> Describing Figure 16, the specification

---

<sup>143</sup> '470 patent, 9:19-52 (emphasis added); see also, e.g., '470 patent, 7:1:25 ("The last phase of this aspect of *the present invention* involves a *ligase detection reaction process*. . . . The ligase detection reaction mixture is subjected to one or more ligase detection reaction cycles having a denaturation treatment and a hybridization treatment . . . . In the hybridization treatment, the oligonucleotide probe sets *hybridize at adjacent positions* in a base-specific manner to the respective secondary extension products if present.") (emphasis added); '470 patent, 25:8:12 ("[P]airs of oligonucleotide probes, having a target-specific portion and a primer-specific portion, are allowed to *anneal adjacent to each other* on target nucleic acids and ligate to one another (*in the absence of mismatches*.")) (emphasis added); '470 patent, 18:54-57 ("During LDR, oligonucleotide probes *ligate to their adjacent oligonucleotide probes* only in the presence of target sequence which give perfect complementarity at the junction cite.") (emphasis added); '470 patent, 23:27-32 ("The oligonucleotide probes in a particular set are *suitable for ligation together when hybridized adjacent to one another* on a corresponding target nucleotide sequence. However, there is a *mismatch which interferes with such ligation* when they are hybridized to any other nucleotide sequence present in the sample.") (emphasis added).

<sup>144</sup> '470 patent, Figure 16.

states “LDR products are only formed on the correct length target sequence, and thus the presence of that target is distinguished (step 4).”<sup>145</sup> Named inventor Dr. Matthew Lubin confirmed in deposition that Figure 16 illustrates unsuccessful ligation where there is a gap between the hybridized oligonucleotide probes:

Q. So, in this case, what is being shown as the mismatch in figure 16 preventing ligation is the gap of a single A between the spots of hybridization for the two LDR primers; correct?

A. That’s what is described.<sup>146</sup>

The specification distinguishes prior art gap ligase chain reaction methods.

Jou, et al., “Deletion Detection in Dystrophin Gene by Multiplex Gap Ligase Chain Reaction and Immunochromatographic Technology,” *Human Mutation* 5:86-93 (1995) relates to the use of so called “*gap ligase chain reaction*” process to amplify simultaneously selected regions of multiple exons with the amplified products being read on an immunochromatographic strip having antibodies specific to the different haptens on the probes for each exon. . . . *However, the prior-art methods described above are not readily adaptable for use in detecting multiple selected sequences in a convenient, automated single-assay format.*<sup>147</sup>

*The gap ligase chain reaction process requires an additional step—polymerase extension. The use of probes with distinctive ratios of charge/translation frictional drag for a more complex multiplex will either require longer electrophoresis times or the use of an alternate form of detection. The need thus remains for a rapid single assay format to detect the presence or absence of multiple selected sequences in a polynucleotide sample.*<sup>148</sup>

During prosecution, Dr. Barany also distinguished the gap ligase chain reaction disclosed in prior art by Zaun:

[T]he LCR procedure utilized by Zaun . . . is known as gap-LCR. . . . [M]y

---

<sup>145</sup> ‘470 patent, 27:61-63.

<sup>146</sup> D.I. 422 at A2757.

<sup>147</sup> ‘470 patent, 2:51-3:5 (emphasis added).

<sup>148</sup> ‘470 patent, 3:59-67 (emphasis added).

*LCR procedure involves use of oligonucleotide probe sets which hybridize to a target nucleic acid in abutting relationship, and, if there is perfect complementarity at their junction, these oligonucleotides can be joined with ligase. By contrast, in gap-LCR, the oligonucleotide probe sets do not hybridize to a target nucleic acid in abutting relation and, therefore, are not potentially suitable for immediate ligation. Instead, there is a gap which must be closed using polymerase before any ligation can occur.*

The claims of the present application clearly refer to an LDR procedure to distinguish single nucleotide differences and require that the oligonucleotide probe be configured to *hybridize “adjacent to one another”* on a corresponding target nucleotide sequence. *Since they do not involve LCR or filling a gap, these claims are readily distinguishable from Zaun.*<sup>149</sup>

Based on the foregoing evidence, the court concludes the claims require the two oligonucleotide probe to hybridize at adjacent positions. Therefore, the court construes “ligase detection reaction” to mean “reaction which detects the presence of target nucleotide sequence in a sample by using a ligase and one or more sets of two oligonucleotide probes in which the ligase joins the two oligonucleotide probes only if they are hybridized at adjacent positions on a target nucleotide sequence” and “suitable for ligation together” to mean “able to be ligated together only when hybridized adjacent to one another on the target nucleotide sequence.”

The parties’ second dispute with whether a ligase detection reaction cycle requires a denaturation step at the beginning of the cycle or whether it can be at the end, after oligonucleotide probes are hybridized and (some) are ligated.

“[A] claim requires an ordering of steps when the claim language, as a matter of logic or grammar, requires that the steps be performed in the order written, or the

---

<sup>149</sup> D.I. 421 at A1310-11 (emphasis added). The ‘470 patent specification describes a ligase chain reaction (“LCR”) as a method of LDR using two sets of complementary oligonucleotides. ‘470 patent, 32:20-25.

specification directly or implicitly requires an order of steps.”<sup>150</sup>

Defendant does not disagree that an additional denaturation step may be included in a ligase detection reaction cycle but insists an initial denaturation step is required for separation of double stranded DNA to create a single stranded target.<sup>151</sup> It points to the figures in the patent and the related descriptions of those figures for its position. For example defendant notes Figure 10 illustrates the cycle, and is described in the specification, in a manner consistent with its proposed order of steps.

FIG. 10 is a schematic diagram depicting an LDR/PCR process for multiplex detection of gene amplifications and deletions. . . . *Following denaturation of DNA at 94° C.*, pairs of oligonucleotide probes, having a target-specific portion and a primer-portion, are allowed to *anneal adjacent to each other* on the target nucleic acids and ligate to one another (in the absence of mismatches).<sup>152</sup>

That and the other figures defendant cites in its brief do require denaturation of double stranded DNA at the beginning of the cycle. Those figures, and related descriptions, are specific embodiments. Plaintiffs, however, note that if the reaction starts with a single-stranded target, such as a strand of RNA, there is nothing to denature as a first step.<sup>153</sup> The court agrees with plaintiffs that in that case, an initial denaturation step is not required as defendant’s proposed construction does. Consequently the court adopts plaintiffs’ proposed construction of “ligase detection reaction cycle” to mean “cycles comprising at least the following steps: denaturation, hybridization, and ligation, with the denaturation step occurring at the beginning or the

---

<sup>150</sup> *mFormation Tech., Inc. v. Research in Motion Ltd.*, 764 F.3d 1392, 1398 (Fed. Cir. 2014) (internal quotation marks omitted).

<sup>151</sup> D.I. 419 at 149.

<sup>152</sup> ‘470 patent, 25:3-11 (emphasis added).

<sup>153</sup> D.I. 419 at 146.

end.”

11. “ligase detection reaction mixture” / “ligation detection reaction mixture” / “reaction mixture” / “polymerase chain reaction (PCR) mixture”

Representative claim 1 of the ‘470 patent recites:

1. A method for identifying one or more different target nucleotide sequences comprising:

providing a sample potentially containing one or more target nucleotide sequences comprising sequence differences;

providing one or more oligonucleotide probe sets, each set comprising (a) a first oligonucleotide probe comprising a target-specific portion and a 5' upstream primer-specific portion and (b) a second oligonucleotide probe comprising a target-specific portion and 3' downstream primer-specific portions, wherein the first and second oligonucleotide probes in each particular set are suitable for ligation together when hybridized on a corresponding target nucleotide sequence, but have a mismatch which interferes with such ligation when first and second oligonucleotide are hybridized to any other nucleotide sequence present in the sample;

providing a ligase;

blending the sample, the one or more oligonucleotide probe sets, and the ligase to form a *ligase detection reaction mixture*;

subjecting *the ligase detection reaction mixture* to one or more ligase detection reaction cycles to form a ligation product sequence comprising (a) the 5' upstream primer specific portion, (b) the target-specific portions, and (c) the 3' downstream primer-specific portion, when the respective target nucleotide sequence of the corresponding oligonucleotide probe set is present in the sample;

providing one or a plurality of oligonucleotide primer sets, each comprising (a) an upstream primer containing the same sequence as the 5' upstream primer-specific portion of the ligation product sequence and (b) a downstream primer complementary to the 3' downstream primer-specific portion of the ligation product sequence;

providing a polymerase;

blending *the ligase detection reaction mixture* with the one or a plurality of oligonucleotide primer sets, and the polymerase to form a *polymerase*



*chain reaction mixture*;

subjecting *the polymerase chain reaction mixture* to one or more polymerase chain reaction cycles to form extension products comprising the ligation product sequence and/or complements thereof; and

detecting the extension products to identify one or more target nucleotide sequences in the sample.<sup>154</sup>

- a. “ligase detection reaction mixture’ / “ligation detection reaction mixture” / “reaction mixture”

Plaintiffs’ proposed construction is: “mixture containing the components or products of a ligase detection reaction.”

Defendant’s proposed construction is: “mixture that contains all of the components used to perform a ligase detection reaction, including a sample, a ligase and one or more oligonucleotide probe sets, in either ligated or unligated form.”

- b. “polymerase chain reaction (PRC) mixture”

Plaintiffs’ proposed construction is: “mixture containing the components or products of a polymerase chain reaction.”

Defendant’s proposed construction is: “mixture that contains all of the components used to perform a polymerase chain reaction, including a polymerase, a template sequence, and unextended and/or extended primer sequences containing sequences that are the same as, and sequences that are complementary to, the template sequence.”

These terms relate to mixtures of components at stages of the claimed methods. The parties’ dispute is whether the components used in a reaction must still be present

---

<sup>154</sup> ‘470 patent, claim 1 (emphasis added).

after the reaction has been performed.<sup>155</sup>

Plaintiffs contend each of these mixtures refer to two mixtures that necessarily contain different components.<sup>156</sup> According to plaintiffs, the first ligase reaction mixture contains the components that are input into the ligase detection reaction and the second ligase detection reaction mixture contains the output of the ligase detection mixture than is, in turn, input into the PCR reaction.<sup>157</sup> They make the same argument regarding the polymerase chain reaction mixture. These arguments are contrary to the claim language and the specification.

Claim 1 of the '470 patent introduces “a ligase detection reaction mixture” and then twice refers back to “*the* ligase reaction mixture.” The meaning of “a ligase detection reaction mixture” does not change in the claim to include a product of the reaction. Also, the claims recites “subjecting the ligase detection reaction mixture to one or more ligase detection reaction cycles to form a *ligation product sequence*,” making clear the “ligase detection reaction mixture” is distinct from “a ligation product.” Furthermore, the ligase detection mixture is subjected to “one or more ligase detection reaction cycles.” For there to be more than one cycle, at least some of each of the original components necessarily must be present.

The same analysis applies to polymerase chain reaction mixture. The claim introduces “a polymerase chain reaction mixture” and refers back to “*the* polymerase chain reaction mixture.” And again, the polymerase chain reaction mixture is subject to

---

<sup>155</sup> D.I. 419 at 153.

<sup>156</sup> *Id.* at 152.

<sup>157</sup> *Id.*

“one or more polymerase chain reaction cycles to form *extension products*.” As with the ligase detection reaction mixture, the polymerase chain reaction mixture is different than the product of the polymerase chain reaction. Because the mixture is subjected to “one or more” cycles, at least some of each of the original components necessarily must be present.

Moreover, the specification describes both mixtures consistent with the above understanding: “[t]he sample, the plurality of oligonucleotide probe sets, and a ligase are blended together to form a ligase detection reaction mixture”<sup>158</sup> and “[t]he ligase detection reaction mixture is blended with the one or a plurality of oligonucleotide primer sets and the polymerase to form a polymerase chain reaction mixture.”<sup>159</sup> Neither description includes the products of LCR/PCR reactions as part of the reaction mixtures.

Because defendant’s proposed constructions are consistent with the claim language and the specification, the court construes “ligase detection reaction mixture” / “ligation detection reaction mixture” / “reaction mixture” to mean “mixture that contains all of the components used to perform a ligase detection reaction, including a sample, a ligase and one or more oligonucleotide probe sets, in either ligated or unligated form” and “polymerase chain reaction (PCR) mixture” to mean “mixture that contains all of the components used to perform a polymerase chain reaction, including a polymerase, a template sequence, and unextended and/or extended primer sequences containing sequences that are the same as, and sequences that are complementary to, the template sequence.”

---

<sup>158</sup> ‘470 patent, 23:32-35.

<sup>159</sup> ‘470 patent, 23:63-65.

12. “target-specific portion(s)”

Representative claim 18 of the ‘521 patent recites:

18. A kit for identifying one or more of a plurality of target nucleotide sequences in a sample comprising:

a ligase;

a plurality of oligonucleotide probe sets, each set characterized by (a) a first oligonucleotide probe, having a *target-specific portion* and an address-specific portion and (b) a second oligonucleotide probe, having a *target-specific portion*; and

a collection of capture oligonucleotides wherein each type of capture oligonucleotide in the collection comprises a nucleotide sequence complementary to an address-specific portion, wherein the address-specific portion is comprised of a nucleotide sequence which is distinct from that of the *target-specific portions*, and wherein each type of capture oligonucleotide in the collection hybridizes to its complement under uniform hybridization conditions but differs by at least 25% in nucleotide sequence, when aligned to another type of capture oligonucleotide in the collection.<sup>160</sup>

Plaintiffs’ proposed construction is: “portion of oligonucleotide capable of hybridizing to a target nucleic acid.”

Defendant’s proposed construction is: “portion of an oligonucleotide capable of hybridizing to a target nucleic acid sequence of interest from naturally occurring nucleic acids.”

The parties’ dispute is whether the “target nucleic acid” that hybridizes to a “portion of an oligonucleotide” is restricted to “naturally occurring nucleic acids” (defendant) or not (plaintiffs). In support of such restriction, defendant notes the specification repeatedly describes target nucleic acids as naturally occurring and

---

<sup>160</sup> ‘521 patent, claim 18 (emphasis added).

contains no description of target-specific portions hybridizing to artificial target nucleic acids.<sup>161</sup> It also points to the specification's description of the invention as being used to detect cancer and other human diseases where the target nucleic acids in the sample are naturally occurring: "[t]he array of the present invention will be universal, making it useful for detection of cancer mutations, inherited (germline) mutations, and infectious diseases."<sup>162</sup> Defendant also cites statements made during prosecution and in depositions relating to use of the invention in disease detection. During prosecution, Dr. Barany submitted a declaration describing how the claimed invention "provides a rapid and reliable method for the detection of genomic mutations (e.g., genetic disease mutations and cancer related mutations), promoter methylation, and infectious diseases (e.g., bacterial, fungal and viral infections."<sup>163</sup> At deposition, Dr. Barany testified that "detection of cancer mutations, inherited (germline) mutations, and infectious diseases" was "a very important *part* of the invention."<sup>164</sup>

Although disease detection, using naturally occurring nucleic acids, is an important focus of the invention, the evidence defendant relies on does not convince the court there was a clear and unambiguous disavowal of detection of non-naturally occurring nucleic acids.<sup>165</sup> Therefore, the court adopts plaintiffs' proposed construction of "target-specific portion(s)" as meaning "portion of oligonucleotide capable of

---

<sup>161</sup> D.I. 419 at 161.

<sup>162</sup> '917 patent, 43:7-9.

<sup>163</sup> D.I. 421 at A1633.

<sup>164</sup> D.I. 422 at A2043 (emphasis added).

<sup>165</sup> *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1357 (Fed. Cir. 2004) (The "choice to describe only a single embodiment does not mean that the patent clearly and unambiguously disavowed other embodiments.").

hybridizing to a target nucleic acid.”

**Order: The Court’s Claim Construction**

At Wilmington, this 6<sup>th</sup> day of May, 2016, having heard oral argument, having reviewed the papers submitted with the parties’ proposed claim constructions, and having considered all of the parties’ arguments (whether or not explicitly discussed herein);

IT IS ORDERED that the disputed claim language in asserted claims of the patent-in-suit, as identified by the parties, shall be construed below consistent with the tenets of claim construction set forth by the United States Court of Appeals for the Federal Circuit in *Phillips v. AWH Corp.*,<sup>166</sup> as follows:

<b>Claim Term</b>	<b>Construction</b>
oligonucleotide probe set(s)	oligonucleotide sequences that hybridize to a target sequence in a ligase detection reaction
primer-specific portion	portion of an oligonucleotide capable of hybridizing to a nucleotide sequence used to initiate PCR amplification
ligation product sequence(s) ligation products	oligonucleotide sequence(s) resulting from a ligase detection reaction
composite oligonucleotide	an oligonucleotide having two or more portions
solid support	a single unitary substrate
an array of positions	positions organized in known locations

---

<sup>166</sup> 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*).

Claim Term	Construction
linker	a molecule that covalently binds an oligonucleotide to the solid support, or is absorbed thereto, without an intervening structure
immobilized	covalently bound or bound via hybridization
attached	covalently bound or absorbed
suitable for attachment	functionalized to permit covalent bonding
coupled to	covalently bound or bound via hybridization
capture oligonucleotide probes capture oligonucleotide(s)	oligonucleotide [probe] which has no homology to a target sequence and is complementary to the addressable array specific portion of an oligonucleotide containing an addressable array specific portion and a target specific portion
capturing said one or more amplification products to a solid support	hybridizing the amplification products to capture oligonucleotides attached on the solid support
each [type of] capture oligonucleotide hybridizes to a nucleic acid molecule comprising a complementary nucleotide sequence  the capture oligonucleotides hybridize to complementary portions of the target nucleic acid molecules	each capture oligonucleotide hybridizes to an oligonucleotide containing a complementary nucleotide sequence
one or more target nucleic acid molecules hybridized [to complementary portions of the capture oligonucleotides on the solid support]	one or more nucleic acid molecules are hybridized to one or more complementary nucleic acid molecules on a solid support
each type of capture oligonucleotide . . . hybridizes to its complement	at least a portion of each capture oligonucleotide hybridizes to its complement

Claim Term	Construction
wherein the zip code portion of each of the composite oligonucleotides . . . hybridizes to its complement	wherein an address portion of each of the composite oligonucleotides, or a portion thereof, hybridizes to its complement
the capture oligonucleotides hybridize to the complementary portions of the nucleic acid molecules	at least a portion of each capture oligonucleotide hybridizes to a complementary portion of a nucleic acid molecule
each capture oligonucleotide probe of the array differs in sequence from its adjacent capture oligonucleotide probe, when aligned to each other by at least 25%	each capture oligonucleotide probe [of the array] differs in sequence from every adjacent capture oligonucleotide probe, when aligned, by at least 25% in nucleotide sequence
each type of capture oligonucleotide . . . differs in nucleotide sequence, when aligned to another type of capture oligonucleotide that is located on an adjacent position of said solid support, by at least 25%	each capture oligonucleotide probe [of the array] differs in sequence from every adjacent capture oligonucleotide probe, when aligned, by at least 25% in nucleotide sequence
<p>each type of capture oligonucleotide . . . differs in nucleotide sequence, when aligned to another type of capture oligonucleotide, by at least 25%”</p> <p>each type of capture oligonucleotide . . . differs by at least 25% in nucleotide sequence, when aligned to another type of capture oligonucleotide</p>	each type of capture oligonucleotide differs by at least 25% in nucleotide sequence, when aligned, to every other type of capture oligonucleotide



Claim Term	Construction
<p>each type of capture oligonucleotide . . . comprises a nucleotide sequence that differs from the nucleotide sequence of other types of capture oligonucleotides in the collection by at least 25% when aligned</p> <p>each type of capture oligonucleotide . . . comprising nucleotide sequence that differs from the nucleotide sequence of other types of capture oligonucleotide of the collection by at least 25% when aligned</p> <p>each type of capture nucleotide . . . with a nucleotide sequence that differs from the nucleotide sequence of other types of capture oligonucleotides on the solid support by at least 25% when aligned</p>	<p>each type of capture oligonucleotide . . . differs by at least 25% in nucleotide sequence, when aligned, to every other type of capture oligonucleotide</p>
<p>uniform hybridization conditions</p>	<p>common conditions at which different oligonucleotides are capable of hybridizing to complementary nucleic acids</p>
<p>addressable array specific portion</p>	<p>portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on the array</p>
<p>address-specific portion</p>	<p>portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on an array</p>

Claim Term	Construction
zip code portion	portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on an array
unique nucleotide sequence unique nucleotide portion	a sequence that is different for each locus
ligase detection reaction	reaction which detects the presence of target nucleotide sequence in a sample by using a ligase and one or more sets of two oligonucleotide probes in which the ligase joins the two oligonucleotide probes only if they are hybridized at adjacent positions on a target nucleotide sequence
suitable for ligation together	able to be ligated together only when hybridized adjacent to one another on the target nucleotide sequence
ligase detection reaction cycles	cycles comprising at least the following steps: denaturation, hybridization, and ligation, with the denaturation step occurring at the beginning or the end
ligase detection reaction mixture ligation detection reaction mixture reaction mixture	mixture that contains all of the components used to perform a ligase detection reaction, including a sample, a ligase and one or more oligonucleotide probe sets, in either ligated or unligated form

Claim Term	Construction
polymerase chain reaction (PCR) mixture PCR mixture	mixture that contains all of the components used to perform a polymerase chain reaction, including a polymerase, a template sequence, and unextended and/or extended primer sequences containing sequences that are the same as, and sequences that are complementary to, the template sequence
target-specific portion(s)	portion of oligonucleotide capable of hybridizing to a target nucleic acid

Pursuant to 28 U.S.C. § 636(b)(1)(B), FED. R. CIV. P. 72 (b)(1), and D. DEL. LR 72.1, any objections to the Report and Recommendation shall be filed within fourteen (14) days limited to twenty-five (25) pages after being served with the same. Any response shall be limited to twenty-five (25) pages.

The parties are directed to the Court's Standing Order in Non-Pro Se Matters for Objections Filed under FED. R. CIV. P. 72 dated November 16, 2009, a copy of which is found on the Court's website ([www.ded.uscourts.gov](http://www.ded.uscourts.gov).)

/s/ Mary Pat Thyng  
UNITED STATES MAGISTRATE JUDGE