IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

NATERA, INC., Plaintiff, v. NEOGENOMICS LABORATORIES, INC., Defendant.	C.A. No. 1:23-CV-629-CCE-JLW

DEFENDANT NEOGENOMICS LABORATORIES, INC.'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

As NeoGenomics predicted, Natera's opening brief confirms that Natera is hiding behind "plain and ordinary meaning" to forestall a ruling as to what the claims actually mean. But the Federal Circuit mandates that "[w]hen the parties present a fundamental dispute regarding the scope of a claim term, it is the court's duty to resolve it." *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1362 (Fed. Cir. 2008).

Natera also wrongly asserts that NeoGenomics is asking for a redo of the preliminary injunction. The "preliminary" injunction stage was just that—preliminary. Claim construction is before the Court now for the first time in accord with the case schedule and Local Rules. Nor is NeoGenomics taking inconsistent positions: NeoGenomics has argued previously that the claims are invalid under ***Natera***'s constructions, as it had every right to do.

II. DISPUTED CLAIM TERMS

A. "SNP [single nucleotide polymorphism] loci . . . associated with cancer" ('035 Patent, Claim 1)

NeoGenomics' proposed construction correctly incorporates the express definition of SNP from the specification combined with the claim language "associated with cancer."

There is no dispute that the specification expressly defines SNP in the "Definitions" section of the patent: "Single Nucleotide Polymorphism (SNP) refers to a single nucleotide that may differ between the genomes of ***two members*** of the same species. The usage of the term should not imply any limit on the frequency with which

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each variant occurs." Dkt. 1-2, '035 patent, 34:46-50 (emphasis added). Natera agrees that these sentences define the term "SNP." *See* Dkt. 262, Natera Op. Br. at 10. Such an express definition must govern. *BookIT Oy v. Bank of Am. Corp.*, 817 F. App'x. 990, 994 (Fed. Cir. 2020) ("There can be no clearer definitions than those expressly recited in the patent.").[1]

Natera contends that NeoGenomics ignored the claim language "associated with cancer" in its construction. Not so. Natera's brief misstates NeoGenomics' position by omitting the words "associated with cancer" from NeoGenomics' proposed construction, which expressly maintains that requirement. *Compare* Dkt. 262, Natera Op. Br. at 7 (omitting "associated with cancer") *with* Dkt. 249, Joint Claim Construction Statement at 4. The question is what it means to have an "SNP" associated with cancer, and NeoGenomics' construction answers that question, consistent with the definition and other specification disclosures. *See, e.g.*, '035 patent, 8:42-43 ("polymorphism . . . associated with an above normal risk for cancer or associated with cancer"); *id*., 20:44-48

[1] Natera's cited cases regarding the standard for finding a definition or disavowal are therefore irrelevant. *See Medicines Co. v. Mylan, Inc.*, 853 F.3d 1296, 1306 (Fed. Cir. 2017) (finding no controlling definition where specification used "is characterized by" rather than "refers to" or "as defined herein"); *GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014) (finding "no lexicography" where "[t]he specifications and their prosecution histories d[id] not define IDC connector or include any indication that the inventors intended to act as their own lexicographers"); *Golden Bridge Tech., Inc. v. Apple Inc.*, 758 F.3d 1362, 1365 (Fed. Cir. 2014) (finding disclaimer of claim scope based on an information disclosure statement (IDS) submitted during prosecution); *Cordis Corp. v. Bos. Sci. Corp.*, 561 F.3d 1319, 1329 (Fed. Cir. 2009) (finding no disavowal of claim scope during prosecution because claim amendment and related argument were not sufficiently clear).

("the target loci includes a sequence (e.g., a polymorphism or other mutation) . . . associated with the disease or phenotype of interest (such as cancer)"). The Court should accordingly adopt NeoGenomics's proposed construction, which simply plugs the express definition of SNP into the claim.

None of Natera's arguments overcome the specification's express definition.

First, Natera wrongly asserts the second sentence of the patent's definition negates the first sentence—such that SNP should refer to "all genomic variants" at a single nucleotide position. Dkt. 262, Natera Op. Br. at 7; 10 ("[T]he second part of the definition . . . makes clear that the term SNP covers not only nucleotides that may differ between genomes of two members of the same species but also refers to variants more generally."). The first sentence is an unambiguous definition. The second sentence clarifies that the first sentence's definition applies regardless of the frequency with which the single nucleotide varies among two members of the same species. *See* '035 patent, 163:5-10, 172:19-20, 181:39-43 (discussing known population frequency as a variable). Thus, "each variant" in the second sentence refers back to the SNPs discussed in the first sentence. *See, e.g.*, '035 patent, 48:53-54 ("frequency of the SNPs within a target population" (plural)); *id*., 172:41-42 ("The best estimate of the true father genotypes are given by the population frequencies at each SNP").

Second, Natera is wrong that the specification uses "SNP" interchangeably with other mutation types (although, as noted, the express definition would govern even if it did). Dkt. 262, Natera Op. Br. at 8. Instead, the specification uses "SNP" or

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"polymorphism" consistent with the definition and the separate term "mutation" when discussing mutations more broadly. *See, e.g.*, 8:41-43 ("the target human loci comprises a polymorphism ***or*** other mutation"); 10:57-65 ("the target loci include a sequence (e.g., a polymorphism ***or*** other mutation)"); 18:29-34 (same); 20:44-48 (same) (emphases added).

As NeoGenomics explained, SNPs are inherited (like variations in the BRCA gene associated with breast and ovarian cancers) and do not include somatic mutations (which arise later). Dkt. 264, Neo Op. Br. at 5; Ex. A, Buckingham & Flaws, *Molecular Diagnostic Fundamental Methods and Clinical Applications* (2007), 228 ("Polymorphisms are inherited."). Natera understands the difference. In the related '454 patent, Natera claimed the somatic mutations found in tumor DNA using a different (and scientifically correct) term—single nucleotide variant ("SNV"). *E.g.*, Dkt. 1-1, '454 patent, 171:25-43. The two are distinct.

Third, Natera dismisses NeoGenomics' construction for allegedly excluding some embodiments. That happens frequently: "precedent is replete with examples of subject matter that is included in the specification, but is not claimed." *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008) (reviewing cases and concluding disclosure of alternative embodiment could not "outweigh the language of the claim" and remaining intrinsic evidence); *Intamin Ltd. v. Magnetar Techs., Corp.,* 483 F.3d 1328 (Fed. Cir. 2007) (affirming construction that "may well not cover [disclosed] embodiment" because "claims of the patent need not encompass all disclosed

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embodiments"). For example, the specification describes evaluating fetal DNA but the claims explicitly exclude the analysis of blood from a pregnant woman.

Fourth, Natera points to Dr. Van Ness's declaration from the preliminary injunction proceedings, but Dr. Van Ness never opined on the proper construction of "SNP loci . . . associated with cancer." Dkt. 116 (Van Ness Decl. ISO NeoGenomics' Opposition to PI), ¶¶ 64-65 (identifying and addressing "amplifying" as the sole term for construction). Instead, Dr. Van Ness showed how the claims are invalid even assuming Natera's construction. NeoGenomics was not obliged to raise every argument at its disposal at the preliminary injunction stage (nor could it). Moreover, even if Dr. Van Ness had addressed construction of the term, claim construction positions and rulings during a preliminary injunction are merely tentative and subject to revision as the record develops. *E.g.*, *Myco Indus., Inc. v. BlephEx, LLC*, 955 F.3d 1, 15 (Fed. Cir. 2020) (recognizing the district court "issue[d] only a tentative claim construction" in the preliminary injunction stage and vacating the claim construction because "there [were] errors in the claim construction analysis"); *Momenta Pharms., Inc. v. Teva Pharms. USA Inc.*, 809 F.3d 610, 619 (Fed. Cir. 2015) ("preliminary injunction opinion . . . is not binding."). Finally, even had Dr. Van Ness offered an opinion, that could not overcome the specification's express definition of SNP. *See Profectus Tech. LLC v. Huawei Techs. Co.*, 823 F.3d 1375, 1380 (Fed. Cir. 2016) ("Extrinsic evidence may not be used 'to contradict claim meaning that is unambiguous in light of the intrinsic evidence.'") (citation omitted); *SunTiger, Inc. v. Scientific Research Funding Group*, 189 F.3d 1327,

1335-36 (Fed. Cir. 1999) (stating it "would be improper . . . to rely upon" expert declaration where the patent "leaves no real doubt" as to the proper construction).

Natera defined the term SNP in the specification, and that definition controls what SNP means in the context of the claim language.

B. "amplifying the tagged products . . . wherein one of the amplification steps comprises targeted amplification" ('035 Patent, Claim 1)

Natera has previously conceded that "Claim 1 requires that DNA be 'tagg[ed] in one step and then [amplified] in one or more subsequent steps." Dkt. 264-2, Natera Appeal Resp. Br. at 37 (citing '035 patent at 249:46-57). Natera now also agrees that tagging and amplifying must be separate steps. Dkt. 262, Natera Op. Br. at 3. That is enough to resolve the dispute. The Court could simply rule: "This step is separate from and must occur after completion of the step of 'tagging . . . with one or more universal tail adaptors to generate tagged products.'" However, the Court should also adopt NeoGenomics' proposed further clarification, which explains what those requirements mean in functional terms. As in *Amgen v. Sandoz,* the language of claim 1 requires "separate steps performed by different solutions," which in this case means different primers. Dkt. 264, Neo Op. Br. at 7-10 (quoting *Amgen Inc. v. Sandoz Inc.*, 923 F.3d 1023 (Fed. Cir. 2019)).[2] That requirement is even clearer here, where the "tagging" and

[2] Natera's citation to *Northern Telecom v. Samsung* for the proposition that unstated limitations cannot be read into a claim is irrelevant. Dkt. 262, Natera Op. Br. at 3-4. NeoGenomics is not seeking to add any words to the claim. *See Northern Telecom Ltd. v. Samsung Elecs. Co., Ltd.*, 215 F.3d 1281, 1290-91 (Fed. Cir. 2000) (rejecting

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"amplifying" steps are set out in different indented paragraphs and separated by a semicolon, which Natera admits "strongly indicates that each step is separate and distinct." Natera Op. Br. at 17 (quoting *In re Affinity Labs of Texas, LLC*, 856 F.3d 902, 907 (Fed. Cir. 2017).

As discussed, Natera concedes claim 13 (which depends on claim 1 via claim 12) refers to tagging performed by an amplification "separate and apart" from the "amplifying" step in claim 1. Dkt. 264, Neo Op. Br., Ex. B (Dkt. 264-2, Natera Appeal Resp. Br. at 39) ("[Claim 13] illustrates that the tagging in claim 1's tagging step may be performed by its own amplification process, ***separate and apart*** from the amplification that occurs in the amplification step.") (emphasis added). Natera tries to distinguish dependent claims 12 and 13 on the ground that they include "open-ended 'comprising' language," therefore "leaving open the possibility" that tagging with universal tail adaptors may also satisfy the "amplifying the tagged products" step. Dkt. 262, Natera Op. Br. at 4-5. But claims 12 and 13 establish their antecedent basis in the "tagging" step, not the "amplifying" step in claim 1: claim 12 refers to the universal tail adaptors only found in the "tagging" step, and claim 13 is expressly limited to the "tagging" step. '035 patent, Claim 12 ("The method of claim 1, wherein the one or more universal tail adaptors comprise . . .") & Claim 13 ("The method of claim 12, wherein tagging the cell free DNA comprises . . .").

Samsung's proposed addition that the claimed aluminum must be arranged in a "layer" because neither the concept of a layer nor a minimum amount of aluminum appeared in the claim).

Nor does Natera's assertion that claim 1 is broader than its dependents help its cause. Dkt. 262, Natera Op. Br. at 5. Claim 1 recites tagging with universal tail adaptors, while its dependents recite different ways to attach those universal tail adaptors—adding them by ligation in claim 2 and by amplification in claim 13. In both cases, the addition of those universal tail adaptors happens as part of the tagging step.

NeoGenomics' proposed construction is not "wholly unsupported by the intrinsic or extrinsic evidence." Dkt. 262, Natera Op. Br. at 3. The specification describes using the universal tail adaptors (after tagging) in a ***subsequent*** (separate) amplification step. Dkt. 264, Neo Op. Br. at 10. Indeed, ***all*** three working examples in the specification that mention universal adaptors describe adding them in a first reaction before targeted amplification in a separate downstream step. *See* '035 patent, 212:6-39 (adding universal adaptors, performing universal amplification using primers specific to universal adaptors, followed by targeted amplification); 214:13-24 (same), 217:58-218:3 (same). This intrinsic evidence is like the intrinsic evidence the court relied on in *Amgen* in construing the claims to require "separate steps performed by different solutions." 923 F.3d at 1028 (citing "four exemplary purification methods using separate washing and eluting steps and discrete solutions").

Natera repeatedly asserts the patent describes its theory that different cycles of a single PCR can satisfy both the tagging and amplification steps. But Natera merely strings together the definitions of "Universal Adapters" and "universal priming sequence" and a separate paragraph (located fifty pages later) stating generally that primers may

contain a common tail sequence. Dkt. 262, Natera Op. Br. at 5-6 (citing '035 patent, at 42:22-23, 42:14-17, 90:38-56). These paragraphs are divorced from any working example. They do not discuss, nor does any other portion of the patent discuss, individual PCR cycles, much less suggest that the same PCR reaction could be considered both "tagging" and "amplifying the tagged products." *See Seal-Flex, Inc. v. Athletic Track and Court Constr.*, 172 F.3d 836, 845 (Fed. Cir. 1999) ("[One] cannot alter the plain meaning of the claim language by referring to parts of the specification out of context.").

The only other intrinsic evidence Natera cites is a portion of the specification describing a step of preferentially enriching fetal DNA for detecting chromosomal abnormalities:

> The targeted PCR may be massively multiplexed, for example with 10,000 primers in one reaction volume, where the primers target SNPs on chromosomes 13, 18, 21, X, and those loci that are common to both X and Y, and optionally other chromosomes as well. The selective enrichment and/or amplification may involve tagging each individual molecule with different tags, molecular barcodes, tags for amplification, and/or tags for sequencing.

'035 patent, 156:25-32). Contrary to Natera's characterization, the portion cited does not include any "express teach[ing]" that the claimed tagging and amplifying steps may occur in different cycles of the same PCR, nor does it even mention universal tail adaptors. Dkt. 262, Natera Op. Br. at 6. Instead, it illustrates that additional tags and barcodes can be added to already tagged products in claim 1's amplifying step. *E.g.*, '035 patent, claim 1 ("wherein one of the amplifying steps introduces a barcode and one or more sequencing

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tags"). Indeed, just two sentences earlier, the same paragraph describes tagging with universal tail adaptors followed by amplifying the tagged DNA using those adaptors. '035 patent, 156:16-20 ("The clinician may use molecular biology techniques described in this disclosure to append universal amplification tags to the DNA in the DNA derived from the plasma sample. The clinician may amplify the universally tagged DNA."). Thus, the very passage on which Natera relies illustrates separately performing claim 1's steps of tagging with universal tail adaptors followed by targeted amplification of the tagged products.

The Court should reject Natera's attempt to blur the lines between the claimed steps and adopt NeoGenomics' proposed clarification.

C. "sequencing the amplicons" ('454 Patent, Claims 1, 14)

Natera's opening brief confirms that it advances "plain and ordinary" meaning so that it may later argue RaDaR infringes even where intervening steps after amplification change what amplicons are present before sequencing. But the claims require that sequencing be performed on "the amplicons" (which is to say, the same amplicons) that resulted from the amplification step.

Natera's brief acknowledges that "the amplicons" must be the product of the preceding targeted amplification step. Dkt. 262, Natera Op. Br. at 12 ("'[T]he amplicons' from the targeted multiplex amplification …."). The issue is thus not whether some ***other*** language in the claim precludes intervening steps. Instead, the Court must give effect to the claim language referring to "the" amplicons: the claim itself requires that the

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sequenced amplicons are the same amplicons obtained from the targeted amplification, and intervening steps such as size selection or barcoding PCR would mean that the amplicons being sequenced are not the same amplicons obtained from performing the targeted multiplex amplification. *See* Dkt. 264, Neo Op. Br. at 11-12 (discussing *Guardant Health, Inc. v. Found. Med., Inc.*, No. CV 17-1616-LPS-CJB, 2019 WL 5677748, at *10 (D. Del. Nov. 1, 2019)).

Natera says nothing about the disclaimer it made during prosecution of the related ’008 patent that was thoroughly addressed at the hearing on its preliminary injunction. *See* Dkt. 162-3 (Nov. 27, 2023 PI Hrg. Tr.) at 56:4-6. As discussed in NeoGenomics’ opening brief, Natera obtained a patent with limitations nearly identical to claim 14 of the ’454 patent “due to lack of intermediate steps between the multiplex amplification and sequencing step.” Dkt. 264, Neo Op. Br. at 14-15 (citing Dkt. 264-3, Ex. C, ’008 Patent File History, May 18, 2020 Interview Summ. at 2). And Natera agrees that the independent claims of the ’454 patent should be construed consistently, so its disclaimer must apply to both independent claims. Dkt. 262, Natera Op. Br. at 11 n.2 (“The language in [claims 1 and 14] should be construed to have the same meaning.”). Natera has no response to the point that it is trying to recapture what it disclaimed during prosecution. *See Elekta Instrument S.A. v. O.U.R. Scientific Int’l, Inc.*, 214 F.3d 1302, 1308 (Fed. Cir. 2000) (“Claims that have been narrowed in order to obtain issuance over the prior art cannot later be interpreted to cover that which was previously disclaimed during prosecution.”).

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The use of "comprising" in the preamble of claims 1 and 14 is thus irrelevant. *See* Dkt. 262, Natera Op. Br. at 13-14. Merely inserting the word "comprising" cannot displace the clear antecedent basis established in the claims. The Federal Circuit has "warned against using terms such as 'comprising,' or 'including,' as 'weasel word[s] with which to abrogate claim limitations.'" *Liberty Ammunition, Inc. v. United States*, 835 F.3d 1388, 1399 (Fed. Cir. 2016). The bounds of "comprising" are also limited by Natera's express disavowal. *Horizon Meds. LLC v. Alkem Lab'ys, Ltd.*, No. CV 18-1014-RGA, 2020 WL 4569472, at *4 (D. Del. Aug. 7, 2020) (rejecting patentee's argument that "comprising" should be construed as an "open-ended transitional phrase" that "permits the inclusion of additional elements" where it "disavowed other ingredients beyond those listed in the claim term").

NeoGenomics' proposal therefore does not "rewrite" the claims to read "'directly' sequencing the amplicons into the sequencing" step. Rather, it reflects the antecedent relationship between "***the*** amplicons" in the sequencing step and "amplicons" obtained by "performing targeted multiplex amplification . . . to obtain amplicons." It also reflects Natera's disclaimer of "intermediate steps between the multiplex amplification and sequencing step from the scope of the claims." Dkt. 264-3, Ex. C, '008 Patent File History, May 18, 2020 Interview Summ. at 3. Natera's reliance on *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014), is therefore misplaced. There the court rejected an argument that "it is proper to rely on the purpose of the invention in construing the claim." *Id.* NeoGenomics' proposal does not rely on the

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"purpose" of the claims; it respects the antecedent relationship between terms.

NeoGenomics' construction also does not "read out preferred embodiments" (although in view of the disclaimer, it would be proper even if it did).[3] Dkt. 262, Natera Op. Br. at 14. Neither of the steps Natera contends must occur before sequencing on an Illumina sequencer is precluded by the claim language. The claim does not contain similar antecedent language in the targeted multiplex amplification step that would preclude prior intervening steps, so sequencing tags and barcodes could be added before targeted multiplex amplification, as described by the specification. *See* Dkt. 264, Neo Op. Br. at 13 (citing '454 patent, 99:12-22; 99:47-49). Thus, dependent claims 11 and 25's recitation of "performing barcoding PCR prior to sequencing" does not open the flood gates to intervening steps that conflict with the claim requirements. *See, e.g.,* Dkt. 262, Natera Op. Br. at 13.

Finally, Natera's proposed plain and ordinary meaning construction would improperly punt claim construction to the jury. *See Every Penny Counts, Inc. v. Am. Express Co.*, 563 F.3d 1378, 1383 (Fed. Cir. 2009) ("[T]he court's obligation is to ensure

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[3] "[P]rosecution history disclaimer can overcome the presumption of claim differentiation." *Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1097 (Fed. Cir. 2013); *see also Elekta Instrument S.A.*, 214 F.3d at 1308 (holding that disclaimer during prosecution may compel a construction even if it "would exclude the preferred and only embodiment disclosed in the specification"). In *Biogen*, the Federal Circuit held that the applicant's disclaimer of particular types of antibodies overcame the presumption of claim differentiation in that case, where dependent claims recited additional types of antibodies. *Id.* The court noted that "the applicants' disclaimer . . . [was] not necessarily inconsistent with other possible embodiments or even the dependent claims, so long as they involve chimeric, humanized, or human antibodies that are similar to Rituxan®." *Id.*

that questions of the scope of the patent claims are not left to the jury. In order to fulfill this obligation, the court must see to it that disputes concerning the scope of the patent claims are fully resolved."); *O2 Micro*, 521 F.3d at 1362 ("[w]hen the parties present a fundamental dispute regarding the scope of a claim term, it is the court's duty to resolve it"). NeoGenomics' proposed construction, by contrast, would resolve the parties' dispute over the scope of this term.

Ultimately, what Natera characterizes as a "second bite at the apple" is the first time this claim construction issue has been squarely before the Court, which has thus far not made any findings regarding the '454 patent. NeoGenomics' proposal respects the claim language and reflects Natera's statements during prosecution, while Natera takes pains to avoid saying what the claims mean. NeoGenomics' construction is correct and should be adopted.

D. "sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads" ('454 Patent, Claims 1, 14)

The parties' dispute is straightforward. NeoGenomics proposes a construction that recognizes the "sequencing" and "detecting" steps in claims 1 and 14 are separate and distinct functions that must occur in order as a matter of logic, grammar, and science. *See* Dkt. 264, Neo Op. Br. at 17 (quoting *Mformation Techs., Inc. v. Research in Motion, Ltd.*, 764 F.3d 1392, 1398-99 (Fed. Cir. 2014)). By contrast, Natera relies almost entirely on punctuation to argue that these distinct actions form a single, amorphous process (but, unlike the case for every other claim term, does not argue for plain and ordinary

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meaning). *See* Dkt. 262, Natera's Op. Br. at 16-17. NeoGenomics' construction adheres to the express language and structure of the claims, while Natera's does not.

Natera's argument hinges on the presence of a semicolon between the three indented subparagraphs forming the body of claims 1 and 14, and a comma instead of a semicolon separating the "sequencing" and "detecting" steps in the third subparagraph. Dkt. 262, Natera's Op. Br. at 16-17. Natera cites *In re Affinity Labs, LLC*, but that case at most stands for the proposition that the presence of a semicolon may indicate that a limitation described for one step may not apply to a subsequent step.[4] *Affinity Labs* says nothing about collapsing two steps into one just because they are separated by a comma rather than a semicolon.

Natera does not address the words of the claims themselves, and as NeoGenomics articulated in its opening brief, the claims recite "sequencing … to obtain sequence reads" and "detecting … SNV mutations … ***from the sequence reads***." '454 patent, claim 1; NeoGenomics' Op. Br. at 17. In other words, the claim recites that "SNV mutations" must be detected from previously obtained "sequence reads." Natera similarly ignores the specification's description of the "sequencing" and "detecting" steps, which clarifies that sequencing generates DNA sequence data, and detecting analyzes that sequence data to determine if any SNVs are present. *See, e.g.*, '454 patent, 5:63–67; 28:19; 31:17-21; 43:15-35; 60:21–63:49; 65:20–33; 67:52-56147:49–151:42; &

[4] Notably, Natera ignores *Affinity Labs* when it comes to '035 patent claim 1, which uses semicolons to separate the tagging and amplifying steps.

Figs. 69, 70.

Finally, Natera is wrong that the "wherein" clauses at the end of the third subparagraph of claims 1 and 14 show that "sequencing" and "detecting" are part of the same step. Dkt. 262, Natera's Op. Br. at 18. Claim 1's wherein clause refers to "the sequencing" and claim 14's wherein clause refers to "detecting." Neither clause shows that the two steps should be treated as one.

E. "clonal" / "subclonal" ('454 Patent, Claims 3-5, 17-19)[5]

Natera argues at length that a POSA would understand the meaning of the words "clonal" and "subclonal." Dkt. 262, Natera Op. Br. at 19-20 (citing Metzker Decl. ¶¶ 34-37, 46-47, 51-64, 70-82, 168:23-26 (Example 13)). That's not the point—NeoGenomics agrees that "clonal" and "subclonal" are basic terms known in the art and refer in principle to whether mutations are present in all or only a subset of tumor cells. *See* Dkt. 264-5, Smith Decl. iso Neo Op. Br. at ¶ 21 (setting forth same definition) ("Smith Decl"). But that does not end the indefiniteness inquiry.

Definiteness requires not just that a person of ordinary skill in the art ("POSA") would understand the basic words in a claim, but also that they be informed of the boundaries of what constitutes infringement of the patent. *Solomon v. Kimberly-Clark Corp.,* 216 F.3d 1372, 1379 (Fed. Cir. 2000); Manual of Patent Examining Procedure

[5] NeoGenomics inadvertently omitted claims 17-19 from earlier claim construction exchanges. As acknowledged by Natera, claims 17-19 contain the same limitations regarding clonality as claims 3-5, except they are dependent on claim 14. NeoGenomics seeks a finding of indefiniteness as to claims 17-19 for the same reasons as claims 3-5.

§ 2173. The '454 patent fails to do so because it fails to guide a POSA on ***how to assess*** whether a mutation is clonal versus subclonal, and in turn, how a POSA should assess the claims' scope.

As NeoGenomics explained, it is not practical to sample and test every cell of a tumor, so there are multiple ways a POSA could go about determining whether a mutation is clonal or subclonal, and those different ways could yield different results. Dkt. 264, Neo Op. Br. at 19-20 (discussing the "illusion of clonality"). The '454 patent fails to inform a POSA which of those multiple possible ways to use. *Id.* For instance, the patent is silent on important parameters such as how many samples should be taken and from where those samples should be taken. *Id.*

Indeed, Natera is itself inconsistent when drawing the line between clonal and subclonal. In places, Natera contends that the '454 patent uses "absolute values: a mutation detected in ***all*** sampled areas of a tumor (clonal) versus a mutation detected in some but not all sampled areas (subclonal)." Dkt. 262, Natera Op. Br. at 18-19 (emphasis added). Elsewhere, Natera contends that a mutation is clonal if it is "present in ***essentially all*** of the cancer cells." *Id.* at 19-20 (emphasis added). Regardless of the label—"absolute values," "essentially all," or something else—Natera does not cite evidence in the specification sufficient to inform a POSA how to reliably determine whether a mutation is clonal or subclonal.

Dr. Metzker's own discussion of Figure 53B illustrates the sampling issue. Figure 53B below shows the results from Example 13 where Natera's assay was used to identify

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clonal and subclonal mutations in cancer patient samples. ’454 patent at 168:20-58; Metzker Decl., ¶ 36. Dr. Metzker highlights the clonal mutations in red boxes (where R1, R2, and R3 all contained values greater than zero) and the subclonal mutations (where R1, R2, or R3 contained one or more zeroes) in green boxes. Metzker Decl., ¶ 36. Blank cells indicate no biopsy sample was taken. ’454 patent at 168:35-36.

Sample	Gene	Chrom	ChromStart	Natera			
				VAF R1	VAF R2	VAF R3	VAF Plasma
L12	BRIP1	chr17	59924572	22.6	7.74	10.07	3.71
L12	CARS	chr11	3062181	22.39	10.47	18.21	5.02
L12	CIC	chr19	42797381	0	0	8.17	1.71
L12	CYFIP1	chr15	22940733	0	0	0	0
L12	FAT1	chr4	187519147	9.81	4.26	0.77	0.57
L12	KDM6A	chrX	44921898	6.33	3.54	0	0.28
L12	MLLT4	chr6	168347475	9.04	4.26	0.73	0.95
L12	NFE2L2	chr2	178098801	73.12	39.92	53.94	23.25
L12	RASA1	chr5	86642517	7.37	0	0.35	0
L12	TP53	chr17	7578406	22.93	9.17	16.97	4.89
L12	TP53	chr17	7578190	21.48	8.67	22.09	5.77
L13	EGFR	chr7	55241708	27.06	23.14	60.79	1.16
L13	EGFR	chr7	55242511	23.93	18.01	56.31	1.09
L13	HERC4	chr10	69793756	0.16	1.92	5.72	0
L13	JAK2	chr9	5022084	0.27	2.79	6.09	0
L13	KMT2C	chr7	151947008	0	0	6.69	0
L13	MSH2	chr2	47693816	5.04	3.33	12.67	0
L13	MTOR	chr1	11292495	2.4	1.38	6.01	0
L13	PLCG2	chr16	81942036	2.8	1.7	6.89	0
L13	TP53	chr17	7579509	6.11	3.76	15.4	0.4
L15	ALK	chr2	29940530	7.2	1.39		0
L15	GABRG1	chr4	46060315	11.84	2.04		0
L15	KDM6A	chrX	44922755	6.54	0.91		0.17
L15	MLL2	chr12	49443815	12.41	0		
L15	ROS1	chr6	117687379	10.82	2.94		0.15
L15	SLC39A4	chr8	145638322	18.59	0		0
L15	TP53	chr17	7578254	12.6	2.5		0
L15	ZFHX4	chr8	77776735	10.26	2.3		0
L15	ZMYM4	chr1	35827319	12.84	3.46		0
L17	BRCA2	chr13	32914959	15.03	27		0
L17	KRAS	chr12	25398284	14.22	23.79		0
L17	NF1	chr17	29653134	18.6	23.1		0
L17	NF1	chr17	29528088	0	0	17.79	0.37
L17	PAX8	chr2	113984793	6.6	0		0
L17	TP53	chr17	7577610	0	0	18.97	0
L17	TP53	chr17	7577079	15.36	33.7		0
L17	TRIM67	chr1	231299607	18.38	30.95		0.57
L17	RIP11	chr14	92471631	6.44	0		0

= mmPCR-NGS

FIG. 53B

Figure 53B shows that the number of samples taken was not consistent even within a single experiment—three samples were taken for L12 and L13, but only two

samples were taken for L15 and for some (but not other) genes in L17. Figure 53B also illustrates why the number of samples can affect whether a gene mutation is called clonal or subclonal. L12 KDM6A (row 6, green) would have been called clonal if only R1 and R2 samples were taken. Similarly, L2 CIC (row 3, green) would have been called clonal if R3 was the only sample taken. L15 KDM6A and ROS1 (rows 23 and 25, red) would have been called subclonal if a third R3 sample was taken and the mutation was missing from that sample. Figure 53B thus illustrates the subjective nature of how a scientist calls a mutation clonal or subclonal without providing sufficient guidance as to the scope of the claims.

The prosecution history does not help Natera's cause. Dr. Metzker's declaration addresses the examiner's statement regarding paragraphs 111 and 748, but is noticeably silent about how paragraph 111 provides any guidance on the claims' scope, presumably because he agrees paragraph 111 refers to a different use of the term "clone." Dkt. 263, Metzker Decl., ¶ 47. Paragraph 748 simply describes the abstract distinction between clonal and subclonal populations without providing any guidance about ***how*** to figure out whether a mutation is clonal or subclonal. '454 patent, 168:20-26 ("Clonal populations had VAF13 allele calls in all biopsied samples assayed and in plasma while subclonal populations had VAF allele calls in at least one biopsy sample, but not all biopsy samples.").

Finally, Natera's argument that NeoGenomics waived indefiniteness because it included these claims in its IPR Petition without raising indefiniteness is misplaced. By

statute, NeoGenomics could not have brought an indefiniteness challenge under Section 112 in its IPR petition. 35 U.S.C. § 311(b) (permitting challenges only under Sections 102 (anticipation) and 103 (obviousness) of the Patent Act); *Samsung Elecs. Am., Inc. v. Prisua Engineering Corp.*, 948 F.3d 1342, 1350 (Fed. Cir. 2020) ("[W]e hold that the Board may not cancel claims for indefiniteness in an IPR proceeding."). Moreover, the Federal Circuit has rejected Natera's premise that asserting claims are obvious in light of prior art is a concession that the claims are definite. *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 801, 813 (Fed. Cir. 2021) ("[I]t is not always impossible to adjudicate a prior-art challenge, one way or other, just because some aspect of a claim renders the claim indefinite."). NeoGenomics could and did rely on Natera's apparent constructions for purposes of the petition.

The Court should find that the terms "clonal" and "subclonal" as recited in the claims are indefinite.

F. "capable of detecting an SNV mutation that is present in [less than or equal to 0.015% / 0.005% to 0.015%] of the cell-free DNA comprising the SNV locus" ('454 Patent, Claims 14, 28)[6]

Natera's argument that claims 14 and 28 do not require any limit of detection is wrong. The plain text of the claims recites methods "capable of detecting" an SNV mutation that is present at certain low levels. As explained by Dr. David Smith, a

[6] Natera identified the broader claim terms including the phrase "capable of detecting an SNV mutation that is" in its opening brief. NeoGenomics initially excluded that phrase from its proposed terms to remove duplicative language, but agrees the broader terms are the proper terms to analyze.

method's limit of detection is the lowest concentration of mutations a method is capable of detecting. Dkt. 264-5, Smith Decl., ¶ 43. This is exactly how the specification explains limit of detection: "In some embodiments, a ***limit of detection*** is such that a mutation (such as an SNV or CNV) that is present in less than or equal to 10, 5, 2, 1, 0.5, 0.01, or 0.005% of the DNA or RNA molecules with that locus in a sample (such as a sample of cfDNA or cfRNA) is detected (or is ***capable of being detected***)." '454 patent, 92:67-93:5 (under heading "Limit of Detection") (emphases added). Accordingly, a POSA would understand that to assess whether a particular method falls within the claim's scope, one would assess the method's limit of detection and then see if that number falls within the recited ranges. The problem is that different approaches to assessing a method's limit of detection leads to different results, and the specification sets forth three "methods for calculating the limit of detection for any of the methods of the invention." '454 patent, 157:51-158:36; Dkt. 264-5, Smith Decl., ¶ 43-44.

Natera makes a single argument for why the claims are not indefinite if they do refer to the limit of detection: it contends Example 6 provides two methods of calculating the limit of detection and "instructs the POSA that if the results are inconsistent, they should rely on whatever the higher number of the two is." Dkt. 262, Natera Op. Br. at 23-24. Example 6 contains no such instruction.

As discussed in NeoGenomics' opening brief, Example 6 provides three "exemplary methods for calculating the limit of detection for any of the methods of the invention" and describes the third method as "calculat[ing] the limit of detection based on

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the maximum value of the above two metrics." '454 patent, 157:51-53, 158:24-26; Dkt. 264, Neo Op. Br. at 22-24. The three methods yield as much as a ten-fold difference in the limit of detection. Dkt. 264, Neo Op. Br. at 22-24. Nowhere does Example 6 suggest that one exemplary method should be used over the others. The claims also do not specify which of the three methods should be used. The Court should find claims 14 and 28 indefinite. *See Dow Chem. Co. v. NOVA Chems. Corp. (Canada)*, 803 F.3d 620, 634-35 (Fed. Cir. 2015); *HZNP Meds. LLC v. Actavis Lab'ys UT, Inc.*, 940 F.3d 680, 696–99 (Fed. Cir. 2019).

Natera's contrived approach for determining whether a method is capable of the claimed level of detection finds even less support in the claims and specification. Natera contends a POSA reading the patent would know to do so "by contriving a sample to contain a certain mutation at the recited percentages in the sample, and performing the method on the contrived sample to see if the mutation is detected or not." Dkt. 262, Natera Op. Br. at 21-22. Natera's proposed method is not mentioned anywhere in the claims or the specification. Instead, Dr. Metzker strings together multiple disparate disclosures in the specification and ***infers*** that a POSA would know to perform that method. Dkt. 263, Metzker Decl., ¶¶ 38-40. Dr. Metzker cites a statement in Example 8—describing an experiment for measuring CNVs (a different class of mutation from SNVs[7])—that one could "create synthetic cancer plasma" by spiking synthetic ctDNA "at

[7] A single nucleotide variant (SNV) affects only a single nucleotide in DNA. Copy number variations (CNVs) "involv[e] both duplications and deletions of sequences that

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known concentrations." *Id.,* ¶ 40. Dr. Metzker then creates a method that involves "creat[ing] a synthetic sample containing a mutation at a known percentage, run[ning] the assay, and evaluat[ing] whether or not the mutation was detected." Dkt. 263, Metzker Decl., ¶ 40. Dr. Metzker's proposed method is simply not disclosed in the patent and does not cure the indefiniteness of the claims.

The Court should find that the '454 patent fails to inform a POSA how to determine the claimed limits of detection and accordingly that claims 14 and 28 are indefinite.

III. CONCLUSION

For the foregoing reasons, NeoGenomics' constructions should be adopted.

This the 22nd day of April, 2024

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typically range in length from 1,000 base pairs (1 kb) to 20 megabases (mb)." '454 patent, 1:35-39.

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CERTIFICATE OF WORD COUNT

The undersigned counsel hereby certifies that this brief complies with the word count limitations of Local Rule 7.3(d).

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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on April 22, 2024, a true and correct copy of the foregoing **DEFENDANT NEOGENOMICS LABORATORIES, INC.'S RESPONSIVE CLAIM CONSTRUCTION BRIEF** was served via electronic notice and electronic mail upon the following:

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