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

PLAINTIFF NATERA, INC.'S OPENING CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

Defendant NeoGenomics, Inc. ("NeoGenomics") did not raise any of the claim terms it now identifies for construction during the preliminary injunction proceeding.[1] Only now, after the Court found that Plaintiff Natera, Inc. ("Natera") is likely to succeed on the merits, has NeoGenomics manufactured ***eight*** new ways to try to escape liability: through unsupported constructions of four terms associated with the independent claims of both Asserted Patents,[2] and indefiniteness challenges to four additional terms of the '454 Patent.[3] None of NeoGenomics' claim construction arguments or indefiniteness-based invalidity challenges find support in the intrinsic record or controlling caselaw—in fact, they are directly contradicted by NeoGenomics' own expert and NeoGenomics' positions in the co-pending, pre-institution IPR proceeding relating to the '454 Patent.

Regarding the four terms proposed for construction, three should be given their plain and ordinary meaning as understood by a person of ordinary skill in the art ("POSA") and

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[1] In the preliminary injunction proceeding, NeoGenomics' expert opined only on construction of the term "amplifying" in connection with Claims 1 and 13 of the '035 Patent, and shared Natera's expert's view regarding its plain meaning as "increasing the number of copies of a molecule, such as a molecule of DNA." Doc. 116 (Van Ness Decl.) at ¶65; Doc. 145 (Metzker PI Reply Decl.) at ¶¶71-73; Doc. 145-1 at ECF 56-57 (219:6-220:16). NeoGenomics is not advancing that construction here.

[2] The "Asserted Patents" in this case are U.S. Patent Nos. 11,519,035 ("'035 Patent") and 11,530,454 ("'454 Patent").

[3] Because the parties have not had an opportunity to develop a record of fact or expert discovery, NeoGenomics' request to include invalidity challenges during claim construction is premature. Moreover, Natera lacks fair notice of NeoGenomics' challenges: to date, NeoGenomics has provided only one conclusory paragraph in its invalidity contentions as to the alleged indefiniteness of each of the challenged terms. Metzker Decl., Ex. 1 at 41-43.

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supported by intrinsic and extrinsic evidence. For the remaining term, Natera proposes a construction consistent with the intrinsic and extrinsic evidence to assist the jury in understanding its meaning. By contrast, NeoGenomics' constructions ignore established canons of claim construction and directly contradict the intrinsic record. They rewrite the claims to import limitations, altering their meanings and distorting what is understood by a POSA.

Further, NeoGenomics' assertions, that the ***four*** additional terms are indefinite and not amenable to construction, are belied by the intrinsic record and by NeoGenomics' expert interpreting these terms in the parallel IPR proceeding under the same governing claim construction standard.[4,5] NeoGenomics' unsupported and litigation-driven constructions will confuse the jury instead of clarifying the terms' proper meaning and scope.

II. STATEMENT OF LAW REGARDING CLAIM CONSTRUCTION

Claim construction begins by examining the words of the claim. Claim terms "are generally given their ordinary and customary meaning," as the terms would have been understood by a POSA at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). "[T]he person of ordinary skill in the art is deemed to read the

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[4] *See* Metzker Decl., Ex. 3 (Lennon Decl.) at Sections IX.B.3-5, 13, 16-18, IX.C.1-3, IX.D.1-2.

[5] *SAS Inst., Inc. v. ComplementSoft, LLC*, 825 F.3d 1341, 1351 (Fed. Cir. 2016), *rev'd on other grounds sub nom. SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 200 L. Ed. 2d 695 (applying the same *Phillips* claim construction standard for IPR and federal courts).

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claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* at 1313. The understanding of a skilled artisan is informed by many sources, including: "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.*

III. CLAIM CONSTRUCTION ARGUMENT

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

Natera's Proposal:	**NeoGenomics' Proposal:**
Plain and ordinary meaning.	This step is separate from and must occur after completion of (and therefore must use distinct PCR primers from) the step of "tagging . . . with one or more universal tail adapters to generate tagged products."

The parties agree that "amplifying the tagged products" is a separate step from "tagging isolated cell-free DNA with one or more universal tail adapters to generate tagged products." However, while Natera seeks a construction of plain and ordinary meaning, NeoGenomics reads into the claims an additional requirement, wholly unsupported by the intrinsic or extrinsic evidence, that the tagging and amplification steps require ***distinct*** PCR processes using separate and ***distinct*** primers. The Federal Circuit "has repeatedly and clearly held that it will not read unstated limitations into claim language," as NeoGenomics seeks to do here. *N. Telecom Ltd. v. Samsung Elecs. Co.,* 215 F.3d 1281, 1290 (Fed. Cir.

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2000). NeoGenomics' strategically narrow and unsupported construction attempts to engineer a non-infringement argument that NeoGenomics does not practice the limitations it seeks to read into the claims. Doc. 107 at 6-7; Doc. 169 at 6.

Natera proposes a plain and ordinary meaning, consistent with the claim language. Claim 1 recites in pertinent part:

> ***tagging isolated cell free DNA with one or more universal tail adaptors*** to generate tagged products, …
>
> ***amplifying the tagged products*** one or more times to generate final amplification products, ***wherein one of the amplification steps comprises targeted amplification*** of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume, . . . [6]

If Natera "so desired," it could have limited the claim to require different PCR processes and primers for the "tagging" and "amplifying" steps but it did not. *Takeda Pharm. Co. Ltd. v. Zydus Pharm. USA, Inc.*, 743 F.3d 1359, 1365 (Fed. Cir. 2014) (refusing to narrow claim to limitations inventors otherwise knew how to include). Moreover, there is nothing—whether express or implicit—in the claim term limiting targeted amplification primers to being distinct from those of the "tagging step," nor requiring a distinct PCR process. *See N. Telecom Ltd.*, 215 F.3d at 1290.

Consistent with this construction, Claims 12 and 13 include open-ended "comprising" language with respect to tagging with universal tail adaptors and primers as recited in claim 1 from which they depend, leaving open the possibility that both may also be used for "amplifying the tagged products." Claims 12 and 13 cover embodiments

[6] Emphases added herein unless otherwise noted.

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wherein tagging involves amplifying with at least two primers, each of which must have at least a universal tail adaptor sequence. The "comprising" terminology permits these primers to contain additional sequences specific for each target, such that they can be used to tag in one PCR cycle, and perform targeted amplification in other PCR cycles. As the Court already noted (Doc. 169 at 7), Claim 1 is "broader than the claims that depend from it," *Littlefuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022).

Moreover, there is no express intent to impart a different meaning to the claim limitation in the specification, which further supports construing the term according to its plain meaning. *See Phillips*, 415 F.3d at 1316. Nothing in the written description narrows the claimed method to require separate PCR processes and distinct primers. The '035 Patent instead discloses that, in some embodiments, a primer may contain a universal tail adapter region and a target-specific sequence, such that it may be used to perform both "tagging" and "amplifying the tagged products" in separate cycles of one PCR process.

The specification makes clear that the same primers can be used for tagging and targeted amplification. For example, the '035 Patent explains that "Universal Adapters" are "DNA molecules containing a universal priming sequence." Doc. 1-2 ('035 Patent) at 42:22-23. The written description further discloses that a "universal priming sequence" may be appended to a target DNA molecule by PCR. *Id*. at 42:14-17. The '035 Patent also discloses that in some embodiments, primers may contain a target-specific region ***plus*** a common tail sequence, including a universal priming sequence:

> In an embodiment, ***tails with no homology to the target genome may also be added to the 3-prime or 5-prime end of***

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> ***any of the primers. These tails facilitate subsequent manipulations, procedures, or measurements***. . . ***Certain tails may be shared among all loci or among subsets of loci***. … In an embodiment, the ***tails can be used as common priming sites among all amplified targets that can be used to add other useful sequences*** . . . In some embodiments, the ***primer may contain a universal priming sequence*** designed to allow PCR amplification.

Id. at 90:38-56.

Moreover, the written description expressly teaches that in some embodiments the same PCR process may be used to accomplish "tagging" and "targeted amplification of tagged products," which a POSA would understand to occur in different cycles of the PCR process. *Id*. at 156:25-32.

Natera's technical expert, Dr. Michael Metzker, further confirmed that a POSA would understand "tagging" and "amplifying the tagged products" to be separate steps that may be performed in different cycles of the same PCR process using the same primers. Doc. 145 (Metzker PI Reply Decl.) at ¶62. During the preliminary injunction proceedings, Dr. Metzker explained that tagging is a known term of art, and that a POSA would understand methods to tag cell-free DNA may involve PCR-based amplification using primers including both a target-specific sequence and a universal tail adaptor. Doc. 246-1 (Technology Tutorial) at 30; Doc. 145 at ¶¶50-54. NeoGenomics' expert, Dr. Brian Van Ness, agreed with this understanding. Doc. 145-1 (Van Ness Depo Tr.) at ECF 56-27 (215:16-219:9). Consistent with fundamental principles of PCR, a POSA would recognize the same primers may be used to (1) tag cell-free DNA in a first PCR cycle to add universal tail adaptors and then to (2) amplify the newly created tagged products in a subsequent

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cycle of the same PCR process in a targeted manner. Doc. 145 at ¶¶62-70. No further construction is needed.

B. "SNP loci . . . associated with cancer" ('035 Patent, Claim 1)

Natera's Proposal:	**NeoGenomics' Proposal:**
Plain and ordinary meaning.	"a single nucleotide that may differ between the genomes of two members of the same species"

The parties agree that "loci" refers to single nucleotide positions. Apart from that, Natera proposes the plain and ordinary meaning for this term, which refers to all genomic variants at single nucleotide positions that are ***associated with cancer***. That plain-meaning construction is consistent with the way the term is used throughout the specification and with the way NeoGenomics' expert, Dr. Van Ness, conceded it is understood by a POSA during the preliminary injunction proceeding. Doc. 116 (Van Ness Decl.) at ¶253 ("SNPs are single-nucleotide variations in DNA, e.g. a variation in a gene where only one base in the gene is different. In the cancer context, SNPs are useful as they can differentiate cancer DNA, which has a mutation, from patient DNA, which is referred to as "wild-type" or lacks any cancerous mutation.").

NeoGenomics' construction is incomplete, ignoring a key part of the claim term—"associated with cancer"—as well as directly relevant disclosure including preferred embodiments in the intrinsic record. The specification makes clear that "SNP loci … ***associated with cancer***" in the context of the claimed method covers all variants at single nucleotide positions that are associated with cancer.

Claim 1 of the '035 Patent recites that "SNP loci comprises 25-2,000 ***loci associated with cancer.***" The claim language "loci associated with cancer" modifies "SNP loci."

Consistent with the "associated with cancer" claim language, numerous embodiments in the specification make clear that the claim covers variants including those that differ as between cancer cells and the other cells within a person's body, not just variants that differ as between two members of a species.

For example, the written description uses the term "polymorphism" interchangeably with "mutation," and explains that polymorphisms, or mutations, may "accumulate" in a subset of a person's cells and be associated with cancer. Doc. 1-2 at 20:48-54 ("For example, in some cancers, multiple mutations accumulate but some of them are not causative mutations."); *id.* at 8:41-43 ("wherein one or more of the target human ***loci comprises a polymorphism or other mutation*** associated with an above normal risk for cancer or ***associated with cancer***"); *id*. at 10:57-65, 18:29-34, 20:42-48.

Moreover, the '035 Patent discloses multiple examples in which SNP loci associated with cancer include more than just differences between the genomes of two members of the same species. NeoGenomics' construction would impermissibly read these embodiments out of the claims. *Nat'l Steel Car. Lid. v. Canadian Pacific Railway, LTD*., 357 F.3d 1319, 1336 n.19 (Fed. Cir. 2004) ("[c]laim interpretations that do not read on the preferred embodiment are rarely, if ever, correct and would require highly persuasive evidentiary support") (internal citation omitted); *Oatey v. IPS Corp*., 514 F.3d 1271, 1276-

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77 (Fed. Cir. 2008) (rejecting construction that excluded embodiments absent clear evidence of disclaimer).

For example, the written description discloses embodiments in which the polymorphic loci associated with cancer may vary in frequency and, in certain embodiments, the number of loci selected for use in the claimed method may increase or decrease accordingly:

> In an embodiment, the invention features a method of decreasing the number of target loci (such as loci that may contain a polymorphism or mutation associated with a disease or disorder or an increased risk for a disease or disorder such as cancer) that need to be detected for a diagnosis ***and/or increasing the disease load that is detected (e.g., increasing the number of polymorphisms or mutations that are detected***). In some embodiments, the ***method includes ranking (such as ranking from highest to lowest) loci by frequency or reoccurrence of a polymorphism or mutation (such as a single nucleotide variation, insertion, or deletion, or any of the other variations described herein) in each locus among subjects with the disease or disorder such as cancer. In some embodiments, PCR primers are designed to some or all of the loci.***

Doc. 1-2 at 56:9-23.

Both parties' experts further agree that "SNP loci … associated with cancer" refers generally to variants including not only those that differ between members of a species but also those that arise in cancer cells and differ from a patient's non-cancer cells. *Compare* Doc. 145 at ¶16 ("a desired single nucleotide polymorphism ("SNP"), which is a genomic variant at a single base position in DNA") and Technology Tutorial Hr'g. Tr. at 14:11-25 *with* Doc. 116 at ¶253.

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NeoGenomics provides none of the "exacting" evidence[7] required to establish Natera either: (1) intended to deviate from the plain and ordinary meaning, or (2) unambiguously disavowed the full scope of the ordinary meaning in favor of the incomplete interpretation NeoGenomics proposes. *Golden Bridge Tech., Inc. v. Apple Inc.*, 758 F.3d 1362, 1365 (Fed. Cir. 2014) (internal citations omitted); *Cordis Corp. v. Boston Sci. Corp.*, 561 F.3d 1319, 329 (Fed. Cir. 2009).

The '035 Patent specification does not provide a special definition for "SNP loci associated with cancer." *See Medicines*, 853 F.3d at 1306. It discloses a two-sentence definition for "Single Nucleotide Polymorphism (SNP)" as "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 each variant occurs***." Doc. 1-2 at 34:46-50. NeoGenomics notably ignores the second part of the definition, which 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, without limit to the frequency at which they occur—including, *e.g.*, variants of very low frequency such as those that arise in a tumor that differ from the rest of the patient's DNA. Doc. 145 at ¶21.

In view of the embodiments and usage of the term throughout the specification as discussed above, there is no clear and unmistakable disavowal of such variants as

[7] *GE Lighting Solutions, LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014).

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NeoGenomics proposes. *GE*, 750 F.3d at 1309 (Fed. Cir. 2014) (disavowal is "exacting" and "requires that the specification [or prosecution history] make[ ] clear that the invention does not include a particular feature") (internal citations omitted).

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

Natera's Proposal:	**NeoGenomics' Proposal:**
Plain and ordinary meaning.	"Sequencing the amplicons obtained from the targeted multiplex amplification step"

Natera proposes the term's plain and ordinary meaning. NeoGenomics' proposed construction is just a second bite at the non-infringement argument it made during the preliminary injunction proceeding (Doc. 107 at 3-4) that "the amplicons" are limited to the molecules produced by targeted multiplex amplification, which NeoGenomics argues—incorrectly—cannot be modified before being sequenced.

Claim 1, which is representative of both claims for purposes here,[8] recites:

> A method … ***comprising***:
>
> …
>
> ***performing targeted multiplex amplification*** to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons having a length of 50-150 bases . . . ; and
>
> ***sequencing the amplicons*** to obtain sequence reads ….

[8] The language in both claims should be construed to have the same meaning. *Omega Eng'g, Inc, v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003).

There is no special lexicography or other special meaning given to this straightforward language; it should be given its plain and ordinary meaning. *Phillips*, 415 F.3d at 1313.

The claim refers to "sequencing the amplicons to obtain sequence reads." The specification discloses: "Sequence Read refers to data representing a sequence of nucleotide bases that were measured…" Doc. 1-1 ('454 Patent) at 31:17-19. Thus, "sequencing … to obtain sequence rads," in this context, refers to the process of obtaining data representing the sequences of the nucleotide bases that were measured. An amplicon is simply a product of amplification. *Id.* at 34:52-53 ("Amplification refers to a method that increases the number of copies of a molecule of DNA or RNA."). "[T]he amplicons" from the targeted multiplex amplification comprise sequences that include the "target loci" referred to in that step. *See* Doc. 145 at ¶270.

A POSA would understand that the plain and ordinary meaning of "sequencing the amplicons" permits—and certainly does not foreclose—intermediate steps after multiplex amplification but before sequencing. *Id*. at ¶¶270-275. The term's plain and ordinary meaning, as read in context, is no bar to unrecited, additional steps being performed on the amplicons prior to sequencing, particularly where those steps are necessary for sequencing to work, as long as what is being sequenced are copies of the DNA being measured. *Id*.; *CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1235 (Fed. Cir. 2005) (affirming the district court's finding that an open-ended claim "does not exclude additional, unrecited elements or method steps").

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Natera's interpretation of the claim is confirmed by the scope of the dependent claims. Claim 11, which depends from claim 1, recites "[t]he method of claim 1, wherein the method further comprises performing ***barcoding PCR <u>prior</u> to the sequencing***."[9] This barcoding PCR is a separate, intermediate PCR reaction that may follow the targeted multiplex amplification step to add "barcode" sequences to the amplicons so different DNA populations (*e.g.*, from different patients) can be sequenced together and deconvoluted afterwards. Doc. 145 at ¶273; PI Hr'g Tr. at 15:22-16:17. The '454 Patent teaches embodiments in which this barcoding occurs after targeted multiplex amplification ***but before*** sequencing. Doc. 1-1 at 164:19-28 ("The barcodes are attached *to the amplification products* via PCR amplification for 12 cycles . . . . Samples are sequenced by NGS . . . ").

Because independent claims are presumed to be broader in scope than their dependents, claim 1 necessarily permits intermediate steps such as barcoding per claim 11 (or adding adaptors for Illumina sequencers) between targeted multiplex PCR and sequencing. *Littlefuse*, 29 F.4th at 1380. Claim 25, which depends from claim 14, likewise recites barcoding PCR *prior to* sequencing.

In addition, a POSA would understand from the claim language and Specification that unrecited steps in between "targeted multiplex amplification" and "sequencing the amplicons" are ***not*** excluded from the claim scope. *See* Doc. 145 at ¶¶267-275; *CollegeNet*, 418 F.3d at 1235. Claims 1 and 14 are both open-ended by virtue of

[9] The same principle applies to dependent claim 25, which depends from claim 14.

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"comprising" in their preambles, which is "generally understood to signify that the claims do not exclude the presence in the accused [method] of factors in addition to those explicitly recited." *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 811 (Fed. Cir. 1999); *CollegeNet*, 418 F.3d at 1235.

Moreover, a POSA would have understood that, while the claims do not expressly recite adding adaptors to the amplicons before sequencing, that modification would be necessary with systems expressly taught by the '454 patent. Doc. 145 at ¶274. Example 1, for instance, teaches a PCR step between targeted multiplex PCR and sequencing to add barcodes to generate a sequencing library. Doc. 1-1 at 152:36-41. The patent's preferred embodiments further use Illumina sequencers for "high-throughput DNA sequencing." *Id*. at 58:33-46, 62:1-13, 96:19-21; 152:44-46, 163:52-59. As Dr. Metzker explained during the preliminary injunction proceeding, POSAs understood that Illumina sequencers require modifying amplicons before sequencing can be performed. Doc. 145 at ¶274; PI Hr'g Tr. at 21:10-22:2. Theis includes attaching sequence tags to the amplicons to allow molecules to bind to a "flow cell", which will then be loaded into the sequencer for sequencing. Doc. 145 at ¶61; PI Hr'g Tr. at 25:12-22. Dr. Metzker also testified that there is a necessary amplification step as part of sequencing that makes additional copies of all amplicons before their sequences are determined. PI Hr'g Tr. at 13:25-14:23.

Thus, based on how sequencing works, a POSA would understand that additional steps are necessary before sequencing on Illumina systems that the '454 Patent teaches to use. Doc. 145 at ¶61. And where samples from multiple sources are run together on the

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Illumina system (in one shared sequencing run), there is another permissible step: adding barcode sequences to amplicons before sequencing. *Id*. at ¶272; *see also* Doc. 141-11 at 1.

NeoGenomics incorrectly argues that the claim language *precludes* modifying amplicons produced in targeted multiplex amplification before sequencing. Doc. 107 at 3. But NeoGenomics' interpretation would require improperly reading the notion of "directly" sequencing the amplicons into the sequencing claim language,[10] which "violates nearly every tenet of claim construction and amounts to a wholesale judicial rewriting of the claim." *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014). It also would read out preferred embodiments, such as those teaching Illumina sequencers (*see supra*), which necessarily involve adding adaptors before sequencing. Doc. 145 at ¶¶61, 274; *see GE*, 750 F.3d at 1311. Such a construction is "rarely, if ever, correct," and this is not the rare case. *Nat'l Steel*, 357 F.3d at 1336 n.19.

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 and 14)

Natera's Proposal:	**NeoGenomics' Proposal:**
The terms are part of one sequencing step.	Plain and ordinary meaning, which is that "detecting...from the sequence reads" is performed on the sequence reads generated by the claimed sequencing step, and not part of the claimed sequencing step.

[10] *Compare* Doc. 116 at ¶81 *with* Doc. 145 at ¶¶267, 270.

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The parties dispute whether the third step of claims 1 and 14—the "sequencing step"—includes "detecting" mutations or whether the "detecting" is separate and part of some other process. The plain claim language and understanding of a POSA leave no doubt that "detecting" is part of the "sequencing step" in the claim as written. To that end, NeoGenomics' proposed construction is not consistent with the plain and ordinary meaning; it seeks to separate parts of the same step in order to manufacture a purported non-infringement theory.

It is axiomatic that a claim term should be viewed "in the context of the particular claim in which the disputed term appears," including its punctuation, grammar, and syntax. *Phillips*, 415 F.3d at 1313; *see also Lear Corp. v. NHK Seating of Am., Inc.*, No. 13-12937, 2022 U.S. Dist. LEXIS 139612, at *32 (E.D. Mich. May 9, 2022); *Deep Nines, Inc. v. McAfee, Inc.*, C.A. No. 9:09-CV-89, 2010 U.S. Dist. LEXIS 79420, at *8-9 (E.D. Tex. Aug. 4, 2010); *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983).

Claim 1, which is representative of both claims, is reproduced below as an annotated screenshot to show its formatting and structure in the patent[11]:

[11] The proposed claim term as shown in the Joint Claim Construction Statement is truncated from the claims and does not show the formatting and the structure.

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1. A method for preparing a plasma sample of a subject having cancer or suspected of having cancer useful for detecting one or more single nucleotide variant (SNV) mutations in the plasma sample, the method comprising:

performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations;

performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons having a length of 50-150 bases, wherein the target loci are amplified together in the same reaction volume; and

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, wherein the sequencing has a depth of read of at least 50,000 per target locus.

As shown here, each recited step of claims 1 and 14—the first *performing* step, the second *performing* step, and then the third and final *sequencing* step—is presented as an indented subparagraph, each separated by a semicolon (red underlining). *See In re Affinity Labs of Texas, LLC*, 856 F.3d 902, 907 (Fed. Cir. 2017) (a semicolon "strongly indicates that each step is separate and distinct"). Unlike those three plainly separate steps, the "detecting" language is not set off from the sequencing step, by semicolon or otherwise. Instead, "detecting" appears in the indented text, nested between the two other limitations of the sequencing step, separated only by commas (green underlining) rather than semicolons. The claim's punctuation, grammar, and syntax all support Natera's interpretation that "detecting" is part of, rather than separate from, the "sequencing" step.

Moreover, the "wherein" clauses at the end of claims 1 and 14 further support Natera's interpretation, as it expressly modifies "the sequencing." This syntax clearly indicates the applicant intended that all of the preceding language—including the "detecting" language—to be part of the same "sequencing" step. *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983).

IV. VALIDITY ARGUMENT

NeoGenomics bears the burden to prove by clear and convincing evidence that the challenged terms are indefinite under 35 U.S.C. §112. *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017). Under *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014), "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." NeoGenomics cannot meet this heavy burden and, to date, its invalidity contentions consist only of a single conclusory paragraph for each disputed term without any supporting evidence. *See* Metzker Decl., Ex. 5 at 41-43.

A. NeoGenomics Has Failed to Show by Clear and Convincing Evidence that the Terms "Clonal" ('454 Patent, claims 3, 5, 17, 19) and "Subclonal" ('454 Patent, claims 4, 5, 18, 19) Are Indefinite

NeoGenomics proposes that the well-understood terms "clonal" and "subclonal" are indefinite. Doc. 249-1 at 15, 17. Not so. The dependent claims at issue recite that the SNV mutations analyzed comprise one or more "clonal" (claims 3, 17) or "subclonal" (claims 4, 18) SNV mutations (or at least one of each in claims 5, 19). There is no dispute

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a POSA would understand that a "clonal" mutation is one that is present in all sampled areas of a tumor and a "subclonal" mutation is one that is present in some but not all sampled areas. Metzker Decl. at ¶¶37, 74. That should end the inquiry, as a POSA would understand the scope of the claims with reasonable certainty and would know what is covered by the claims. *Id*. at ¶¶23-24, 34-37, 73-82.

NeoGenomics asserts that these terms are indefinite because, allegedly, there are different ways to distinguish between clonal and subclonal mutations. Metzker Decl., Ex. 5 at 41. But NeoGenomics does not, and cannot, assert that any of these purportedly different methods lead to different results. Metzker Decl. at ¶80.

The intrinsic record—and arguments and evidence from NeoGenomics itself—show that POSAs understand the scope and meaning of "clonal" and "subclonal." There is no evidence to the contrary. *Id*. at ¶¶34-37, 46-47, 51-64, 70-82.

For example, when discussing ways to overcome limitations in identifying variant alleles due to tumor heterogeneity,[12] Example 13 of the '454 Patent explains that: "Clonal populations had VAF[13] 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." Doc. 1-1 at 168:23-26. This is consistent with the understanding that clonal

[12] Tumor "heterogeneity" refers to different cells within the tumor having different mutations. This may arise from subclonal mutations that arise after the tumor has already grown to some extent, and thereafter are only propagated into a subset of the tumor as the cells continue to divide. Metzker Decl. at ¶¶24, 34.

[13] "VAF" stands for variant allele frequency, which is the frequency at which a particular variant is detected in a specimen. *Id*. at ¶¶35, 38.

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mutations are present in essentially all of the cancer cells and subclonal mutations are present in only a subset. Metzker Decl. at ¶¶23-24, 34-37, 73-82. Example 13 applies these definitions when categorizing clonal and subclonal mutations. *Id*. at ¶¶35-37, 78. This use of "clonal" and "subclonal" is consistent with the terms' ordinary meaning and does not require any further definition to inform a POSA of the claims' scope. *Id.* at ¶¶37, 74.

In addition, in its IPR Petition relating to the '454 Patent, NeoGenomics consistently applied the ordinary meaning of "clonal" and "subclonal" and admitted these are "well-known and common categories of cancer-related mutation." Metzker Decl., Ex. 2 at 48. NeoGenomics' definitions of "clonal" and "subclonal" did not hinge upon particular methods of categorizing mutations nor any limits or proportions of mutations detected in samples: "Mutations found in all of the tumors' cells are 'clonal,' while those found in only some are 'sub-clonal.'" *Id.* at 9-10. NeoGenomics and its expert, Dr. Lennon, consistently applied these definitions throughout its Petition and argued a POSA would readily understand these terms. *Id.* at 35-36, 49; Metzker Decl. at ¶¶51-64, 79.

In its invalidity contentions, NeoGenomics contends these terms are indefinite based on an argument that there are different ways to distinguish between clonal and subclonal mutations. Metzker Decl., Ex. 5 at 41. NeoGenomics does not identify what those purportedly different ways are, or assert they would produce different results. *See* Metzker Decl., ¶¶80-81; *Ball Metal Beverage Container Corp. v. Crown Packaging Tech., Inc.*, 838 F. App'x 538, 542 (Fed. Cir. 2020) ("Consistent with the purpose of the definiteness

requirement, differences in measurement methods must matter for determining whether or not a claim limitation is met by those who might realistically be practicing the other claim limitations."). As discussed above, 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). Metzker Decl. at ¶¶78, 80. This ordinary understanding is sufficient to inform a POSA of the claims' respective scopes with reasonable certainty. *Id*. at ¶82.

B. NeoGenomics Has Failed to Show by Clear and Convincing Evidence that "capable of detecting an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus" (Claim 14) and "capable of detecting an SNV mutation that is present in 0.005% to 0.015% of the cell-free DNA comprising the SNV locus" (Claim 28) Are Indefinite

NeoGenomics proposes that two terms reciting the method's capability to detect SNV mutations present in certain frequencies are indefinite. Doc. 249-1 at 19, 22. The claim language requires a method "capable of detecting an SNV mutation that is present in less than or equal to 0.015% [or in 0.005% to 0.015%] of the cell-free DNA comprising the SNV locus." Doc. 1-1 at 172:27-30, 173:1-4. A POSA would easily have been able to determine whether a method is capable of this level of detection 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.[14] Metzker Decl.

[14] Notwithstanding, to the extent NeoGenomics contends a skilled artisan would need to know whether its method infringed before even performing it, this misstates the law. *See Nevro Corp. v. Bos. Sci. Corp.*, 955 F.3d 35, 40 (Fed. Cir. 2020) (vacating order

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at ¶¶40, 88.

NeoGenomics overly complicates this issue by reading into the claims a requirement for a certain ***limit of detection***, which is the lowest frequency at which a particular variant allele can be detected in a sample with statistical confidence,[15] then contending that there are different ways of determining limit of detection. Metzker Decl., Ex. 5 at 42-43. But the claims do not require any limit of detection. Metzker Decl. at ¶¶86-91. The claims recite a ***capability*** of detecting mutations comprising the SNV locus when it is present in the stated percentages of the cfDNA—even if the limit of detection is lower. *Id*. at ¶¶27-28, 38-45, 86-94. The claims do not recite a ***calculation*** of the limit of detection or the measured sensitivity of the method overall. *Id*. at ¶87. In other words, the claims only require that the method is capable of detecting an SNV present in the sample at the recited percent—even if the method would also be able to detect it at a lower percent (*i.e*., have a lower limit of detection). *Id*.; Doc. 1-1 at 172:27-30, 173:1-4. A POSA reading the claims would understand that any method that performs the steps of claims 14 and 28, and that is ***capable*** of detecting an SNV mutation present in less than or equal to 0.015% of the cfDNA comprising the SNV locus would practice the claim regardless of how the method's limit of detection could be calculated or what the method's limit of detection actually is. Metzker Decl. at ¶¶38-45, 49, 83-94.

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finding indefinite a "paresthesia-free" signal even though some patients, but not others, experienced paresthesia-free treatment and noting, "Definiteness does not require that a potential infringer be able to determine *ex ante* if a particular act infringes the claims.").

[15] Metzker Decl. at ¶41.

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NeoGenomics and its expert had no problem understanding what these claim limitations mean in connection with its IPR Petition. *Id*. at ¶¶65-69. There, NeoGenomics did not perform a calculation of the limit of detection when comparing the prior art to the '454 Patent claims. *Id*. at ¶¶68-69. Instead, when attempting to invalidate claim 14 as obvious, NeoGenomics simply pointed to a prior art method it contends was *capable* of detecting an SNV mutation that is actually present in less than or equal to 0.015% of the cfDNA comprising the SNV locus. *Id*. at ¶¶66-67. NeoGenomics understood and applied the ordinary meaning of the term without reference to any calculation of the limit of detection. *Id*. at ¶¶65-69.

In attempting here to find indefiniteness where there is none, NeoGenomics improperly reads an example from the specification regarding how to calculate the limit of detection into the claim language, even though the claim language does not recite any limit of detection or related calculation. *Phillips*, 415 F.3d at 1323; *Conoco, Inc.*, 460 F.3d at 1358 (Fed. Cir. 2006). Specifically, NeoGenomics points to Example 6,[16] which provides two methods to calculate 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. Doc. 1-1 at 157:51-158:36; Metzker Decl. at ¶¶41-45, 91-92. Thus, even if a calculation of the limit of detection were required by the claims (it is not), Example 6 does not show that using one or the other of the different methods disclosed would make any difference—because

[16] Metzker Decl., Ex. 5 at 42-43.

the patent explains exactly what to do if there is an inconsistency. Metzker Decl. at ¶¶41-45, 91-92. The existence of multiple methodologies to measure a parameter does not by itself render a claim indefinite—especially where, as here, the parameter is not recited in or relevant to the claims. *Ball Metal Beverage Container Corp.*, 838 F. App'x at 542 ("Under such circumstances, the relevant indefiniteness inquiry then becomes whether the differing methodologies lead to materially different results in defining the boundaries of the claim.").

NeoGenomics further argues that the differences in the claimed numerical values in claim 14 ("less than or equal to 0.015%") compared with dependent claim 28 ("0.005% to 0.015%") render the claims indefinite. Metzker Decl., Ex. 5 at 42-43. This argument does not make sense. A POSA would understand there are numerical values that fall within the former, but not within the latter ranges. Metzker Decl. at ¶93.

V. CONCLUSION

For at least the foregoing reasons, the Court should adopt Natera's constructions and should not find that any asserted claim is indefinite.

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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 certify that on this day, I electronically filed the foregoing using the Court's CM/ECF system, which will send a notification of such filing to all counsel of record.

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