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

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I. INTRODUCTION

The disputed claim terms are presumed to take on the ordinary and customary meanings attributed to them by a person of ordinary skill in the art ("POSA"). NeoGenomics' Opening brief (Doc. 264) ignores the established law and distorts the evidence. NeoGenomics' constructions rewrite the patentee's chosen words, improperly narrow the patents' express definitions, fall short of the requirements for ***clear and unmistakable*** disavowal of claim scope, and ignore multiple disclosures in the specifications. Finally, NeoGenomics' indefiniteness arguments flatly contradict the representations it made to the PTAB in the '454 Patent IPR regarding a POSA's understanding of those same terms. The Court should adopt Natera's proposed claim constructions.

II. 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:[1]
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."

[1] Doc. 264 at 7.

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NeoGenomics incorrectly argues that Natera "collapses the claimed tagging and amplifying steps into a single process step." Doc. 264 at 7. But NeoGenomics has admitted that the "parties agree the claim requires tagging ***before*** amplifying."[2,3] *Id*. Natera disputes not the separateness of the steps, but rather NeoGenomics' unfounded requirement that each step requires the use of "distinct" PCR processes (referring to an entire series of amplification cycles) and "distinct" primers (referring to primers with different sequences) for tagging and amplifying.

Claim 1 does not require distinct PCR processes and primers for the claimed tagging and amplifying steps. To the extent the non-limiting claim language does not end the inquiry, Natera and its expert explained that "tagging" and "amplifying the tagged products" may occur consecutively in different cycles of the same multi-cycle PCR process and can involve the same primers. *Id*. at 4-6; Doc. 246-1 (Technology Tutorial) at 30; Doc. 145 (Metzker PI Reply Decl.), ¶¶50-54, 62-70. The '035 Patent teaches using primers containing multiple functional regions (*e.g*., (1) a universal tail adapter region and (2) a target-specific sequence region) that are capable of tagging and performing subsequent targeted amplification of the tagged product in sequential cycles of a PCR process. Doc.

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[2] The claimed "tagging" in the present tense followed by "tagged" in the past tense supports that the claim requires tagging to occur before amplifying the previously tagged products. *See Function Media, LLC v. Google, Inc*., 708 F.3d 1310, 1319-21 (Fed. Cir. 2013), which NeoGenomics likewise cites. Doc. 264 at 8. As Natera explained, these *separate* steps may be performed in different cycles of the same PCR process using the same primers. Doc. 262 at 6.

[3] Emphases added herein unless otherwise noted.

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1-2 ('035 Patent) at 96:8-9 ("In an embodiment, the initial primers may carry the tags."), 42:14-23, 90:38-56, 156:25-32; *see also* Doc. 262 at 5-6.

Consistent with these teachings, dependent Claims 12 and 13 use the open-ended term "comprising" and permit the use of the same primers for the steps of "tagging" and "amplifying the tagged products." Doc. 262 at 4-5; *see Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1380 (Fed. Cir. 2006) (holding that under the doctrine of claim differentiation, "limitations stated in dependent claims are not to be read into the independent claim from which they depend"). Together, these claims permit the tagging of Claim 1 to be performed in one cycle of the ***same PCR process*** that may subsequently amplify the tagged products using the same primers in later cycles.

Rather than focus on intrinsic support for its construction, NeoGenomics misdirects to *Amgen, Inc. v. Sandoz, Inc.*, 923 F.3d 1023 (Fed. Cir. 2019). Doc. 264 at 7-10. *Amgen*, however, does not overcome the inescapable truth that Claim 1 does not require distinct PCR processes with distinct primers. *Amgen* dealt with whether two steps could occur simultaneously; but here, both parties agree the steps must be performed separately and in sequence.

Amgen's patent concerned: a "method of purifying a protein" that involved separate steps of "washing the separation matrix" and then "eluting the protein from the separation matrix." *Amgen*, 923 F.3d at 1026. The accused product—according to the defendant—performed the "washing" and "eluting" steps simultaneously, and thus did not infringe. *Id.* at 1028. Amgen argued that the simultaneous washing-eluting step met the claim language.

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Id. at 1028 ("[W]ashing precedes elution at any given point in the separation matrix; that is, washing may occur toward the bottom of the matrix at the same time that elution occurs toward the top."). Because of the explicit recitation in the claims at issue, the Federal Circuit disagreed and found "the claim language logically requires that the process steps . . . be performed in sequence." *Id*.

Here, as explained above, Natera agrees that "tagging" is a separate step that precedes "amplifying the tagged products." But there is no language in Claim 1 requiring distinct PCR processes with distinct PCR primers for both steps, and NeoGenomics' reading in of claim limitations finds no support in the law. Nothing in *Amgen's* reasoning or holding precludes Claim 1's separate steps of tagging and amplifying from being performed in different cycles of a single PCR process.

NeoGenomics contends that, similar to *Amgen*, Claim 1 requires "distinct solutions added to the matrix at different times" for tagging and amplifying the tagged products. Doc. 264 at 9. NeoGenomics attempts to analogize to Amgen's patent specification, which "consistently described" washing and eluting as "separate steps performed by different solutions." *Id*. at 8. Again, here, there is no dispute that the steps are performed separately. But, again, no claim language or disclosure of the '035 Patent requires distinct PCR processes with distinct PCR primers for these steps.

Finally, NeoGenomics makes the conclusory assertion that "[b]ecause amplifying occurs separate from and after the completion of tagging, the PCR reaction in the claimed amplifying step would ***necessarily*** use distinct primers in 'distinct solutions added . . . at

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different times.'" Doc. 264 at 9.[4] NeoGenomics' argument directly contradicts fundamental scientific principles known to a POSA. *See* Doc. 262 at 6-7 (citing Dr. Metzker's testimony).

NeoGenomics cannot point to any express or implied disclosure that would impart a different meaning to the disputed term. The Court should give the term its plain and ordinary meaning, which does not require distinct PCRs or distinct primers to perform the "tagging" and "amplifying" steps. *N. Telecom Ltd. v. Samsung Elecs. Co.,* 215 F.3d 1281, 1290 (Fed. Cir. 2000).[5]

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

Natera's Proposal:	**NeoGenomics' Proposal:**[6]
Plain and ordinary meaning.	"A single nucleotide that may differ between the genomes of two members of the same species and is associated with cancer."

The plain meaning of this term broadly refers to genomic variants at single nucleotide positions associated with cancer, and, contrary to NeoGenomics' assertion

[4] Internal citations omitted herein unless otherwise noted.

[5] In the Preliminary Injunction appeal briefing, Natera did not disclaim any claim scope by asserting that in Claim 13 "tagging may be performed by its own *amplification* process, separate and apart from the amplification that occurs in the amplification step." Doc. 264 at 10; *see also Natera, Inc. v. NeoGenomics Labs., Inc*., Nos. 24-1324, 24-1409 (consolidated), Dkt. 36 at 39 (Fed. Cir. Mar. 11, 2024). Natera did not limit or otherwise equate "amplification process" to a separate PCR process. Instead, Natera explained that tagging may be accomplished through amplification in one cycle of a PCR process while targeted amplification could occur in a subsequent PCR cycle of the same PCR process.

[6] Doc. 264 at 3.

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(Doc. 264 at 5), covers both inherited mutations and those acquired in a person's cancer cells. This construction is confirmed by the intrinsic and extrinsic record.

NeoGenomics argues this term is narrowly limited to *inherited* mutations at single nucleotide positions. Doc. 264 at 4-5. But NeoGenomics erroneously interprets the definition of "SNP" provided in the '035 Patent specification. NeoGenomics' construction reads non-existent exclusionary language into the definition's first sentence, disregards the definition's second sentence regarding low-frequency variants, and contradicts both the way the term is used throughout the intrinsic record and its own expert's interpretation of the term.

The written description discloses a definition for "Single Nucleotide Polymorphism (SNP)." That definition of SNP is: "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; Metzker Resp. Decl., ¶¶29, 38. The use of permissive language ("may") coupled with the express reference to a lack of any limitation on the frequency of variants in the definition supports a construction of "SNP loci" that is consistent with Natera's proposed plain and ordinary meaning of the term "SNP loci . . . associated with cancer." *Id.*, ¶¶38-39.

NeoGenomics argues that the Court should simply plug the first sentence of the "SNP" definition into the claim. Doc. 264 at 6. But NeoGenomics is, in reality, asking the Court to substitute NeoGenomics' erroneous *interpretation* of this definition into the claim. Metzker Resp. Decl., ¶¶37-41. NeoGenomics argues that the first sentence of the "SNP"

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definition limits the term "SNP loci … associated with cancer" to "inherited mutations (also called germline mutations)" and excludes "acquired mutations (also called somatic mutations)." Doc. 264 at 5. But the definition does not address the origin of mutations at all, much less recite terminology such as "inherited," "germline," "somatic," or "acquired" to restrict it. Metzker Resp. Decl., ¶38. NeoGenomics' assertion (Doc. 264 at 5) that "differ between the genomes of two members of the same species" necessarily means inherited mutations erroneously reads into the definition a narrow embodiment and ignores the proper frame of reference for "genome." Metzker Resp. Decl., ¶¶37-41.

POSAs understand that almost every cell in a person's body has a complete copy of their full genetic code (*i.e*. genome). *Id.*, ¶¶17-19, 39. Consistent with the specification's definition, a POSA would understand that the genome present in any cancer cell may differ from the genome of a cell in any healthy or "reference" individual, thus capturing both inherited and acquired types of mutations. *Id.*, ¶39. The definition only requires that a single nucleotide ***may*** differ between the genomes of two members of the same species; it in no way restricts "genome" to that of a healthy cell as opposed to that of a cancer cell. Doc. 1-2 at 34:46-50; Metzker Resp. Decl., ¶39. To the contrary, by removing the limitation on variant frequency, the written description confirms the claim's broad application to both inherited and acquired changes (mutations or variants) at single nucleotide positions. Metzker Resp. Decl., ¶¶21-25, 40. NeoGenomics fails to point to any "exacting" evidence that Natera unambiguously disavowed the full scope of the ordinary meaning. *Id*., ¶¶29-35, 39-44; *Golden Bridge Tech., Inc. v. Apple Inc.*, 758 F.3d

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1362, 1365 (Fed. Cir. 2014); *Cordis Corp. v. Boston Sci. Corp*., 561 F.3d 1319, 1329 (Fed. Cir. 2009). In fact, the '035 Patent discloses multiple examples of targeting of both inherited and acquired variants at single nucleotide positions associated with cancer. Metzker Resp. Decl., ¶¶30-35, 42-43. It is well-settled that constructions like NeoGenomics', that read disclosed embodiments out of the claims are rarely, if ever, correct. *Nat'l Steel Car. Ltd. v. Canadian Pac. Railway, Ltd*., 357 F.3d 1319, 1336 n.19 (Fed. Cir. 2004); *see, e.g*., *Oatey v. IPS Corp*., 514 F.3d 1271, 1276-77 (Fed. Cir. 2008).

NeoGenomics relies on an extrinsic textbook by Buckingham *et al.* to argue that "polymorphisms are inherited." Doc. 264 at 5. But this reference actually explains that the term "polymorphism" is sometimes used to describe both inherited and acquired DNA sequence changes. Metzker Resp. Decl., Ex.1, at 156; *id*., ¶¶46-47. Moreover, even if the extrinsic textbook did say what NeoGenomics claims, established rules of claim construction require that it be discounted to the extent it is "clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent." *Phillips v. AWH Corp*., 415 F.3d 1303, 1318 (Fed. Cir. 2005); *see also Seabed Geosolutions (US) Inc. v. Magseis FF LLC*, 8 F.4th 1285, 1290 (Fed. Cir. 2021).

Tellingly, NeoGenomics ignores the testimony of its own expert, Dr. Van Ness, confirming a POSA's understanding that "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

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DNA, which is referred to as 'wild-type' or lacks any cancerous mutation." Doc. 116 (Van Ness Decl.), ¶253; *see also* Metzker Resp. Decl., ¶¶20-25, 45; Doc. 262 at 9.

NeoGenomics also ignores that the remainder of the disputed term—"associated with cancer"—modifies "SNP loci" and confirms the term encompasses acquired variants. Metzker Resp. Decl., ¶¶25, 42. The entire claim term at issue, not just the first two words, must be considered to "inform[] the proper construction." *Abbott Labs. v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, 1351 (Fed. Cir. 2003). As Natera explained in its Opening brief (Doc. 262 at 10), the '035 Patent does not provide any special definition or otherwise define the entire disputed term and nothing in the intrinsic record compels a departure from its plain and ordinary meaning to cover both inherited and acquired mutations associated with cancer.[7] Metzker Resp. Decl., ¶48.

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

Natera's Proposal:	**NeoGenomics' Proposal:**[8]
Plain and ordinary meaning.	"Sequencing the amplicons obtained from the targeted multiplex amplification step"

[7] *See GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014) ("[T]he specification and prosecution history only compel departure from the plain meaning in two instances: lexicography and disavowal. . . The standards for finding lexicography and disavowal are ***exacting***. To act as its own lexicographer, a patentee must 'clearly set forth a definition of ***the disputed claim term***,' and 'clearly express an intent to define the term.' Similarly, disavowal requires that 'the specification [or prosecution history] make[] clear that the invention does not include a particular feature.'") (alterations in original).

[8] Doc. 264 at 11.

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There is no dispute that both "sequencing" and "amplicons" have well-understood plain and ordinary meanings, consistent with Natera's proposal. NeoGenomics' arguments distort the meaning of "***the*** amplicons" based on an alleged antecedent basis. Doc. 264. at 11. NeoGenomics' interpretation would preclude any and all intermediate steps, some of which may be necessary to modify "the amplicons" prior to sequencing—including steps expressly recited by dependent Claims 11 and 25. NeoGenomics' arguments should be rejected.

Unlike NeoGenomics' proposal, Natera's construction reflects what POSAs would understand "amplicons" to refer to in context. Doc. 145, ¶¶270-275. The patent explains that "[a]mplification refers to a method that increases the number of copies of a molecule of DNA or RNA." Doc. 1-1 ('454 Patent) at 34:52-53. Amplicons are products of amplification, and "the amplicons" of Claims 1 and 14 are simply copies of DNA that represent the sequences of the "target loci" referred to in the claims. *See* Doc. 145, ¶270; Doc. 262 at 12.

Consistent with this plain and ordinary meaning, the '454 Patent teaches modifying the amplicons from the targeted multiplex amplification prior to sequencing, such as by adding adaptors necessary for sequencing or adding barcodes. Doc. 262 at 13-15. NeoGenomics reads these disclosures out of the claims completely.

NeoGenomics asks the Court to ignore the understanding of a POSA and the disclosures in the specification, and instead require that the amplicons from the targeted multiplex amplification be ***directly*** sequenced, without any modification. Doc. 264. at 11.

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This argument—which relies exclusively on "the" in the phrase "sequencing ***the*** amplicons"—runs afoul of the open-ended "comprising" nature of the claims and impermissibly re-writes the claim language. *Cybersettle, Inc. v. Nat'l Arbitration Forum, Inc.,* 243 F. App'x 603, 607 (Fed. Cir. 2007).

NeoGenomics' construction also cannot be reconciled with the dependent claims. Under the doctrine of claim differentiation, dependent Claims 11 and 25 make clear that modifying the amplicons before sequencing is within the scope of Claims 1 and 14, respectively. Doc. 262 at 13. Those claims each recite "wherein the method further comprises performing barcoding PCR ***prior to the sequencing***." Contrary to NeoGenomics' arguments (Doc. 264 at 13), Claim 11 as plainly written recites "barcoding PCR prior to ***sequencing***," not prior to targeted multiplex amplification.

Barcoding PCR, in some embodiments, refers to performing an intermediate PCR before sequencing to add "barcode" sequences, allowing for different DNA populations to be sequenced together and deconvoluted afterwards. *Id*. The patent teaches embodiments where barcoding involves a separate PCR that follows targeted amplification (but precedes 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 . . . ."); Doc. 145, ¶273; PI Hr'g Tr. at 15:22-16:17. Under claim differentiation, independent Claims 1 and 14 are presumed to be inclusive of the barcoding PCR in their dependent claims. *See InterDigital Commc'ns, LLC v. Int'l Trade Comm'n*, 690 F.3d 1318, 1324

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(Fed. Cir. 2012); *see also Littlefuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022). NeoGenomics offers nothing to rebut this presumption.

NeoGenomics mistakenly relies on *Guardant Health, Inc. v. Found. Med., Inc.*, Nos. 17-1616-LPS-CJB, 17-1623-LPS-CJB, 2019 WL 5677748, at *10 (D. Del. Nov. 1, 2019). Doc. 264 at 11-13. In *Guardant*, the claim at issue recited "sequencing . . . to produce *a plurality of sequence reads*" and "grouping *the plurality of sequence reads* . . . into families[.]" The patentee argued that, despite the claim language, less than all of "the plurality of sequence reads" required grouping because the claim permitted filtering out certain sequence reads from the plurality prior to grouping. *Guardant*, 2019 WL 5677748 at *10. The court rejected that argument, reasoning that the use of "the" before "plurality of sequence reads" required that ***all*** of the "plurality of sequence reads" be grouped, not some subset of them. *Id.* at *11-12.

Here, the issue is completely different. It addresses not whether the amplicons get sequenced, which would be analogous to *Guardant*, but whether, as Natera's construction correctly recognizes, the open-ended "comprising" nature of the claims permits additional steps to modify the amplicons before sequencing. *See* Doc. 262 at 12-13; *see also CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1235 (Fed. Cir. 2005) (an open-ended claim "does not exclude additional, unrecited elements or method steps"). This is precisely what dependent Claims 11 and 25 recite: an additional PCR step that takes place ***before sequencing*** to prepare the amplicons for sequencing. Under Natera's construction,

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the same amplicon sequences are sequenced regardless of whether they are modified by barcoding or otherwise. *See* Doc. 145, ¶270.

Finally, NeoGenomics rehashes the same flawed argument it made in the preliminary injunction proceeding about an alleged disclaimer of '454 Patent claim scope during prosecution of U.S. Patent No. 11,486,008 ("the '008 Patent"), which is a ***different, unasserted*** patent with ***different claims***. *Compare* Doc. 107 at 4-6, *with* Doc. 264 at 13-16. But statements made during prosecution of related patent applications generally do not operate as disclaimers except in narrow circumstances such as where, unlike here, the "two patents share the same claim language." *Compare* Doc. 108-1 ('008 Patent), Claim 1 *with* Doc. 1-1, Claim 1; *ResQNet.com v. Lansa*, 346 F.3d 1374, 1383 (Fed. Cir. 2003).

Claim 1 of the '008 Patent recites:

> performing high-throughput sequencing to sequence the amplicons ***obtained in the multiplex targeted amplification reaction*** to obtain sequence reads.

Doc. 264 at 14.

The '454 Patent claims do not recite the limitation "obtained in the multiplex targeted amplification reaction," and thus their scope cannot be limited by it as NeoGenomics' own authority makes clear. *See Invitrogen Corp. v. Clontech Lab'ys, Inc.*, 429 F.3d 1052, 1078 (Fed. Cir. 2005) ("[T]he use of the distinct terms . . . canonically suggests that these limitations be given a different scope."). NeoGenomics refers to this language difference as "minor" (Doc. 264 at 15), but the '454 Patent claims are not just

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"worded differently"; they lack a whole additional, material limitation that the '008 Patent claims recite. Doc. 145, ¶¶278-79.

NeoGenomics also contends Natera disavowed scope of the '454 Patent claims vis-a-vis arguments it made to distinguish then-pending Claim 1 of the '008 Patent from the "Forshew" reference during prosecution. Doc. 264 at 14-15. There, Natera explained that Forshew requires a "subsequent and separate targeted amplification step . . . and therefore Forshew's amplicons for sequencing are not ***obtained from the alleged multiplex targeted amplification***"—a clear reference to claim language not present in the '454 patent claims. *Id*. As Natera specifically stated, Forshew requires a "subsequent and separate ***targeted*** amplification step," but this statement says nothing about an ***untargeted***, universal amplification step to add adaptors and/or barcodes, which the '454 Patent expressly permits. *Id*.; Doc. 145, ¶280.

Lastly, NeoGenomics cites out-of-context quotes from an interview a Natera inventor, Dr. Zimmermann, had with the patent examiner during prosecution of the '008 Patent, in which he stated that the "highly accurate mutation detection" claimed in the '008 Patent was achieved by not having intermediate targeted amplification steps. Doc. 264 at 15-16. NeoGenomics argues from this that because Claim 14 of the '454 Patent also has a "highly accurate mutation detection" limitation, Dr. Zimmermann's alleged "disclaimer" applies equally to the '454 Patent. *Id*. at 16. Setting aside that Dr. Zimmerman made no disclaimer at all, his statements have no application to the '454 Patent because he addressed

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specific ’008 Patent claim language not present in, and materially different from, the ’454 Patent claims.

NeoGenomics’ reliance on *NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1288-89 (Fed. Cir. 2005) and *Invitrogen*, 429 F.3d at 1078, as support for importing limitations from the ’008 Patent misses the mark. *NTP* and *Invitrogen* concerned the distinguishable fact pattern of statements from prosecution of a parent patent application being applied to its direct children (continuation applications). *Id.*; *see* Doc. 1-1 at cover page; Doc. 108-1 at cover page; Doc. 145, ¶277. The ’008 Patent is neither a parent nor grandparent of the ’454 Patent.

Natera’s proposal 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 And 14)

Natera’s Proposal:	**NeoGenomics’ Proposal:**[9]
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.

The claim term, when viewed in its proper grammatical and syntax setting shown by screenshot below, clearly denotes that “sequencing” and “detecting” are part of one step, with the “wherein” clause after “detecting" further modifying “the sequencing”:

[9] Doc. 264 at 16.

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> sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products, wherein the plurality of SNP loci comprises 25-2,000 loci associated with cancer.

Doc. 262 at 16. NeoGenomics' argument is based on truncated claim language, ignoring the "wherein" clause at the end of the step, and a misunderstanding of the science. Doc. 264 at 16-17. Claim terms do not exist in a vacuum; they must be read in full context. *Phillips*, 415 F.3d at 1313.

NeoGenomics' argument on what constitutes "detecting" (Doc. 264 at 17-18) misses the mark. A POSA would understand that, in the context of the specific methods at issue here, tumor-specific SNVs contained in the cell-free DNA are detected as soon as the tumor-specific SNV loci are read and outputted into the sequence reads that the sequencer generates. This is a necessary result of the way the claimed methods are designed—sequencing here is not random or scattershot. Rather, the target SNVs are known ahead of time, and primers designed to target and selectively amplify them create amplification products containing them, which are then sequenced. Accordingly, there is already an expectation of the tumor-specific nucleotide at a target SNV locus and the targeted SNV loci are the only things being sequenced. As soon as the sequence read is generated for a target position, the sequencer detects whether the tumor-specific SNV is present or not.

NeoGenomics cites to certain embodiments of the specification to argue that "detecting," as written in the ***claim***, must involve using a computer even though no

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computer, processor, algorithm, or related analytical step is recited. Doc. 264 at 17-18. It is axiomatic that "a court may not read a limitation into a claim from the specification." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1117 (Fed. Cir. 2004). Specifically, the Federal Circuit has cautioned that "particular embodiments appearing in the written description will not be used to limit claim language that has broader effect." *Id.* Here, NeoGenomics' unjustified computer-centric view of "detecting" should not be read into the claim language.

Indeed, NeoGenomics' own corporate witness agrees with Natera that detection of SNV mutations can happen during sequencing. During the preliminary injunction proceeding, when asked about detecting mutations, NeoGenomics' corporate witness, Dr. Sikri, testified that "[t]he SNVs are ***detected through the sequencer*** [] where the sample is run." Doc. 144-7 (Sikri Tr.) at ECF 21, 74:20-21; Doc. 145, ¶284. This binding corporate testimony, which the Court is free to consider, supports Natera's interpretation of this term. *Kyowa Hakko Bio, Co., Ltd v. Ajinomoto Co., Ltd.*, No. 17-cv-00313-MSG, 2019 WL 10092522, at *1 (D. Del. Apr. 1, 2019) (finding the deposition testimony by a corporate representative can be considered for claim construction purposes because "[e]xperts and courts sometimes rely on industry practice as background in determining how a person skilled in the art would have understood claim language.").

III. VALIDITY ARGUMENT

NeoGenomics fails to satisfy its burden to show indefiniteness by clear and convincing evidence. The disputes NeoGenomics attempts to raise about the application

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of testing methodologies in particular cases are questions of infringement, not indefiniteness, and certainly not questions of claim construction. The Court should reject NeoGenomics' misplaced invalidity/noninfringement arguments at this juncture.

A. NeoGenomics Confirms That "clonal" ('454 Patent, Claims 3, 5, 17, 19) and "subclonal" ('454 Patent, Claims 4, 5, 18, 19) Are Definite

The parties do not dispute that that the terms "clonal" and "subclonal" have definite meanings. Doc. 264 at 19; Doc. 264-5, ¶¶21-22. These are not subjective, terms of degree, or functional terms; they are well-understood by a POSA and simply refer to two different types of mutations. *See* Metzker Resp. Decl., Section VIII.B. Indeed, NeoGenomics itself provided a clear definition: "Mutations shared by all cells in a tumor are referred to as clonal, while mutations that differ, due to further mutation as cancer develops, are referred to as subclonal." Doc. 264 at 19. That alone confirms that the claims inform those skilled in the art with reasonable certainty about the scope of the invention. Metzker Resp. Decl., ¶¶50-51. NeoGenomics certainly does not justify how its position here can square with the lack of any indication that the same terms are not understandable to a POSA in its IPR Petition, or its failure in the Petition to raise the purported ambiguity as to which particular method of determining or categorizing mutations to use on which its instant briefing is based. Doc. 262 at 20; Doc. 263-2 at 35-36, 47-51; *see also* Doc. 263-3, ¶¶200, 202, 205-206; Doc. 263, Section VII.C.

In fact, as a threshold matter, NeoGenomics errs in asserting the claims require any form of ***classifying*** mutations as clonal or subclonal or ***determining*** clonality. Metzker Resp. Decl., ¶58. That language does not appear in the claims. All the claims require is

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that the SNV mutations comprise at least one "clonal" (Claims 3, 17) or "subclonal" (Claims 4, 18) mutation (or at least one of each in Claims 5, 19). Those are the boundaries of the claims. Nowhere do they require particular methods for ***determining*** clonality for all (or any) SNV mutations.

Even if the '454 Patent claims did require some sort of result from a method for determining whether a mutation is "clonal" or "subclonal" (they do not), disputes about the application of that method would be an issue of infringement, not indefiniteness. For example, in *Presidio Components, Inc. v. American Technical Ceramics Corp.*, 875 F.3d 1369 (Fed. Cir. 2017), the claim required an apparatus "with a fringe-effect capacitance between external contacts that is 'capable of being determined by measurement in terms of a standard unit.'" *Id.* at 1375. The Court noted:

> [E]ven where the claims require a particular test result, there may be (and often are) disputes between the parties as to the proper application of the test methodology in the circumstances of an individual case. But those disputes are disputes about whether there is infringement, not disputes about whether the patent claims are indefinite.

Id. at 1377. In finding the claim language definite, the Court found that a POSA would understand the general approach. *Id.* Here, there is no claim language requiring "determining" or "measuring," but even if there were, *Presidio Components* instructs that disputes about the application of the methodology would be an issue of infringement, not indefiniteness. And "[t]he test for indefiniteness is not whether infringement of the claim must be determined on a case-by-case basis." *Nevro Corp. v. Bos. Sci. Corp.*, 955 F.3d 35, 39 (Fed. Cir. 2020).

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NeoGenomics' indefiniteness argument also demands more certainty than the law requires, especially where there are well-understood limitations in the scientific field.[10] *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 899 (2014) ("The standard adopted here mandates clarity, while recognizing that absolute precision is unattainable."). NeoGenomics' contention that "[s]cientists in this field understand the distinction between 'clonal' and 'subclonal' to be inherently vague," thus misses the point. Doc. 264 at 19.

NeoGenomics' cited case, *Icon Health & Fitness, Inc. v. Polar Electro Oy*, 656 Fed.Appx. 1008 (Fed. Cir. 2016), is inapposite.[11] Doc. 264 at 19. In that case, the evidence showed that two terms, "in-band" and "out-of-band," were different, but the patentee did not put forward any evidence showing that a POSA reading the specification would understand the boundaries between the two terms. *Id.* at 1014. "Clonal" and "subclonal," in contrast, are well-understood, unambiguous terms (Metzker Resp. Decl., Section VIII.B) and NeoGenomics concedes that a POSA understands the difference between them (Doc. 263, Section VII.C).

NeoGenomics is also wrong about what the '454 Patent specification teaches and the prosecution history shows. As NeoGenomics admits, during prosecution, the Examiner pointed to the specification "to interpret 'clonal SNV mutations' and 'subclonal SNV

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[10] Under NeoGenomics' standard, no term involving a well-understood property that is difficult to measure with certainty could be definite. Courts have recognized that some degree of uncertainty is inherent, especially in scientific endeavors. *See, e.g.*, *Evonik Degussa GmbH v. Materia, Inc.*, 274 F. Supp. 3d 241, 246 (D. Del. 2017) .

[11] The only other case NeoGenomics cites, *Halliburton Energy Services, Inc. v. M-I LLC*, 514 F.3d 1244 (Fed. Cir. 2008), applied the pre-*Nautilus* indefiniteness standard.

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mutations.'" Doc. 264 at 20-21. The Examiner did not raise any indefiniteness rejection regarding these terms (Doc. 263, ¶46; Doc. 263-1 at 29-31) and, as NeoGenomics acknowledges, the Examiner pointed to the discussion in Example 13 as support for the terms. Doc. 264 at 21.

As discussed in Natera's Opening Brief, the relevant passage in Example 13 explains what is "clonal" and what is "subclonal," and applies those concepts in the context of the example. Doc. 262 at 19-20 (citing Doc. 1-1 at 168:23-26). NeoGenomics misses the fact that this explanation depends on the *presence* or *absence* of the mutation; it does not require any statistical protocol. Metzker Resp. Decl., ¶54. For the same reason, NeoGenomics' argument about sample contamination (Doc. 264 at 20) is a straw-man: the presence of non-cancerous cells in a sampled area does not alter the analysis of whether a mutation is present or absent when that sampled area is tested. Metzker Resp. Decl., ¶66.

In sum, NeoGenomics admits that a POSA understands the scope of terms "clonal" and "subclonal," as well as the unambiguous difference between these terms. That is all that is required to find the claims definite.

B. NeoGenomics Confirms 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" ('454 Patent, 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" ('454 Patent, Claim 28) Are Definite

NeoGenomics improperly attempts to manufacture indefiniteness by importing language from the specification into the claims. *Phillips*, 415 F.3d at 1323; *Conoco, Inc. v. Energy & Env't Int'l, L.C.*, 460 F.3d 1349, 1358 (Fed. Cir. 2006). All the claims require

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is that the method be "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. The claims do not recite a mean or median limit of detection ("LOD"), which is discussed in one example in the '454 Patent specification. Metzker Resp. Decl., ¶70. NeoGenomics' attempt to equate the capability of detecting an SNV mutation that is present at, below, or between certain percentages with a calculated limit of detection should be rejected.

NeoGenomics' discussion of Example 6 reveals the flaw in NeoGenomics' approach. NeoGenomics states that "multiple different statistical representations of LOD are disclosed, which also yield different results," pointing to differences between the calculated mean and median LOD. Doc. 264 at 24. But the mean or median LOD does not reflect the method's capability of detecting any particular SNV mutation; by definition, it reflects the total data set, which in this case NeoGenomics admits includes many different SNV mutations. Metzker Resp. Decl., ¶72; Doc. 264-5, ¶49 ("[T]he x-axis appears to represent different SNVs assayed."). The calculated average or median values do not reflect the method's capability of detecting a particular SNV mutation that is present in less than or equal to 0.015% [or in 0.005% to 0.015%] of the cfDNA. Metzker Resp. Decl., ¶72. NeoGenomics' purported "problem" with "multiple different statistical representations of LOD" is illusory. *Id.*, ¶¶70-72.

Moreover, even if a LOD is calculated for a particular SNV mutation, that calculation is conceptually distinct from the method's capability of detecting mutations

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comprising the SNV locus when it is present in the stated percentages of the cfDNA. *Id.*, ¶72. The claims recite that the method is capable of detecting an SNV present in the sample at the recited percentages, regardless of what the calculated LOD is, or whether it might be lower than the recited percentages. *Id.*; Doc. 1-1 at 172:27-30, 173:1-4; *see also* Doc. 262 at 21. There is thus no dispute that a POSA would understand the scope of these claim limitations.

Even if the calculation of a LOD were relevant to the claims (it is not), NeoGenomics has not shown there is any inconsistency in the results. Metzker Resp. Decl., ¶73. As NeoGenomics notes, Example 6 teaches *two* methods to calculate limit of detection, but NeoGenomics ignores that Example 6 also tells the POSA to resolve any purported inconsistencies between the two methods by using a third method that simply relies on the higher of the two calculated LODs. Doc. 264 at 23; Doc. 264-5, ¶¶45-47. Indeed, the '454 Patent discloses the third method as preferred embodiment compared to the other two methods. Metzker Resp. Decl., ¶73; Doc. 1-1 at 93:35-37. NeoGenomics does not offer any opinion that a POSA would fail to understand how to resolve any alleged inconsistencies by using this method.

The cases NeoGenomics cites present completely different facts. In *Dow Chemical Co. v. Nova Chemicals Corp. (Canada)*, 803 F.3d 620 (Fed. Cir. 2015), the term at issue was expressly recited in the claim. *Id.* at 624-25. Here, in contrast, NeoGenomics seeks to improperly inject a non-recited calculation of the LOD into the claims and then use it to create some ambiguity. In *HZNP Medicines LLC v. Actavis Laboratories UT, Inc.*, 940

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F.3d 680 (Fed. Cir. 2019), the claim recited "better drying time," which the Court held was a basic and novel property of the invention but also a subjective property that was indefinite because it was unclear how to test for something that is "better." *Id.* at 684. Here, the term "capable of detecting" is not subjective, nor is it a basic and novel property of a "consisting essentially of" claim as in *HZNP Medicines*. Rather, it is a straightforward limitation that a POSA would clearly understand. And *Media Rights Technologies, Inc. v. Capital One Financial Corp.*, 800 F.3d 1366 (Fed. Cir. 2015) involved a means-plus-function limitation where the patent failed to disclose sufficient structure, which is not at issue in the present case. *Id.* at 1375.

NeoGenomics' indefiniteness arguments are based on language found nowhere in the claims and thus should be rejected. Even if a calculated LOD were required by the claims (it is not), the '454 Patent teaches how to resolve any purported inconsistencies when making that calculation. Metzker Resp. Decl., ¶73. NeoGenomics has failed to present any evidence—much less the required clear and convincing evidence—that these limitations are indefinite.

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I hereby certify that I filed the foregoing document via the CM/ECF system which will cause the document to be served on all counsel of record.

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