

**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
REGARDING U.S. PATENT NO. 11,319,596

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I. INTRODUCTION

After multiple failed attempts¹ in this Court and before the Patent Trial and Appeal Board (“PTAB”) to narrowly interpret the asserted claims of U.S. Patent No. 11,530,454 (“the ’454 Patent”), Defendant NeoGenomics, Inc. (“NeoGenomics”) uses the ’454 Patent’s sister patent, U.S. Patent No. 11,319,596 (“the ’596 Patent”), as a pretext for a *fourth* bite at the apple based largely on the same flawed theories. NeoGenomics is seeking hooks to evade liability in four terms of Claim 1 of the ’596 Patent, three of which closely parallel the ’454 Patent claim terms² previously construed by the Court. The ’454 and ’596 Patents, however, share an identical specification and priority date and contain similar claim language. Nothing even suggests, much less requires, departure from the Court’s prior *Markman* ruling.³

For each of the four disputed terms, NeoGenomics mischaracterizes its constructions as “plain and ordinary.” But what it is in fact doing is rewriting the claim

¹ See, e.g., Doc. 107 (NeoGenomics’ PI Opposition) at ECF 8-10; Doc. 366-1 (NeoGenomics Petition for *Inter Partes* Review of the ’454 Patent) at ECF 36, 48-49; Doc. 264 (NeoGenomics’ ’454 Patent Opening Claim Construction Brief) at ECF 15-20; Doc. 271 (NeoGenomics’ ’454 Patent Responsive Claim Construction Brief) at ECF 15-19.

² ’454 Patent terms: “sequencing the amplicons” 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.” Doc. 280 (*Markman* ruling) at 15-16.

³ In apparent acknowledgement of these unfavorable odds, NeoGenomics belatedly asks this Court to reconsider its construction of the ’454 Patent claim term “sequencing the amplicons” (Doc. 364) though its request is based entirely on an unsupported theory that Natera disavowed claim scope in the pre-institution IPR proceeding. Natera will substantively respond to and address the flaws of NeoGenomics’ motion in a separate briefing.

language, reading out elements, importing limitations, and improperly narrowing claim scope to reach what it erroneously contends are the plain and ordinary meanings. NeoGenomics' strained constructions contradict how a person of ordinary skill in the art ("POSA") would understand these terms in context and its contention that the same constructions it offered with respect to the '454 Patent are now, for the purpose of the '596 Patent, the plain and ordinary meaning are baseless. NeoGenomics is just repeating the same tired arguments, which suffer from the same deficiencies as before. The intrinsic record, governing caselaw, and extrinsic evidence belie NeoGenomics' litigation-driven constructions.

Natera proposes that each of the disputed terms should be given its *true* plain and ordinary meaning as understood by a POSA that is consistent with the intrinsic and extrinsic evidence. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995). Doing so will assist the jury in understanding 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) (citation omitted). "[T]he person of ordinary skill in the art is deemed to read the 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.* at 1314 (citation omitted).

III. CLAIM CONSTRUCTION ARGUMENT

The Parties dispute the meaning of four terms in Claim 1 of the '596 Patent. With the disputed terms identified as Terms A-D, respectively (terms A, C, and D are underlined and term B is highlighted), Claim 1 states:

1. A method for preparing biological samples useful for monitoring the progression of cancer in a subject, the method comprising:

- (a) performing sequencing on a tumor biopsy sample of the subject to identify a plurality of tumor-specific mutations, wherein the tumor-specific mutations comprise one or more single nucleotide variant (SNV) mutations;
- (b) evaluating results of the sequencing on the tumor biopsy sample to determine a plurality of target loci specific to the subject, wherein each target locus spans a tumor-specific mutation of the identified plurality of tumor-specific mutations; and
- (c) assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points, wherein the assaying comprises:
 - performing targeted multiplex PCR amplification to amplify the plurality of target loci together in the same reaction volume from the isolated cell-free DNA using primers specific to the plurality of target loci for the individual subject; and
 - performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads, wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads.

Doc. 352-10 ('596 Patent) at Claim 1. Each disputed term is addressed in turn below.

A. “the isolated cell-free DNA”

<u>Natera’s Proposal:</u>	<u>NeoGenomics’ Proposal⁴:</u>
Plain and ordinary meaning, which includes cell-free DNA isolated from any of the plurality of biological samples obtained from the subject at different time points.	Plain and ordinary meaning, which is cell-free DNA isolated from a plurality of biological samples obtained from the subject and excludes cell-free DNA isolated from a single biological sample obtained from the subject.

In broader context, pertinent portions of the claim recite:

(c) assaying **cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points**, wherein the assaying comprises:

performing targeted multiplex PCR amplification to **amplify the plurality of target loci together in the same reaction volume from the isolated cell-free DNA** using primers specific to the plurality of target loci for the individual subject...

Id. (emphasis added).

The parties agree that the term “the isolated cell-free DNA” finds antecedent basis support earlier in the claim in the term “assaying **cell-free DNA isolated** from a plurality of biological samples obtained from the subject at different timepoints.” However, the parties dispute the scope of what is encompassed by the plain and ordinary meaning of the term. Natera proposes that “the isolated cell-free DNA,” in the context of Claim 1,

⁴ NeoGenomics clarified that its “proposed construction of ‘the isolated cell-free DNA’ as ‘cell-free DNA isolated from a plurality of biological samples obtained from the subject’ (i.e., its plain and ordinary meaning) would exclude cell-free DNA isolated from a single biological sample obtained from the subject.” Ex. 1 at 1 (M. Stephens email dated 01/12/25).

properly refers to *any* of the cell-free DNA isolated from a plurality of biological samples obtained from the subject at any of the different time points recited, consistent with the claim language and specification. NeoGenomics, however, omits recited elements about different timepoints and reads into the claims a separate requirement, unsupported by the intrinsic or extrinsic evidence, that excludes cell-free DNA isolated from a single biological sample obtained from the subject (*i.e.*, from a single timepoint alone).

The Federal Circuit “has repeatedly and clearly held that it will not read unstated limitations into claim language”—just as NeoGenomics seeks to do here. *N. Telecom Ltd. v. Samsung Elecs. Co.*, 215 F.3d 1281, 1290 (Fed. Cir. 2000). NeoGenomics’ strategically narrow and unsupported construction attempts to engineer a non-infringement theory and sets up an argument that NeoGenomics does not practice the limitations it seeks to read into the claims. According to NeoGenomics, the claims require pooling samples from multiple different timepoints before assaying the isolated cell-free DNA, but NeoGenomics does not infringe because it assays the isolated cell-free DNA separately at each timepoint (rather than pooling before assaying). NeoGenomics’ construction, however, contradicts the intrinsic record and, thus, Natera’s plain and ordinary meaning should prevail.

Natera’s plain and ordinary meaning proposal is consistent with the claim language. In full context, the antecedent basis for “*the* isolated cell-free DNA” is “cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points.” See *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342-43 (Fed. Cir.

2008) (“[i]n grammatical terms,” definite articles (*i.e.*, “said” or “the”) “are anaphoric phrases, referring to the initial antecedent phrase”).

The use of “the” particularizes “isolated cell-free DNA”⁵ but not to the exclusion of isolated cell-free DNA obtained from a single biological sample as NeoGenomics contends. If Natera “so desired,” it could have disclaimed performing targeted multiplex PCR amplification on cell-free DNA isolated from a single biological sample, but it did not. *See Takeda Pharm. Co. 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). Indeed, Natera could have required pooling different samples from different timepoints before assaying the cell-free DNA. Again, it did not. There is nothing in the claim term—express or implied—limiting targeted multiplex PCR amplification to be performed *only on two or more of the plurality of isolated cell-free DNA samples*. *See N. Telecom Ltd.*, 215 F.3d at 1290; *Phillips*, 415 F.3d at 1316.

Consistent with this construction, the preamble recites “[a] method for preparing biological samples useful for monitoring the progression of cancer in a subject” and is followed by open-ended “comprising” terminology. The preamble recites preparing biological ***samples***—in the plural—indicating it is meant to prepare one ***or more*** samples each using the steps of the method’s workflow. The preamble does not recite preparing a

⁵ *See Gen-Probe Inc. v. Becton Dickinson and Co.*, No. 09-cv-2319-BEN-NLS, 2011 WL 7167137, at *5 (S.D. Cal. Nov. 22, 2011) (“‘the’ particularizes the subject which it precedes”) (citation omitted).

single biological sample through the method's workflow by pooling samples from different timepoints, as NeoGenomics' construction would require. Moreover, it is axiomatic that **monitoring** cancer progression (as recited) must occur over a period of time.⁶ Thus, "the biological samples," which are central to the dispute, are obtained from different timepoints and cell-free DNA isolated at each time point is separately assayed according to the claimed steps so that one can monitor cancer progression through the differences between the cell-free DNA at the different timepoints. *See Power Mosfet Techs., L.L.C. v. Siemens AG*, 378 F.3d 1396, 1409 (Fed. Cir. 2004) ("‘Comprising,’ while permitting additional elements not required by a claim, does not remove the limitations that are present.") (citation omitted).

NeoGenomics' construction would lead to an absurdity. Mixing samples obtained from a subject at different timepoints (as NeoGenomics' construction would require) and testing them all together would fundamentally prohibit monitoring progression over time and render the claim inoperable. *Atlas IP, LLC v. St. Jude Medical, Inc.*, 804 F.3d 1185, 1189 (Fed. Cir. 2015) ("a construction that renders the claimed invention inoperable should be viewed with extreme skepticism") (citation omitted). It logically follows from the claim language that "assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points" in order to monitor cancer progression permits, for any one of the biological samples at a given timepoint, "performing targeted

⁶ NeoGenomics concedes that in the context of cancer recurrence and progression, "[m]onitoring patient samples from multiple timepoints is how MRD [minimal residual disease] monitoring works." Doc. 341 (NeoGenomics' Opposition to Amending the Complaint) at 7.

multiplex PCR amplification to amplify the plurality of target loci together in the same reaction volume from the isolated cell-free DNA.” Doing so for at least two timepoints would provide the ability to monitor cancer progression.

NeoGenomics’ proposed construction is also contrary to the plain and ordinary meaning of the term in the context of the claim. By mandating that performing targeted multiplex PCR on cell-free DNA isolated from a single biological sample is excluded from the claim scope, NeoGenomics not only ignores the import of the “different timepoints” language to the context of the claim and the overall purpose of the claim to monitor cancer progression, but also improperly reads in an unsupported “simultaneous” or “pooling” requirement into the claims. *See N. Telecom Ltd.*, 215 F.3d at 1290.

Natera’s plain and ordinary construction is also supported by dependent Claim 17, which covers embodiments in which “the biological sample” is used in a singular form. Claim 17 recites: “[t]he method of claim 1, wherein the biological sample is a blood, serum, plasma, or urine sample” and thus encompasses performing targeted multiplex PCR on the cell-free DNA isolated from a single biological sample. By definition, Claim 1 “is broader than a claim that depends from it, so if a dependent claim reads on a particular embodiment of the claimed invention, the corresponding independent claim must cover that embodiment as well.” *Littlefuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022).

NeoGenomics’ construction is not only devoid of support in the intrinsic record, as set forth below, it excludes preferred embodiments expressly directed to monitoring cancer

progression. A construction that excludes preferred embodiments is “rarely, if ever, correct.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996). And NeoGenomics provides none of the “exacting” evidence⁷ required to establish Natera either: (1) intended to deviate from the true 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).

For example, the ’596 Patent’s specification discloses that, in some embodiments, “a subject diagnosed with a disease or disorder (such as cancer) ***undergoes repeat testing*** using a method of the invention or known testing for the disease or disorder at ***multiple time points to monitor the progression*** of the disease or disorder or the remission or reoccurrence of the disease or disorder.” Doc. 352-10 (’596 Patent) at 27: 48-54 (emphasis added); *see also id.* at 140:59-63.

The specification clarifies that the claimed method may be performed on cell-free DNA isolated from a *single biological sample at a given timepoint* and repeated on a different biological sample obtained at another point in time to monitor cancer progression. For example, the ’596 Patent discloses databases containing information associated with the claimed methods, which include, *inter alia*, the “fraction of cancerous DNA,” the

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

“source of *sample* used to identify the polymorphisms/mutations (such as a *blood sample* or sample from a particular tissue),” and “results from later repeating the test (such as repeating the test to monitor the progression or remission of the cancer).” *Id.* at 139:35-47. The patent refers to “sample” in a singular form, clarifying that that the claimed method may be repeated on different samples at different timepoints to test for the fraction of cancerous DNA and monitor cancer progression. A construction that mandates combining biological samples from multiple timepoints in order to isolate cell-free DNA and perform targeted multiplex PCR amplification in a single reaction volume reads such express disclosure out of the claims and is at odds with the intention of the patentee as expressed in the specification. *PPC Broadband, Inc. v. Corning Optical Commc’ns RF, LLC*, 815 F.3d 747, 756 (Fed. Cir. 2016).

For all these reasons, Natera’s plain and ordinary meaning construction should be adopted.

- B. “performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads, wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads”**

<u>Natera’s Proposal:</u>	<u>NeoGenomics’ Proposal:</u>
Plain and ordinary meaning, which means that the terms are part of the “performing high-throughput sequencing . . . to obtain sequence reads” step and the “wherein” clause informs the mechanics of how the high-throughput sequencing is performed.	Plain and ordinary meaning, no construction necessary beyond the constructions of Terms C and D below

The parties dispute whether the entirety of the “performing high-throughput sequencing . . . detected from the sequence reads” should be construed, whether “the amplified DNA” is limited to the molecules produced by targeted multiplex PCR amplification, whether the “wherein” clause is part of the high-throughput sequencing, and the meaning of “detected” in the context of sequencing. As explained below, the plain claim language makes clear the constituent elements are interrelated and informs a POSA’s understanding that (1) the terms are all part of the “performing high-throughput sequencing . . . to obtain sequence reads” step, (2) the “wherein” clause informs the mechanics of how the high-throughput sequencing is performed, and (3) “the amplified DNA” may be modified before being sequenced.

NeoGenomics contends that construction of the entire term is not necessary beyond the two discrete sub-terms⁸ it identifies. In doing so, NeoGenomics improperly separates various elements from their context, omits recited elements, rewrites the claim language, and ignores a POSA’s understanding of high-throughput sequencing. *IGT v. Bally Gaming Int’l, Inc.*, 659 F.3d 1109, 1117 (Fed. Cir. 2011) (cautioning against divorcing terms from the context of surrounding limitations, which “can lead construction astray”). NeoGenomics’ proposed construction is not consistent with the plain and ordinary meaning; it seeks to distort a POSA’s interpretation to manufacture purported non-infringement theories.

⁸ See *supra* at 3, Terms C and D; see also *infra* at Sections III.C-D.

1. The terms are all part of the “performing high-throughput sequencing . . . to obtain sequence reads” step

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; *accord In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983).

Claim 1 is reproduced below as an annotated screenshot to show its formatting and structure in the patent:

1. A method for preparing biological samples useful for monitoring the progression of cancer in a subject, the method comprising:

- (a) performing sequencing on a tumor biopsy sample of the subject to identify a plurality of tumor-specific mutations, wherein the tumor-specific mutations comprise one or more single nucleotide variant (SNV) mutations;
- (b) evaluating results of the sequencing on the tumor biopsy sample to determine a plurality of target loci specific to the subject, wherein each target locus spans a tumor-specific mutation of the identified plurality of tumor-specific mutations; and
- (c) assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points, wherein the assaying comprises:
 - performing targeted multiplex PCR amplification to amplify the plurality of target loci together in the same reaction volume from the isolated cell-free DNA using primers specific to the plurality of target loci for the individual subject; and
 - performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads, wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads.

As shown here, several recited steps of Claim 1—the first *performing* step, the second *evaluating* step, and the third *assaying* step—are presented as indented subparagraphs designated “(a),” “(b),” and “(c),” respectively, and each is separated by a

semicolon (red underlining). *See Beckmann v. Gandhi*, 646 F. App'x 950, 959 (Fed. Cir. 2016) (structure and line indentation “indicates that the claimed method comprises” different steps”); *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”). The “assaying” step of 1(c) is further divided into two sub-steps—a *performing targeted multiplex PCR amplification* step and a *performing high-throughput sequencing . . . to obtain sequence reads* step—signaled by the use of a preceding colon (blue underline) and each presented as a hanging indented subparagraph separated by a semicolon (red underline).

Unlike any of these steps, the “wherein” language is not set off from the sequencing step by semicolon or otherwise. Instead, “wherein” appears in the indented text of the *performing high-throughput sequencing . . . to obtain sequence reads* step, separated only by a comma (green underlining) rather than semicolon. Grammatically, the “wherein” clause—“wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus *is detected from the sequence reads*”—uses the passive voice to refer back to the immediately preceding language “performing high-throughput sequencing . . . to obtain sequence reads.” *See Mformation Techs., Inc. v. Research in Motion Ltd.*, 764 F.3d 1392, 1398 (Fed. Cir. 2014) (holding a claim may, “as a matter of logic or grammar,” require an order).

The claim’s punctuation, grammar, and syntax all support Natera’s interpretation that the terms (as highlighted above) are part of one high-throughput sequencing step. Thus, the entirety of the “wherein” clause is part of, and modifies, the process of

“performing high-throughput sequencing . . . to obtain sequence reads,” rather than being separate from the “performing high-throughput sequencing . . . to obtain sequence reads” step. *See Hyatt*, 708 F.2d at 714 (holding “[a] claim must be read in accordance with the precepts of English grammar”); *Tris Pharma, Inc. v. Teva Pharms. USA, Inc.*, No. 20-CV-5212, 2021 WL 3879153, at *3 (D.N.J. Aug. 25, 2021) (stating a person of ordinary skill in the art “still follows the basics of English”).

2. The “wherein” clause specifically informs the mechanics of how the high-throughput sequencing is performed

Substantively, the elements of the “wherein” clause at the end of Claim 1 further support Natera’s interpretation that the terms impose a limitation on how the claimed high-throughput sequencing is performed. The clause recites “wherein an SNV mutation that is present in *less than or equal to 0.015%* of the cell-free DNA having the SNV locus is detected from the sequence reads.” The express language regarding the method’s capability to detect SNV mutations present in certain frequencies (less than or equal to 0.015%) informs the mechanics of how the high-throughput sequencing is performed. *See L’Oreal USA, Inc. v. Olaplex, Inc.*, 844 F. App’x. 308, 324 (Fed. Cir. 2021).

The “is detected” language also supports Natera’s construction and view that the “wherein” clause expressly modifies “performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads.” The ’596 Patent’s preferred embodiments use Illumina sequencers for “high-throughput DNA sequencing.” Doc. 352-10 (’596 Patent) at 58:32-45, 62:1-13, 96:37-40, 152:61-67, 164:7-14. The specification of the ’596 Patent discloses a product data sheet published in 2015

for an Illumina high-throughput sequencing instrument, called HiSeq 2500. *Id.* at p. 24 (citing Ex. 2). The product sheet explains the operations occurring *within* the sequencing platform, stating:

With the HiSeq 2500 System, high data quality is ensured by leveraging the most widely adopted chemistry in the industry: sequencing by synthesis (SBS). SBS technology on the HiSeq 2500 utilizes a proprietary reversible terminator-based method that ***detects single bases as they are incorporated into DNA template strands.***

Id. at 1 (emphasis added). In the context of sequencing at the time of the April 2015 priority date, a POSA would understand that the plain and ordinary meaning of the claimed “detected” limitation refers back to and modifies how the high-throughput sequencing is performed and that the detecting is part of the high-throughput sequencing happening in the sequencer. *See* Doc. 272 (Natera’s ’454 Patent Responsive Claim Construction Brief) at 16-17.

Under the pretense of defining the “plain and ordinary meaning,” NeoGenomics rewrites the claim language in the “wherein” clause, contending that “is detected” means “determined to be present.” But this not only ignores a POSA’s familiarity with sequencing and the intrinsic record, it conflates the meanings of “detect” and “determine” in this context. According to the Oxford English Dictionary, the definition of detect is:

(1) “to discover or identify the presence or existence of,” (2) discover or investigate (a crime or its perpetrators), (3) discern (something intangible or barely perceptible).”

Ex. 3 at NEOGEN00289221. Likewise, according to the Collins English Dictionary, the definition of detect is:

(1) “to perceive or notice”, (2) “to discover the existence or presence of (esp something likely to elude observation)”, or (3) “to extract information from (an electromagnetic wave).”

Ex. 4 at NEOGEN00289063. In contrast, the definition of determine is:

(1) “to cause to occur in a particular way; be the decisive factor in,” (2) “firmly decide”, (3) “ascertain or establish by research or calculation,” or (4) “specify the value, position, or form of (a mathematical or geometrical object) uniquely.”

Ex. 3 at NEOGEN00289221.

None of these sources suggests that the plain and ordinary meaning of “detect” imparts the same meaning as “determine;” all instead point to “determine” as mandating a higher level of stringency to ascertain or establish information compared to “detect,” which is more closely tied to discovering the presence of information. Given a POSA’s familiarity with this terminology, particularly in the sequencing context, NeoGenomics’ substitution of “is detected” for the nonsynonymous “determined to be present” would fundamentally alter the plain meaning of the claim as written.

NeoGenomics’ construction is an obvious attempt to bolster its manufactured noninfringement argument that it somehow does not infringe because one of its computer servers, which it will contend does the claimed detecting, is located outside the United States. But NeoGenomics’ attempt to write algorithmic computations—that it will argue occur in its overseas servers—into the claim is inconsistent with the claim language and the intrinsic and extrinsic record.

3. The term permits intermediate steps between targeted multiplex PCR amplification and sequencing

Natera proposes the entirety of the term should be given its plain and ordinary meaning, which allows “the amplified DNA” to be modified prior to being sequenced. NeoGenomics’ proposed construction rehashes the same non-infringement argument it has raised on numerous occasions based on the ’454 Patent term “the amplicons,” including in the preliminary injunction proceeding,⁹ ’454 Patent *inter partes* review petition,¹⁰ claim construction briefing related to the ’454 Patent,¹¹ and most recently, its Motion for Reconsideration of the Court’s prior *Markman* ruling.¹² As with “the amplicons” in the ’454 Patent, NeoGenomics contends that “the amplified DNA” in the ’596 Patent is limited to the molecules produced by targeted multiplex PCR amplification, which NeoGenomics argues—incorrectly—cannot be modified before being sequenced.

As an initial matter, in the absence of a compelling reason to deviate (and there is none here),¹³ the Court should construe claim terms in the ’596 and ’454 Patents consistently as both patents are derived from a common parent application (U.S. Patent

⁹ Doc. 107 (NeoGenomics’ PI Opposition) at ECF 8-10.

¹⁰ Doc. 366-1 (NeoGenomics Petition for *Inter Partes* Review of the ’454 Patent) at ECF 36, 48-49.

¹¹ Doc. 264 (NeoGenomics’ Opening Claim Construction Brief) at ECF 15-20; Doc. 271 (NeoGenomics’ Responsive Claim Construction Brief) at ECF 15-19.

¹² *See generally* Doc. 365.

¹³ As Natera will explain its upcoming Opposition, contrary to NeoGenomics’ contentions in its Motion for Reconsideration regarding the construction of “sequencing the amplicons” (Doc. 365), there was no disavowal of claim scope in the pre-institution ’454 Patent IPR proceeding.

Application No. 14/692,703),¹⁴ contain the same specification, and share many common terms. *See NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005) (“Because NTP’s patents all derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents We thus draw distinctions between the various patents only where necessary.”); *see also Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003).

As shown below, Claim 1 of the ’596 Patent recites language similar to that of Claim 1 of the ’454 Patent. As with the ’454 Patent’s “the amplicons,” there is no lexicography or special meaning given to the straightforward language of “the amplified DNA” in the ’596 Patent. *Phillips*, 415 F.3d at 1313. The similarity of the two claims supports the conclusion that the plain and ordinary meaning of “performing high-throughput sequencing of the amplified DNA” in the ’596 Patent should be interpreted consistently with the Court’s prior plain-and-ordinary interpretation of “sequencing the amplicons” in the ’454 Patent, which does not prohibit the performance of additional steps on the amplicons before they are sequenced. Doc. 280 at 8, 15.

¹⁴ Compare Doc. 1-1 (’454 Patent) at cover page, with Doc. 352-10 (’596 Patent) at cover page.

'454 Patent, Claim 1	'596 Patent, Claim 1
A method ... <i>comprising</i>: ... <i>performing targeted multiplex amplification</i> 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 <i>sequencing the amplicons</i> to obtain sequence reads, and ...	A method ... <i>comprising</i>: ... <i>performing targeted multiplex PCR amplification to amplify the plurality of target loci</i> together in the same reaction volume from the isolated cell-free DNA using primers specific to the plurality of target loci for the individual subject; and performing high-throughput sequencing of <i>the amplified DNA comprising the plurality of target loci</i> to obtain sequence reads, wherein...

As further support for Natera's construction, Claim 1 of the '596 Patent refers to "performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads." The specification discloses: "Sequence Read refers to data representing a sequence of nucleotide bases that were measured...." Doc. 352-10 ('596 Patent) at 31:17-19. Thus, "performing high-throughput sequencing . . . to obtain sequence reads," in this context, refers to the process of obtaining data representing the sequences of the nucleotide bases that were measured. Amplified DNA 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."). Similar to "the amplicons" recited in the '454 Patent, "the amplified DNA" from the targeted multiplex amplification comprise sequences that include the "target loci" referred to in that step. *See* Doc. 145 (Metzker PI Reply Decl.), ¶ 270.

Given that the '454 and '596 Patents share the same specification and priority date, a POSA would understand that the plain and ordinary meaning of “performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads” permits—and certainly does not foreclose—intermediate steps after targeted multiplex amplification but before sequencing. *Id.*, ¶¶ 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.*; see *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”).

Like the '454 Patent, the '596 Patent teaches embodiments of possible intermediate steps, such as barcoding that occurs after targeted multiplex PCR amplification ***but before*** high-throughput sequencing. Doc. 352-10 ('596 Patent) at 164:44-48 (“The barcodes are attached *to the amplification products* via PCR amplification for 12 cycles Samples are sequenced by NGS”).

In addition, a POSA would understand from the claim language and specification that unrecited steps in between “targeted multiplex PCR amplification” and “performing high-throughput sequencing of the amplified DNA” are ***not*** excluded from the claim scope similar to the '454 Patent. See Doc. 145 (Metzker PI Reply Decl.), ¶¶ 267-275; *CollegeNet*, 418 F.3d at 1235. Claim 1 of the '596 Patent is open-ended by virtue of reciting

“comprising” in its preamble, 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); *see also CollegeNet*, 418 F.3d at 1235.

Moreover, a POSA would have understood that, while the claims do not expressly recite adding adaptors to amplified DNA before sequencing, that modification would be necessary with systems expressly taught by the ’596 and ’454 Patents. Doc. 145 (Metzker PI Reply Decl.), ¶ 274. Example 1, for instance, teaches a PCR step between targeted multiplex PCR and sequencing to add barcodes to generate a sequencing library. Doc. 352-10 (’596 Patent) at 152:55-60. The patent’s preferred embodiments further use Illumina sequencers for “high-throughput DNA sequencing.” *Id.* at 58:32-45, 62:1-13, 96:37-40, 152:61-67, 164:7-14. As Dr. Metzker explained during the preliminary injunction proceeding, POSAs understood that Illumina sequencers require modifying amplified DNA before sequencing can be performed. Doc. 145 (Metzker PI Reply Decl.), ¶ 274; PI Hr’g Tr. at 21:10-22:2. These include attaching sequence tags to the amplified DNA to allow molecules to bind to a “flow cell”, which will then be loaded into the sequencer for sequencing. Doc. 145 (Metzker PI Reply Decl.), ¶ 61; PI Hr’g Tr. at 25:12-22. Dr. Metzker also testified that there is a necessary amplification step that occurs as part of sequencing that makes additional copies of all amplified DNA before their sequences are determined. PI Hr’g Tr. at 13:25-14:23.

Thus, based on how high-throughput sequencing works, a POSA would understand that additional steps are necessary before sequencing on Illumina systems that the '596 and '454 Patents each teaches to use. Doc. 145 (Metzker PI Reply Decl.), ¶ 61. And where samples from multiple sources are run together on the Illumina system (in one shared sequencing run), there is another permissible step: adding barcode sequences to amplified DNA before sequencing. *Id.*, ¶ 272; *see also* Doc. 141-11 (Illumina protocol) at 1.

As it did with the '454 Patent, NeoGenomics incorrectly argues that the claim language *precludes* modifying the amplified DNA produced in targeted multiplex PCR amplification before sequencing.¹⁵ But NeoGenomics' interpretation would require improperly *rewriting* the claims to recite “amplified DNA obtained from the targeted multiplex PCR amplification step” and thus reading the notion of “directly” sequencing the amplified DNA into the claim language,¹⁶ 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) (citation omitted). It also would read out preferred embodiments, such as those using Illumina sequencers (*see supra*), which necessarily involve adding adaptors before sequencing. Doc. 145 (Metzker

¹⁵ Doc. 107 (Van Ness PI Decl.) at ECF 8-10; Doc. 366-1 (NeoGenomics' '454 Patent IPR Petition) at ECF 36, 48-49; Doc. 264 (NeoGenomics' '454 Patent Opening Claim Construction Brief) at ECF 15-20; Doc. 271 (NeoGenomics' '454 Patent Responsive Claim Construction Brief) at ECF 15-19.

¹⁶ *Compare* Doc. 116 (Van Ness PI Decl.), ¶ 81 *with* Doc. 145 (Metzker PI Reply Decl.), ¶¶ 267, 270.

PI Reply Decl.), ¶¶ 61, 274; *see GE Lighting*, 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.

C. “performing high-throughput sequencing of the amplified DNA”

<u>Natera’s Proposal:</u>	<u>NeoGenomics’ Proposal:</u>
Plain and ordinary meaning, which permits intermediate steps after multiplex amplification but before sequencing.	Plain and ordinary meaning, which is performing high-throughput sequencing of the amplified DNA obtained from the targeted multiplex PCR amplification step.

The sub-term “performing high-throughput sequencing of the amplified DNA” identified by NeoGenomics should be given its plain and ordinary meaning in the context of the broader term of Claim 1 as described in Section III.B *supra*.

D. “wherein an SNV mutation . . . is detected from the sequence reads”

<u>Natera’s Proposal:</u>	<u>NeoGenomics’ Proposal:</u>
Plain and ordinary meaning, which means that the terms are part of the “performing high-throughput sequencing . . . to obtain sequence reads” step and the “wherein” clause informs the mechanics of how the high-throughput sequencing is performed.	Plain and ordinary meaning, which is wherein an SNV mutation is determined to be present from the sequence reads.

The sub-term “wherein an SNV mutation . . . is detected from the sequence reads” identified by NeoGenomics should be given its plain and ordinary meaning in the context of the broader term of Claim 1 as described in Section III.B *supra*.

IV. CONCLUSION

For at least the foregoing reasons, the Court should adopt Natera’s constructions.

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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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