

**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 RESPONSIVE CLAIM CONSTRUCTION BRIEF
REGARDING U.S. PATENT NO. 11,319,596

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	CLAIM CONSTRUCTION ARGUMENT.....	2
A.	“the isolated cell-free DNA”	2
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”	6
1.	The entirety of the term should be construed because the terms are all part of the “performing high-throughput sequencing . . . to obtain sequence reads” step	7
2.	An SNV is detected as part of the high-throughput sequencing process from sequence reads as they are being generated	12
(a)	NeoGenomics’ Construction is Undermined by Its Inconsistent Positions, Dr. Lennon’s Testimony, and Corporate Representatives	18
3.	The term permits intermediate steps between targeted multiplex PCR amplification and sequencing.....	20
C.	“performing high-throughput sequencing of the amplified DNA”	24
D.	“wherein an SNV mutation . . . is detected from the sequence reads”	24
III.	CONCLUSION	24

TABLE OF AUTHORITIES

	<u>Page</u>
<u>Cases</u>	
<i>In re Affinity Labs of Texas, LLC</i> , 856 F.3d 902 (Fed. Cir. 2017).....	10
<i>ArcherDX, LLC v. QIAGEN Sciences, LLC</i> , 1:18-cv-01019, D.I. 487 (D. Del. Aug. 25, 2021).....	1
<i>Baldwin Graphic Sys., Inc. v. Siebert, Inc.</i> , 512 F.3d 1338 (Fed. Cir. 2008).....	3
<i>Barnhart v. Thomas</i> , 540 U.S. 20 (2003).....	11
<i>Beckmann v. Gandhi</i> , 646 F. App'x 950 (Fed. Cir. 2016)	10
<i>Bell Atl. Network Servs. v. Covad Commc'ns Grp., Inc.</i> , 262 F.3d 1258	15
<i>CollegeNet, Inc. v. ApplyYourself, Inc.</i> , 418 F.3d 1225 (Fed. Cir. 2005).....	21
<i>Cont'l Paper Bag Co. v. E. Paper Bag Co.</i> , 210 U.S. 405 (1908).....	9
<i>Cordis Corp. v. Boston Sci. Corp.</i> , 561 F.3d 1319 (Fed. Cir. 2009).....	23
<i>Curtiss-Wright Flow Control Corp. v. Velan, Inc.</i> , 438 F.3d 1374 (Fed. Cir. 2006).....	18
<i>Eastman Chem. Co. v. Aktiengesellschaft</i> , 47 F. App'x 566 (Fed. Cir. 2002)	4
<i>GE Lighting Sols., LLC v. AgiLight, Inc.</i> , 750 F.3d 1304 (Fed. Cir. 2014).....	23
<i>Gen-Probe Inc. v. Becton Dickinson and Co.</i> , No. 09-cv-2319-BEN-NLS, 2011 WL 7167137 (S.D. Cal. Nov. 22, 2011)	4

<i>Golden Bridge Tech., Inc. v. Apple Inc.</i> , 758 F.3d 1362 (Fed. Cir. 2014).....	23
<i>In re Hyatt</i> , 708 F.2d 712 (Fed. Cir. 1983).....	9
<i>IGT v. Bally Gaming Int’l, Inc.</i> , 659 F.3d 1109 (Fed. Cir. 2011).....	4, 8
<i>Innonva/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.</i> , 381 F.3d 1111 (Fed. Cir. 2004).....	9, 16
<i>Innovative Memory Sys., Inc. v. Micron Tech., Inc.</i> , 781 F. App’x 1013 (Fed. Cir. 2019)	4
<i>Intamin Ltd. v. Magnetar Techs., Corp.</i> , 483 F.3d 1328 (Fed. Cir. 2007).....	15
<i>Intel Corp. v. Qualcomm Inc.</i> , 21 F.4th 801 (Fed. Cir. 2021)	7
<i>Kyowa Hakko Bio, Co. v. Ajinomoto Co.</i> , No. 17-cv-00313-MSG, 2019 WL 10092522 (D. Del. Apr. 1, 2019)	20
<i>Mayne Pharma Int’l Pty. Ltd. v. Merck & Co.</i> , No. CV 15-438-LPS, 2016 WL 7441069 (D. Del. Dec. 27, 2016) <i>aff’d</i> <i>sub nom. Maybe Pharma Int’l Pty. Ltd. v. Merck Sharp & Dohme Corp.</i> , 927 F.3d 1232 (Fed. Cir. 2019)	16
<i>Merck & Co. v. Teva Pharms. USA, Inc.</i> , 395 F.3d 1364 (Fed. Cir. 2005).....	3, 8
<i>N. Telecom Ltd. v. Samsung Elecs. Co.</i> , 215 F.3d 1281 (Fed. Cir. 2000).....	3
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303, 1313 (Fed. Cir. 2005).....	9, 11
<i>Roche Diagnostics Operations, Inc. v. Lifescan Inc.</i> , 660 F. App’x 932 (Fed. Cir. 2016)	6
<i>Source Vagabond Sys. Ltd. v. Hydrapak, Inc.</i> , 753 F.3d 1291 (Fed. Cir. 2014).....	13

<i>Tris Pharma, Inc. v. Teva Pharms. USA, Inc.</i> , No. 20-CV-5212, 2021 WL 3879153 (D.N.J. Aug. 25, 2021)	11
<i>Vitronics Corp. v. Conception Inc.</i> , 90 F.3d 1576 (Fed. Cir. 1996).....	8

I. INTRODUCTION

Each of the four disputed claim terms of U.S. Patent No. 11,319,596 (“the ’596 Patent”) are presumed to take on the customary meanings attributed to them by a person of ordinary skill in the art (“POSA”). NeoGenomics’ constructions—which are not plain and ordinary—rewrite the patentee’s chosen words, turn on unclaimed embodiments, ignore multiple disclosures in the specification, and fall short of the requirements for *clear and unmistakable* disavowal of claim scope. Moreover, while reliance on case law is scarce in NeoGenomics’ brief, even the few cited cases are either distinguishable or support Natera’s positions.

NeoGenomics treats the intrinsic record superficially, rehashes its co-pending motion¹ for reconsideration of the Court’s construction² of U.S. Patent No. 11,530,454 (“the ’454 Patent”) term “sequencing the amplicons,” and resorts to extrinsic evidence from its expert that fundamentally misses the mark. Notably, its expert previously testified that high-throughput sequencing and detection are part of a single step³—tracking Natera’s proposed construction for the ’596 Patent term “performing high-throughput sequencing . . . detected from the sequence reads”—and undermining NeoGenomics’ argument that the claims require a separate “data processing” step after the sequencing is completed. Finally, NeoGenomics’ arguments contradict the representations it made to the PTAB in the ’596

¹ See Doc. 365.

² See Doc. 280 at 15-16.

³ See Doc. 378-1 (trial testimony of Dr. Niall Lennon from *ArcherDX, LLC v. QIAGEN Sciences, LLC*, 1:18-cv-01019, D.I. 487 (D. Del. Aug. 25, 2021)) at 40:22-41:8.

Patent pre-institution *inter partes* review (“IPR”)⁴ regarding a POSA’s understanding of this same term.

The Court should adopt Natera’s proposed claim constructions.

II. CLAIM CONSTRUCTION ARGUMENT

A. “the isolated cell-free DNA”

<u>Natera’s Proposal:</u>	<u>NeoGenomics’ Proposal</u> ⁵ :
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.

The 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...

Doc. 352-10 (’596 Patent) at claim 1 (emphasis added).

⁴ More than a month after the Court granted Natera’s motion for leave to amend the pleadings to add the ’596 Patent (Doc. 345), NeoGenomics filed a petition for *inter partes* review of the ’596 Patent. *See generally* Doc. 378-2 (*NeoGenomics Laboratories, Inc. v. Natera, Inc.*, IPR2025-00455, Paper 2 (P.T.A.B. Jan. 15, 2025)).

⁵ 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.” Doc. 372-1 at 1 (M. Stephens email dated 01/12/25).

There is only one plain and ordinary meaning for this term. NeoGenomics mischaracterizes Natera's position and is silent on the actual dispute. The parties agree that the term "the isolated cell-free DNA" finds its antecedent basis earlier in the claim, but the parties dispute exactly what constitutes this antecedent.

The antecedent basis for "the isolated cell-free DNA" is the phrase "assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject *at different timepoints*" (emphasis added). NeoGenomics' argument omits the emphasized language. As Natera explained in its Opening Brief, "the" in "the isolated cell-free DNA" refers back to "cell-free DNA isolated from a plurality of biological samples obtained from the subject at different timepoints." Doc. 372 at 4-5; *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1343 (Fed. Cir. 2008) ("[i]n grammatical terms," definite articles (i.e., "said" or "the") "are anaphoric phrases, referring to the initial antecedent phrase").

While reading *out* the requirement that the samples be obtained "at different timepoints," NeoGenomics simultaneously reads *in* a requirement that cell-free DNA be isolated only after multiple samples taken from the subject are pooled. Doc. 373 at 12; *N. Telecom Ltd. v. Samsung Elecs. Co.*, 215 F.3d 1281, 1290 (Fed. Cir. 2000) (court should not read unstated limitations into the claim); see *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so."). NeoGenomics' omission is intentional and designed to manufacture a noninfringement position that it does not practice this term. But NeoGenomics' construction is not supported by the claim language, the

purpose of the claimed invention, or the unclaimed embodiments it cites from the specification.

NeoGenomics' argument does not even address the "at different time points" requirement, which is expressly recited and part of the context that informs the meaning of "the isolated cell-free DNA." *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). NeoGenomics fails to mention any rationale for why the "at different time points" language should be excluded from being part of the antecedent. *See 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").⁶

Contrary to NeoGenomics' argument (Doc. 373 at 13), Natera's construction does not "rewrite[] the claim language" or fail to give effect to the "plurality" requirement. The claim requires assaying cell-free DNA isolated from a "plurality" (i.e., two or more) of biological samples obtained at different timepoints. Nothing in the claim language,

⁶ NeoGenomics' reliance on *Eastman Chem. Co. v. Aktiengesellschaft*, 47 F. App'x 566 (Fed. Cir. 2002) and *Innovative Memory Sys., Inc. v. Micron Tech., Inc.*, 781 F. App'x 1013 (Fed. Cir. 2019) is inapposite. *Eastman* simply held that the patent in question's reference to "the salt" referred back to the only prior mention of "salt" in the claim. 47 F. App'x at 573. *Innovative Memory* instructs courts to consider "the claim in full" when determining "the antecedent basis for each element." 781 F. App'x at 1017. NeoGenomics violates that principle by ignoring the "at different points in time" limitation.

however, requires that the plurality of samples be pooled and that the recited multiplex PCR amplification be performed on the pooled sample. Doc. 372 at 6.

As NeoGenomics argues elsewhere in its brief, a patent’s “statement of the described invention’s purpose informs the proper construction of the claim terms.” Doc. 373 at 18. That purpose here—which NeoGenomics’ expert confirms—is provided by the claim’s preamble, which states that the invention is “[a] method for preparing biological samples useful for *monitoring the progression of cancer* in a subject” (emphasis added). Doc. 378-4 (Lennon Tr.) at 36:14-22. Monitoring the progression of a patient’s cancer occurs, not by pooling samples obtained at different time points into one mixture, but instead by testing the plurality of samples obtained at different time points to see how the results change over time. NeoGenomics’ assertion that “ctDNA is present in such low levels in the blood” (Doc. 373 at 12-13) does not alter that conclusion. Regardless of the amount of ctDNA in a sample, the progression of a patient’s cancer cannot be monitored over time if all the samples are pooled and tested together.

Contrary to NeoGenomics’ characterization (Doc. 373 at 12), the disclosures it cites from the specification are *unclaimed embodiments* that do not involve cell-free DNA at all.⁷ NeoGenomics quotes passages stating that “*cells* from multiple samples from the same individual are combined” and “combining multiple samples can allow *multiple tissues* to be tested for cancer simultaneously.” Doc. 373 at 12 citing Doc. 352-10 (’596

⁷ NeoGenomics does not contend that the embodiments it cites are the only disclosed embodiments.

Patent) at 95:31-38) (emphasis added). The disputed claim term is, however, “isolated *cell-free DNA*,” not “cells” or “tissues.” Embodiments that involve combining cells or tissues are, therefore, not relevant or claimed in this patent. *See, e.g., Roche Diagnostics Operations, Inc. v. Lifescan Inc.*, 660 F. App’x 932, 938 (Fed. Cir. 2016) (adopting a construction that excluded certain embodiments as unclaimed where the “claims are limited to methods testing blood samples, while the examples disclose embodiments that were evaluated testing saline”). NeoGenomics fails to acknowledge other disclosures in the specification, which support performing the claimed method on cell-free DNA isolated from a single biological sample at a given timepoint and repeating it on a different biological sample obtained at a different timepoint to monitor cancer progression. Doc. 372 at 9-10; Doc. 352-10 (’596 Patent) at 139:35-47.

The Court should give the terms its 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.

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”

Natera’s Proposal:	NeoGenomics’ Proposal:
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

There is only one plain and ordinary meaning for the term. Central to determining the scope of this meaning, the parties dispute the following:

(1) whether the entirety of the “performing high-throughput sequencing . . . detected from the sequence reads” should be construed, given the style and structure of the claim and that each of the terms therein collectively provides necessary context and is thus part of the plain and ordinary meaning;

(2) whether an SNV is detected as part of the high-throughput sequencing process from sequence reads as they are being generated; and

(3) whether “the amplified DNA” permits intervening steps between “performing targeted multiplex amplification” and high-throughput sequencing, some of which may be necessary to modify the amplified DNA prior to sequencing.

Each dispute is addressed in turn below.

1. The entirety of the term should be construed because the terms are all part of the “performing high-throughput sequencing . . . to obtain sequence reads” step

NeoGenomics contends that construction of the entire term is not necessary beyond the two discrete sub-terms⁸ it identifies. Doc. 373 at 13-14. Its constructions for the two sub-terms, however, give no meaning to, and render superfluous, the connecting phrase “comprising the plurality of target loci to obtain sequence reads.” *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 801, 809-10 (Fed. Cir. 2021) (“It is highly disfavored to construe terms in a

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

way that renders them void, meaningless, or superfluous.”) (internal citations omitted); *Merck*, 395 F.3d at 1372. By improperly separating various elements from their context, omitting recited elements, and rewriting the claim language, NeoGenomics injects confusion and ignores a POSA’s understanding of what is occurring during high-throughput sequencing. *IGT*, 659 F.3d at 1117 (cautioning against divorcing terms from the context of surrounding limitations, which “can lead construction astray”).

Fatal to its distorted interpretation, NeoGenomics assigns very little weight to the intrinsic record—oscillating between ignoring critical pieces and pointing to unclaimed embodiments—and relies heavily on its expert whose opinions are undermined by the tumor-specific context of the claim as well as his own contradictory testimony in the co-pending pre-institution IPR and at trial. *See Vitronics Corp. v. Conceptronic Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (“It is well-settled that, in interpreting an asserted claim, the court should look *first to the intrinsic evidence of record*,” which “is *the most significant source* of the legally operative meaning of disputed claim language.”) (emphasis added) (citation omitted).

In construing the terms, NeoGenomics conveniently skips over the starting place—the claim language—likely because it has no way to reconcile the claim’s structure, formatting, grammar, and syntax with its interpretations.⁹ *See Innonva/Pure Water, Inc. v.*

⁹ NeoGenomics’ expert testified that grammar and “the placement of colons, semicolons, commas, [and] periods” “can be important” in interpreting patent claims, but did not consider any of these criteria—which are “not [his] area of expertise”—in forming

Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1116 (Fed. Cir. 2004) (“[A] claim construction analysis must begin and remain centered on the claim language itself, for that is the language the patentee has chosen to ‘particularly point[] out and distinctly claim[] the subject matter which the patentee regards as his invention’”) (internal citation omitted).

Notwithstanding NeoGenomics’ silence, 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 v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005); accord *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983); see also *Cont’l Paper Bag Co. v. E. Paper Bag Co.*, 210 U.S. 405, 419 (1908) (A patentee is at “**liberty to choose his own form of expression**; and while the courts may construe the same in view of the specifications and the state of the art, they **may not add to or detract from the claim.**”) (emphasis added) (internal citation omitted).

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

his opinions about the plain and ordinary meaning of the disputed term. Doc. 378-4 (Lennon Tr.) at 19:11-20:20.

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 explained in Natera's Opening brief (Doc. 372 at 12-14), Claim 1 recites three primary steps¹⁰ signaled by the use of indented subparagraphs designated "(a)," "(b)," and "(c)," respectively, and separated by a semicolon (red underlining). *Beckmann v. Gandhi*, 646 F. App'x 950, 959 (Fed. Cir. 2016); *In re Affinity Labs of Texas, LLC*, 856 F.3d 902, 907 (Fed. Cir. 2017). The "assaying" step of 1(c) is then subdivided into two secondary steps¹¹ through the use of a preceding colon (blue underline) with both sub-steps being

¹⁰ The first *performing* step, the second *evaluating* step, and the third *assaying* step.

¹¹ A *performing targeted multiplex PCR amplification* step and a *performing high-throughput sequencing . . . to obtain sequence reads* step.

formatted as separate subparagraphs further indented under 1(c) and separated by a semicolon (red underline).

Unlike these preceding steps, the “wherein” language is not presented as a separate paragraph or set off from the sequencing step by a semicolon or otherwise. Instead, “wherein” appears in the middle of the indented text of the *performing high-throughput sequencing . . . to obtain sequence reads* step, separated only by a comma (green underlining). According to the doctrine of last antecedent, a grammatical rule of interpretation, “a limiting clause or phrase . . . should ordinarily be read as modifying only the noun or phrase that it immediately follows.” *Barnhart v. Thomas*, 540 U.S. 20, 26 (2003). Consistent with this precedent, 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*”—refers back to the immediately preceding phrase “performing high-throughput sequencing . . . *to obtain sequence reads*.”

NeoGenomics’ construction does not consider how the claim is drafted or address the meaning of “wherein” at all. Doc. 373 at 14-18. Claim terms do not exist in a vacuum, however, and must be read in full context. *Phillips*, 415 F.3d at 1313; *Tris Pharma, Inc. v. Teva Pharms. USA, Inc.*, No. 20-CV-5212, 2021 WL 3879153, at *3 (D.N.J. Aug. 25, 2021). Careful scrutiny of 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 and that the “wherein” clause is modifies the process of “performing high-

throughput sequencing . . . to obtain sequence reads,” consistent with a POSA’s understanding. *See* Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 54-56.

2. An SNV is detected as part of the high-throughput sequencing process from sequence reads as they are being generated

The pertinent portions of the claim recite:

(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.

The Court should decline NeoGenomics’ invitation to substitute “detected” with “determined to be present.” Doc. 373 at 14-17.

First, constructions that merely rewrite the claim are disfavored. *See Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014) (citation omitted) (cautioning against a construction that amounts to a rewriting of the claim).

Second, NeoGenomics contends that “[b]ecause the claim requires detecting an SNV mutation ‘from’ the sequence reads,” data processing is required *after* sequencing is complete to determine whether an SNV mutation is present. Doc. 373 at 14-15, 19-20. But this ignores the preceding claim language and incorrectly assumes that there is no prior knowledge about the target SNV loci or specific steps to amplify the target SNV loci. *See* Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 59-69.

As shown in the bold and underlined text *supra*, the claim language expressly requires identifying a plurality of tumor-specific SNVs (step 1(a)), determining a plurality of target loci each spanning an SNV (step 1(b)), and amplifying these target SNV loci using target-specific primers in the same multiplex PCR reaction volume (step 1(c)). A POSA would understand that, in the context of the claimed methods, tumor-specific SNVs contained in the cell-free DNA are detected as soon as the SNV loci are each read from the growing sequence reads that the sequencer generates one base at a time. Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 61-64. This is a ***necessary result of the way the claimed methods are designed***—sequencing here is not random or scattershot. *See id.*, ¶ 68. Rather, the target SNVs and their precise positions are known ahead of time, and primers are designed to target the SNVs at specific locations (*e.g.*, a certain number of base pairs upstream and downstream from the target SNV). *See id.*, ¶¶ 62-63. Through multiplex PCR in the same

reaction volume, these primers selectively amplify the plurality of SNV target loci and create amplification products containing SNV target loci, which are then sequenced. *See id.* Accordingly, there is already an expectation of the tumor-specific nucleotide at each target SNV locus. *See id.*, ¶ 63.

NeoGenomics erroneously argues that “sequence reads alone do not identify what portion of the genome has been read” and “the sequence read must first be mapped to a reference” before detection can occur. Doc. 373 at 5, 20. But nowhere does NeoGenomics or its expert even acknowledge that the claimed method is designed to target specific SNV loci (as explained *supra*) and how this necessarily informs a POSA what to look for in the sequence reads. Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 59, 64-69. A POSA would understand that the target loci spanning each SNV are unique and would know the start and stop positions of the amplification products, which both provide orientation as sequence reads are being generated. *Id.*, ¶¶ 64-67.

Third, NeoGenomics overlooks the intrinsic disclosure that directly supports a sequencer detecting SNVs from sequence reads at they are being generated. 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 also discloses an Illumina high-throughput sequencing product data, which states the instrument “*detects single bases as they are incorporated into DNA template strands.*” *See id.* at p. 24 (citing Doc. 372-2). Moreover, ’596 Patent sets forth a definition for “Sequence Read:”

Sequence Read refers to data representing a sequence of nucleotide bases that were measured, *e.g.*, using a clonal sequencing method.... A sequence read may also have associated ***quality score at each base position of the sequence indicating the probability that nucleotide has been called correctly.***

Id. at 31:16-24 (emphasis). Natera's lexicography for "sequence read" intentionally uses the same express language about a "quality score" as Illumina's contemporaneous product brochure. *Bell Atl. Network Servs. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001). According to Illumina, base calls are made one at a time as the read is generated by the sequencer detecting the base's fluorescence and ***a quality score*** is assigned to every base as a measure of accuracy. Doc. 374-2 at 1-2; Doc. 378-4 (Lennon Tr.) at 33:8-34:13; Doc. 379 (Metzker '596 Patent CC Decl.), ¶¶ 38-40. Accordingly, the quality score will indicate the probability that the base corresponding to the SNV is called correctly when the sequencer reaches this position in the growing sequence read. Doc. 379 (Metzker '596 Patent CC Decl.), ¶¶ 47, 67, 86.

Fourth, NeoGenomics' argument that the "specification confirms" that SNV mutations are detected outside of the sequencing process (Doc. 373 at 15) rests on a misreading of the patent. The statement NeoGenomics cites refers to an unclaimed embodiment about generating a predictive model to determine a set of probabilities that SNVs result from real mutations, none of which even recite sequencing, much less the claimed steps of identifying and targeting SNVs beforehand. *Id.* at 15-16 (citing '596 Patent at 5:4-26, 14-67); Doc. 379 (Metzker '596 Patent CC Decl.), ¶ 74; *see Intamin Ltd. v. Magnetar Techs., Corp.*, 483 F.3d 1328, 1336-37 (Fed. Cir. 2007) ("[A] claim need not cover all embodiments.").

Fifth, NeoGenomics argues that “detected,” as written in the *claim*, must involve “several data processing steps” in order to distinguish “noise,” which is disclosed in some embodiments (Doc. 373 at 19-20), even though no noise, computer, processor, algorithm, or related analytical step is recited in the claim. *See* Doc. 378-4 (Lennon Tr.) at 34:15-16; Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 54, 74. It is axiomatic that “a court may not read a limitation into a claim from the specification.” *Innova/Pure Water*, 381 F.3d at 1117. Here, NeoGenomics’ unjustified computer-centric view of “detecting” should not be read into the claim language.

Sixth, NeoGenomics’ reliance on the prosecution history is misplaced. Doc. 373 at 16-18. It cites to *Mayne Pharma Int’l Pty. Ltd. v. Merck & Co.* for the proposition that “wherein” clauses may be material to patentability. No. CV 15-438-LPS, 2016 WL 7441069 (D. Del. Dec. 27, 2016), *aff’d sub nom. Maybe Pharma Int’l Pty. Ltd. v. Merck Sharp & Dohme Corp.*, 927 F.3d 1232 (Fed. Cir. 2019). But the fact that the “wherein” clause was added overcome the asserted references does not mean that the clause does not inform the mechanics of how the high-throughput sequencing is performed. Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 76-83. NeoGenomics’ erroneous interpretation is based on a misreading of the prosecution history. *See id.*

Seventh, contrary to NeoGenomics’ assertion (Doc. 373 at 18-19), Natera’s construction is consistent with the purpose of the claimed invention, which is a method for preparing biological samples useful for monitoring the progression of cancer in a subject. *See* Section II.A. *supra*; *KEYnetik, Inc. v. Samsung Elecs. Co.*, 837 F. App’x 786, 793 (Fed.

Cir. 2020). NeoGenomics argues that Natera’s construction “does not require a determination that an SNV is present.” However, base calls made in the sequencer already contain a quality score as a measure of their correspondence to an SNV, as explained *supra*. Doc. 379 (Metzker ’596 Patent CC Decl.), ¶ 86. Moreover, NeoGenomics’ expert confirmed that the claim does not recite a specific threshold amount or proportion of tumor-specific SNV loci that must be called correctly among the plurality of SNV mutations to be useful for monitoring cancer progression. Doc. 378-4 (Lennon Tr.) at 32:12-15. The claim only requires that “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. 379 (Metzker ’596 Patent CC Decl.), ¶ 87. As an illustration, a POSA would understand that a sequencer detecting one SNV from a single sequence read among 7,000 other reads of that same position—which amounts to 1/7000 or about 0.014%—is sufficient to meet the claim, which NeoGenomics’ expert expressly acknowledged in the co-pending pre-institution IPR. *Id.*; Doc. 378-3 (Lennon IPR Decl.)¹², ¶ 240.

As alleged support, NeoGenomics relies on Claim 12 (Doc. 373 at 19), which recites “wherein the method *further comprises* detecting recurrence and/or metastases of the cancer from the tumor-specific mutations detected in the cell-free DNA.” The “further comprises” language makes clear that “detecting recurrence and/or metastases” is not part of the actions recited in Claim 1, consistent with NeoGenomics’ own expert’s view. *See*

¹² Doc. 378-3, Declaration of Niall Lennon, *NeoGenomics Laboratories, Inc. v. Natera, Inc.*, IPR2025-00455, Exhibit 1004 (P.T.A.B. Jan. 15, 2025).

Doc. 378-4 (Lennon Tr.) at 37:9-38:4; Doc. 379 (Metzker '596 Patent CC Decl.), ¶ 75. Under the doctrine of claim differentiation, “an independent claim should not be construed as requiring a limitation added by a dependent claim.” *Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1380 (Fed. Cir. 2006). The Court should, therefore, not read into Claim 1 a requirement that the claim detect cancer.

(a) NeoGenomics’ Construction is Undermined by Its Inconsistent Positions, Dr. Lennon’s Testimony, and Corporate Representatives

NeoGenomics’ attempt to write algorithmic computations—that it will argue occur in its overseas servers to evade liability—into the claim is not only unsupported, it is inconsistent with views it, its expert, and its corporate representatives previously espoused.

For example, NeoGenomics admits that “sequencing to obtain sequence reads and detecting an SNV mutation from the sequence reads” requires base calling (Doc. 373 at 20), which *is* the detection occurring in the sequencer as explained *supra*. This view is shared by Dr. Lennon who testified in a previous case that the process of growing a sequence read and calling a base based on “the interrogation of the colors to understand what bases are there” is what “*we call the detection step.*” Doc. 378-1 at 40:22-41 (emphasis added); *see also* Doc. 379 (Metzker '596 Patent CC Decl.), ¶ 73.

Dr. Lennon’s more recent testimony in this case is consistent. *See* Doc. 378-4 (Lennon Tr.) at 23:4-20 (inside the sequencer, “the camera, essentially, takes a photograph or, essentially, you know, *detects any* emission spectra or any, you know, *signal that comes off of those incorporated bases*”) (emphasis added); *see also id.* at 24:21-25:1 (the

sequencer is “producing data as it goes along which are digital files which incorporate what the bases are in this contiguous stretch that we call a sequencing read and then the associated sort of quality information with those base calls in the sequencing read”). He also confirmed that base calling in the sequencer—where the detection occurs—is a necessary prerequisite for variant calling—a subsequent comparative data processing step, that is not recited in Claim 1(c). *See* Doc. 378-4 (Lennon Tr.) at 27:17-8, 28:9-15, 30:10-22, 31:8-15, 32:18-21; *see also* Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 70-71.

NeoGenomics’ position that “detected” means “determined to be present” reflects the plain and ordinary meaning of this term is also undermined by its and its expert’s representations in the parallel pre-institution IPR. *See* Doc. 379 (Metzker ’596 Patent CC Decl.), ¶ 72. In its IPR petition, NeoGenomics did not equate “detected” with “determined to be present.” NeoGenomics never once used the phrase “determined to be present” in describing the claims or the asserted references. *See generally* Doc. 378-2. Likewise, Dr. Lennon never opines that the plain and ordinary meaning of “detected” means “determined to be present.” Doc. 378-3, ¶¶ 15, 19. Dr. Lennon instead acknowledges that high-throughput sequencing platforms use “sequencing and detection biochemistry . . . to produce sequence reads,” (*id.*, ¶ 81), consistent with Natera’s interpretation that sequencing and detection are part of one high-throughput sequencing step.

Multiple of NeoGenomics’ corporate witnesses also agree with Natera that detection of SNV mutations happens during sequencing. NeoGenomics’ Rule 30(b)(6) deponent, Dr. Tim Forshew, testified that during each sequencing cycle in the sequencer, base calls

are made because “[t]he detector sees a color and this gives you some information” that corresponds to a specific nucleotide. Doc. 378-5 (July 19, 2024 Forshew 30(b)(6) Tr.) at 71:2-18. Similarly, 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. See *Kyowa Hakko Bio, Co. v. Ajinomoto Co.*, 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”).

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

There is no dispute that both “sequencing” and “amplified DNA” have well-understood plain and ordinary meanings, consistent with Natera’s proposal. NeoGenomics’ arguments distort the meaning of “*the* amplified DNA” based on an alleged antecedent basis. Doc. 373 at 20-23. It paradoxically contends that its construction “permits intervening steps” between multiplex PCR and sequencing as long sequencing is performed *directly* on the products obtained from the multiplex PCR amplification. *Id.* at 1-2. This is illogical and an obvious pretext for its actual construction that would preclude any and all intermediate steps, some of which may be necessary to modify “the amplicons” prior to sequencing. Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 91, 93.

NeoGenomics’ construction rehashes the same argument it has raised on numerous occasions based on the ’454 Patent term “the amplicons,” including in the preliminary

injunction proceeding,¹³ '454 Patent IPR petition,¹⁴ claim construction briefing related to the '454 Patent,¹⁵ and most recently, its Motion for Reconsideration of the Court's prior *Markman* ruling.¹⁶ NeoGenomics' arguments are not new and thus should be rejected.

NeoGenomics asks the Court to read into the claim a requirement that the amplicons from the targeted multiplex amplification be **directly** sequenced, without any modification. Doc. 373 at 20. This argument—which relies exclusively on “the” in the phrase “sequencing **the** amplified DNA”—runs afoul of the open-ended “comprising” nature of the claims and impermissibly re-writes the claim language. *See CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1235 (Fed. Cir. 2005) (“The transitional term comprising is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.”) (cleaned up).

Unlike NeoGenomics' proposal, Natera's construction reflects what POSAs would understand “amplified DNA” to refer to in context and similar to the claimed “amplicons” in the '454 Patent, which shares an identical specification and priority date and contains similar claim language as the '596 Patent. Doc. 145 (Metzker PI Decl.), ¶¶ 270-275. The '596 Patent explains that “[a]mplification refers to a method that increases the number of

¹³ Doc. 107 (NeoGenomics' PI Opposition) at ECF 8-10.

¹⁴ Doc. 366-1 (NeoGenomics Petition for *Inter Partes* Review of the '454 Patent) at ECF 36, 48-49.

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

¹⁶ *See generally* Doc. 365.

copies of a molecule of DNA or RNA.” Doc. 352-10 (’596 Patent) at 34:52-53. Amplified DNA is the product of amplification, and “the amplified DNA” of Claim 1 of the ’596 Patent refers to copies of DNA that represent the sequences of the “target loci” referred to in the claims just as the claimed “amplicons” in the ’454 Patent. *See* Doc. 145, ¶ 270; Doc. 372 at 17-22. Consistent with the plain and ordinary meaning, the ’596 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. 372 at 20-21. NeoGenomics reads these disclosures out of the claims completely.

NeoGenomics devotes the majority of its argument to an alleged disclaimer of ’454 Patent claim scope during the pre-institution IPR proceeding (Doc. 373 at 21-23), which is recapitulation of its co-pending Motion for Reconsideration of the Court’s prior construction of the term “sequencing the amplicons” (Doc. 365). As more fully explained in Natera’s Opposition (Doc. 376), nothing in the pre-institution IPR proceeding suggests that the ’454 Patent requires sequencing the exact, unaltered molecules directly obtained from the multiplex amplification step, as opposed to copies of those molecules that contain the same sequences. Natera did not assert,¹⁷ nor did the Patent Trial and Appeal Board (“PTAB”) adopt,¹⁸ a specific construction for the purposes of denying institution. Doc. 376 at 6-9, 14-17.

¹⁷ Doc. 366-2 (Patent Owner Preliminary Response) at ECF 28-29.

¹⁸ Doc. 366-3 (Decision Denying Institution) at ECF 13-14.

NeoGenomics provides none of the “exacting” evidence¹⁹ 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).

Natera expects NeoGenomics to argue in its Responsive Brief that the composition of the amplified DNA resulting from multiplex PCR is somehow changed by the subsequent addition of barcodes or sequencing adaptors. Doc. 378-4 (Lennon Tr.) at 54:17-56:24. However, similar to the ’454 Patent—as Natera and its expert explained during the Preliminary Injunction proceeding—the goal of the ’596 Patent’s claimed method is to obtain sequence reads that contain the sequences of the target loci and the amplified DNA is a proxy for the target loci to produce enough material to do so. PI Hr’g Tr. at 20:21-22:18, 52:12-54:11. Nothing in the claim prevents intervening steps, particularly if they are required make the amplified DNA “sequence ready,” as long as this goal is achieved. *Id.*; see also Doc. 379 (Metzker ’596 Patent CC Decl.), ¶¶ 90-94.

Further undermining NeoGenomics’ argument, its expert agrees that if “target loci from the first reaction that are well-represented that you then put into a subsequent PCR amplification to add adapter sequences, for instance, they will get copied, amplified, and

¹⁹ *GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014).

the amplicons that are created will have, you know, presumably the correct adapters appended to the tails.” Doc. 378-4 (Lennon Tr.) at 53:1-8; *see also id.* at 42:2-13, 53:10-54:16; Doc. 379 (Metzker ’596 Patent CC Decl.), ¶ 95.

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 II.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 II.B *supra*.

III. 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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CERTIFICATE OF SERVICE

I hereby certify that I caused the foregoing document to be served via electronic mail on all counsel of record for Defendant.

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