

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

NATERA, INC.,

Plaintiff,

v.

NEOGENOMICS LABORATORIES,
INC.,

Defendant.

C.A. No. 1:23-CV-629-CCE-JLW

**DEFENDANT NEOGENOMICS LABORATORIES, INC.'S
OPENING CLAIM CONSTRUCTION BRIEF**

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I. INTRODUCTION

Although the Joint Claim Construction Statement identified four terms in claim 1 of U.S. Patent No. 11,319,596 (“the ’596 patent”), the parties only dispute the meanings of three of them. For each term, both parties assert that their respective constructions reflect the terms’ plain and ordinary meanings.

For the first term, NeoGenomics’ proposed construction for “the isolated cell-free DNA” directly tracks its antecedent definition in the claim. Natera, on the other hand, changes the claim language in an effort to expand the scope of the term.

The next three terms relate to the last clause of claim 1. Natera seeks to construe the entirety of the clause, even though it has not identified a dispute as to its meaning apart from its two discrete sub-terms identified by NeoGenomics. NeoGenomics believes that the construction of the sub-terms will resolve the parties’ dispute as to the entire clause. For the first sub-term—“wherein an SNV mutation . . . is detected from the sequence reads”—NeoGenomics’ proposed construction is supported by the plain meaning of the words, the intrinsic evidence and the basic purpose of the claimed invention, and is further supported by the declaration of expert Dr. Niall Lennon. Detecting an SNV mutation means determining whether the SNV mutation is present.

For the second sub-term—“performing high-throughput sequencing of the amplified DNA”—NeoGenomics’ proposed construction follows the plain language of the term “the amplified DNA,” which is the amplified DNA that results from the prior amplification step. To be clear, NeoGenomics’ construction permits intervening steps, so

long as the sequencing step is performed on the amplified DNA from the earlier claim step (rather than other DNA that has been altered by intervening amplification), just like the claim says.

II. BACKGROUND

Natera currently asserts the '596 patent and U.S. Patent No. 11,530,454 (“the '454 patent”) against NeoGenomics. The Court has issued a *Markman* order construing certain terms in the '454 patent. Dkt. 280. NeoGenomics has moved for reconsideration of the Court’s construction of the term “sequencing the amplicons,” which appears in every asserted claim of the '454 patent. Dkt. 364-366. The '596 patent shares a specification with the '454 patent and is the subject of the parties’ present claim construction briefing.

The '596 patent is titled “Detecting Mutations and Ploidy in Chromosomal Segments,” and states that the “invention provides methods, systems, and computer readable medium[, i.e., software] for detecting ... single nucleotide variants[.]” '596 patent at Abstract. The '596 patent’s claims are directed to a test that determines whether cell-free DNA from the cancer is present in a patient’s blood. *See, e.g.*, '596 patent at 133:64-134:15 (recognizing cell-free DNA is “biomarker for breast tumors”); *id.* at 134:24-50 (detecting “cell-free circulating DNA in blood of patients” for purposes of colorectal cancer diagnosis). Because cell-free DNA is cleared from the body very quickly, (typically in about 2 hours), the detection of cell-free cancer DNA in the patient’s blood is a strong indication that the patient currently has cancer. Dkt. 17, Metzker Declaration in Support of Natera’s Motion for Preliminary Injunction at ¶ 36 (“A liquid biopsy may be used to

specifically detect and quantify circulating tumor DNA (ctDNA) in a patient to determine MRD. ctDNA is a type of cell-free DNA (cfDNA) characterized by tumor-specific genomic and epigenomic alternations.”).

The test claimed by the '596 patent is a “tumor informed” test that proceeds in two parts. *See, e.g.*, '596 patent, claim 1. First, the DNA of a tumor biopsy sample is sequenced to identify single nucleotide variant (SNV) mutations that are specific to the tumor and to identify the locations, or “loci,” in the cancer genome where those SNV mutations occur. '596 patent at 171:51-63. Second, samples of cell-free DNA from the subject’s blood are assayed, *i.e.*, analyzed, to detect whether any of those tumor specific SNV mutations are present. *Id.* at 172:1-14.

The assay to detect whether SNVs are present is further divided into two general steps. In the first step, “targeted multiplex PCR amplification” is used to amplify or create copies of the cell-free DNA of interest from the tumor DNA. *Id.* at 172:4-8. In the second step, high-throughput sequencing is used to sequence that DNA of interest to obtain sequence reads. *Id.* at 172:9-14. Any SNV mutations are then detected from those obtained sequence reads. *Id.*

Claim 1 is the only independent claim in the '596 patent, and is shown below with the disputed terms emphasized:

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*.

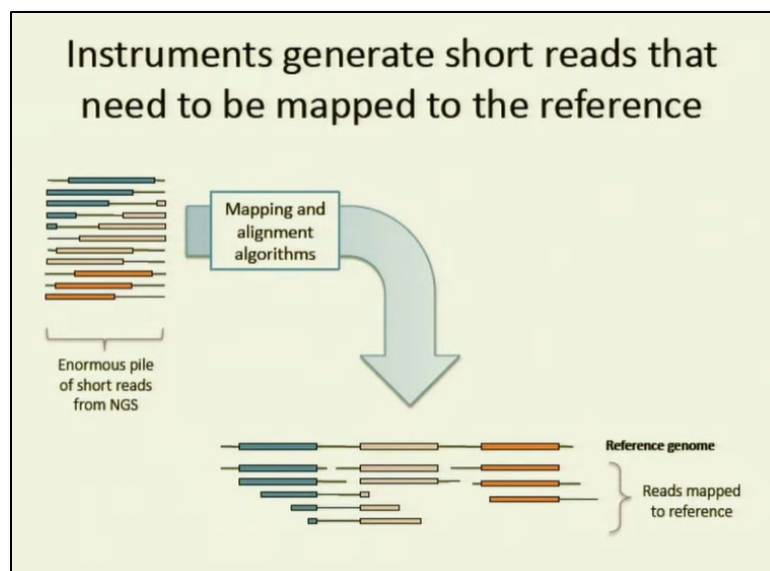
The '596 patent identifies high-throughput sequencers that were commercially available as of its 2015 priority date. Examples include the Illumina HiSeq and MiSeq sequencers, '596 patent at 169:39-40, and the Illumina GAIIIX sequencer, *id.* at 152:63-65. The basic operation of these next-generation sequencers would have been well-understood by a skilled scientist in 2015. Declaration of Niall Lennon, Ph.D on Claim Construction ("Lennon Decl.") at section (IV); Ex. 8, *Sequencing technologies — the next generation*, 11 NATURE REV. GENETICS 31-46 (2010).

These sequencers "read" the sequences of the DNA in the sample (*e.g.*, A, T, G, C) by adding complementary bases (*e.g.*, T, A, C, G) one at a time and measuring a fluorescent signal for each complementary base as it is added. That reading process is referred to as

“base calling” and results in short “sequence reads.” Lennon Decl. ¶¶ 19-22, 24. Base calling typically generates millions of short reads in a single sequencing run. *Id.*, ¶ 24.

The sequence reads obtained from a high-throughput sequencer are short. These short reads correspond to places that are spread throughout the subject’s genome, which is billions of bases long. The sequence reads alone do not identify what portion of the genome has been read, and thus one cannot tell from the sequence read alone whether it has any alterations or mutations from the genomic base sequences at the locations of interest (the target loci). *Id.*, ¶¶ 20-25.

Accordingly, in order to detect whether there is such a mutation, the sequence read must first be mapped to a reference—a portion of the human genome—as illustrated in the diagram below:

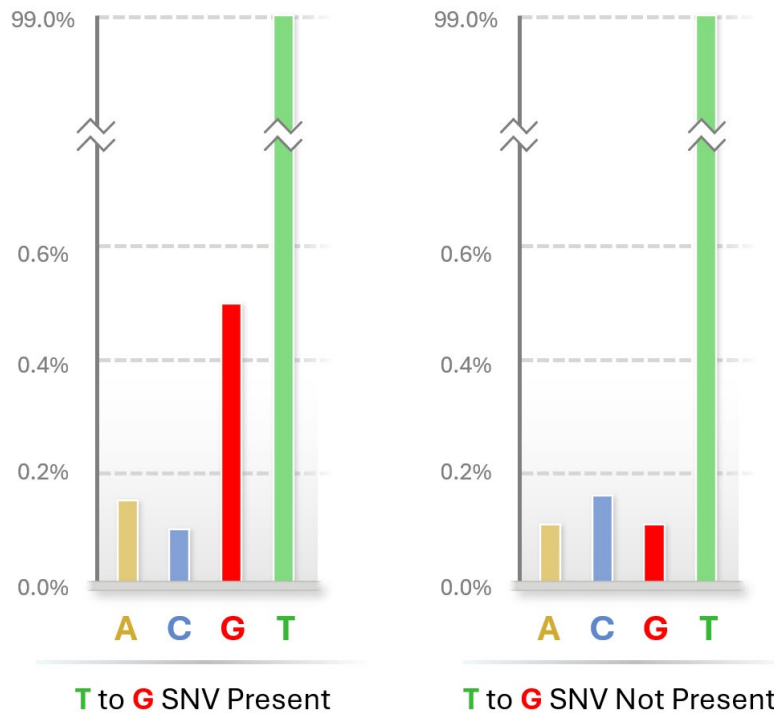


Lennon Decl. ¶¶ 19, 24; Ex. 3, Broad Institute, *BroadE: Introduction to data processing and variant detection for next-generation DNA sequencing*, at 4:28-5:45, YouTube (March

4, 2013), <https://www.youtube.com/watch?v=1m0ZiEvzDKI> (“Broad Institute Presentation”).¹

The next step of the process involves analyzing the bases from the sequence reads that have been mapped to a particular locus to determine whether an SNV mutation is present at that location. Lennon Decl. ¶¶ 26-30. An SNV mutation is a single-base change from the normal sequence at the locus. However, not all differences between a sequence read and the normal sequence are SNVs. Both PCR amplification and high-throughput sequencing can add the wrong bases during amplification and sequencing respectively. ’596 patent at 65:34-37, 66:39-42; Lennon Decl. ¶28. These amplification or sequencing errors can create background “noise” in the data that can make detecting actual SNVs difficult, particularly if an SNV is only present at low levels. Lennon Decl. ¶ 28. This “noise” can, for example, cause sequence reads to include multiple bases for a single location on the reference genome, as shown below. *Id.*

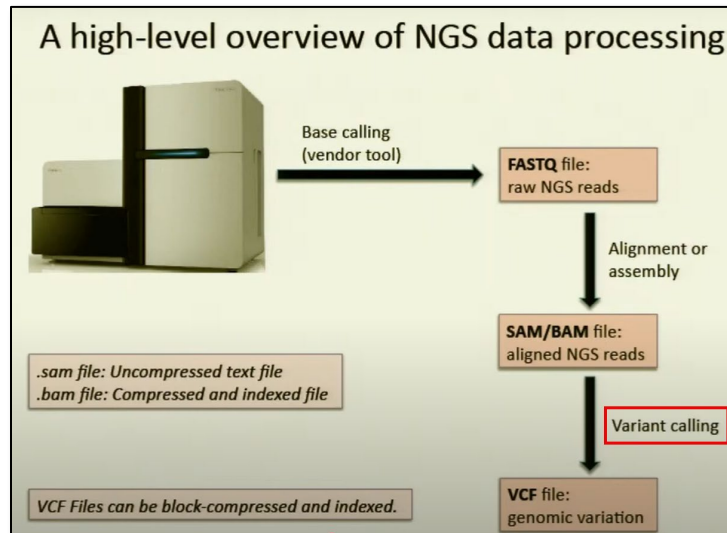
¹ This presentation was delivered by the Broad Institute in 2012 and uploaded to YouTube in 2013. It describes an overview of the then-existing high throughput sequencing technologies and data processing methods for variant calling. Lennon Decl. ¶ 22. In addition to the URL identified above, a copy of this video is being filed conventionally.



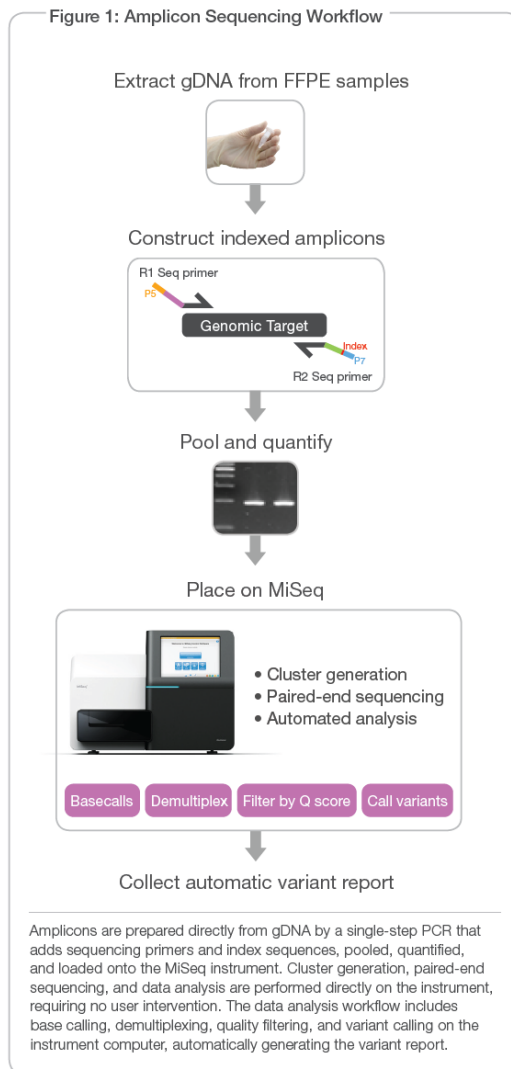
The most prevalent base, in this example “T,” is the normal base at that position. Lennon Decl. ¶ 29. Each of the other three bases (A, C, and G) were included in the sequence reads but may be noise from amplification or sequencing, or may be an SNV. *Id.* The figure on the left shows that an SNV mutation of “T” to “G” is determined to be present, and the figure on the right shows that it is not. *Id.* Thus, it is not the case that an SNV is detected every time a base in a sequence read differs from the normal base at the corresponding locus. *Id.*

Instead, some type of data processing is required to separate the noise from a base call representing a true SNV and thereby detect whether an SNV is present in the sample. Lennon Decl. ¶¶ 29, 33-37. This process is often referred to as “variant calling.” *Id.*, ¶¶ 22-23. As of the ’596 patent’s 2015 priority date, and still today, the variant calling process can be performed by software that is separate from and downstream of the sequencer, or it

can be performed by the sequencer itself. For example, the image below from the Broad Institute Presentation discussed by Dr. Lennon illustrates an example in which the base calling is performed by the sequencer, and then the alignment process and variant calling are performed by an additional software.



Lennon Decl. ¶ 22; Ex. 3, Broad Institute Presentation at 12:544-13:29. As another example, Illumina’s MiSeq instrument can perform “base calling, demultiplexing, quality filtering, and variant calling on the instrument computer.”



Lennon Decl. ¶ 23; Ex. 4 (describing the Illumina MiSeq™ System described in Illumina Application Note: *Sequencing, Amplicon Sequencing from FFPE tissues on the MiSeq™ System* (2011)).

The '596 patent discloses several examples of data processing techniques for detecting SNVs from sequence reads. *See, e.g.*, '596 patent at 5:44-67 (describing using a computer to compare SNV positions with statistically significant depths of read compared to the background error at that position (or loci) and “thereby detecting one or more single

nucleotide variants”); *id.* at 67:30-53 (same). These methods use normal (cancer free) samples as controls on the same sequencing run as the test sample “to account for run-specific artifacts.” *Id.* at 68:12-19 (explaining that noisy loci are removed from the analysis). The patent describes an alternative method that estimates background error using training data and using that to “differentiate the background error from real mutations” to detect an SNV. *Id.* at 165:48-55. The background error based on the controls or training data can then be used when analyzing the data to help detect real SNV mutations as distinguished from noise such as run-specific artifacts caused by amplification or sequencing. *Id.* at 68:12-19, 165:48-55.

III. LEGAL STANDARDS

There is a “heavy presumption” that claim terms receive their ordinary and customary meaning as would be understood by a skilled scientist at the time of the invention. *Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1358 (Fed. Cir. 2017). “Properly viewed, the ‘ordinary meaning’ of a claim term is its meaning to the ordinary artisan after reading the entire patent.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1321 (Fed. Cir. 2005) (*en banc*). Intrinsic evidence includes the patent’s claims, specification, and prosecution history. *Id.* A skilled scientist “is deemed to read [a] 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. However, “extrinsic evidence ‘can shed useful light on the relevant art[.]’” *Id.* at 1317 (citations omitted). “The construction that stays true to the claim language and most naturally aligns with the patent’s

description of the invention will be, in the end, the correct construction.” *Id.* at 1316. “A determination that a claim term ‘needs no construction’ or has the ‘plain and ordinary meaning’ may be inadequate when a term has more than one ‘ordinary’ meaning or when reliance on a term’s ‘ordinary’ meaning does not resolve the parties’ dispute.” *O2 Micro Int’l, Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1361 (Fed. Cir. 2008); *see also Eon Corp. IP Holdings LLC v. Silver Spring Networks, Inc.*, 815 F.3d 1314, 1319 (Fed. Cir. 2016) (“[T]he parties actively disputed the scope of the ‘portable’ and ‘mobile’ terms. . . [D]etermining only that the terms should be given their plain and ordinary meaning . . . was legal error.”); *OptoLum, Inc. v. Cree, Inc.*, 336 F. Supp. 3d 571, 585 (M.D.N.C. 2018) (“plain and ordinary meaning . . . would ‘not resolve the parties’ dispute[,]’ specifically whether ‘plane’ should be construed as referring to physical, flat surfaces alone”).

IV. DISPUTED CLAIM TERMS

A. “the isolated cell-free DNA” (’596 Patent, Claim 1)

Natera’s Proposed Construction	NeoGenomics’ Proposed Construction
Plain and ordinary meaning, which includes cell-free DNA isolated from <i>any</i> 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.

NeoGenomics’ proposed construction for “the isolated cell-free DNA” tracks the unambiguous language of the claim. “The isolated cell-free DNA” refers back to the “cell-free DNA” that is found earlier in the claim, which is “cell-free DNA *isolated from a plurality of* biological samples obtained from the subject.”

Claim 1 states:

(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

'596 patent at 172:1-9 (emphasis added). The parties agree that “the” in the term “the isolated cell-free DNA” refers to the antecedent “cell-free DNA isolated from a plurality of biological samples obtained from the subject” recited in the preceding clause. *Eastman Chem. Co. v. Aktiengesellschaft*, 47 F. App'x 566, 574 (Fed. Cir. 2002) (construing “the salt” following its antecedent mention of “salt (III)” in the claim). This means that “the isolated cell-free DNA” referred to in the performing step must be the same isolated cell-free DNA that is assayed in the prior step. That cell-free DNA is isolated from multiple samples taken from the same subject.

NeoGenomics' plain reading of the claim is consistent with the specification: “cells from *multiple* samples from the same individual are combined” to obtain the benefit of “reduc[ing] the amount of work compared to analyzing the samples separately.” '596 patent at 95:31-34 (emphasis added). As an illustration of additional benefits, “[c]ombining *multiple* samples can also allow multiple tissues to be tested for cancer simultaneously (which can be used to provide or more thorough screening for cancer or to determine whether cancer may have metastasized to other tissues).” *Id.* at 95:34-38 (emphasis added). NeoGenomics' proposed construction also makes practical sense in the

context of the '596 patent because ctDNA is present in such low levels in the blood.

Natera's construction rewrites the claim language from "a plurality" to "any plurality." Natera intends for this change to expand the claim scope. Instead of a requirement that the amplification be performed on "*the* isolated cell-free DNA," Natera would then argue that the amplification step could be performed only on "some of the isolated cell-free DNA" from the prior step. That is not what the claim requires on its face. *See Innovative Memory Sys., Inc. v. Micron Tech., Inc.*, 781 F. App'x 1013, 1015-16 (Fed. Cir. 2019) (construing the claim term "the correspondence" based on its antecedent mention as "defined in the claim" and rejecting a construction "unreasonably broad in light of the plain language of the claims and the specification.").

For these reasons, NeoGenomics' proposed 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" ('596 Patent, Claim 1)

Natera's Proposed Construction	NeoGenomics' Proposed Construction
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 the two terms discussed in Sections IV.C and IV.D below.

NeoGenomics is not aware of, and Natera has not identified, any disputed issues as to the meaning of this term beyond the disputes presented by the sub-terms addressed in

Sections IV.C and IV.D below.

C. “wherein an SNV mutation . . . is detected from the sequence reads” (’596 Patent, Claim 1)

Natera’s Proposed Construction	NeoGenomics’ Proposed Construction
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 parties dispute what it means for an SNV mutation to be detected and what information is required for that detection to occur. The plain and ordinary meaning of detecting an SNV is determining that an SNV mutation is present. This plain and ordinary meaning is supported by the plain language of the claims, the patent’s intrinsic record, and NeoGenomics’ expert (Dr. Lennon) opinion about what a skilled scientist would have known about how high-throughput sequencing methods work.

In contrast, Natera’s proposal suggests that an SNV can be “detected” from a sequence read even if a scientist could not tell if an SNV is present without doing more work in order to make that determination.

1. The claim language, specification, and prosecution history demonstrate that the claims require determining whether an SNV mutation is present from the sequence reads

NeoGenomics’ proposed construction flows from the plain claim language, which requires “performing high-throughput sequencing to obtain sequence reads” and “wherein an SNV mutation . . . *is detected* from the sequence reads.” Because the claim requires

detecting an SNV mutation “from” the sequence reads, the information in the sequence reads is obtained first, and that information is used to detect an SNV mutation. This is entirely consistent with how high throughput sequencing works. The DNA is sequenced to generate sequence reads. An SNV mutation is detected by analyzing the sequence reads and determining whether an SNV mutation is present. *See, e.g.*, ’596 patent at 5:44-67; 67:30-53; Lennon Decl. ¶¶ 26-30.

Natera’s suggestion that an SNV is detected as part of the process of obtaining the sequence read itself is contrary to the straightforward meaning of the claim. Natera would have the claim merely require detecting an SNV by obtaining a sequence read with a G, even if you have no idea whether that G is an SNV. Not so. While you may identify a G in a sequence read, you do not know whether it is an SNV until you figure out where in the genome it comes from, and whether the G is a mutation or an error. Only then have you detected an SNV.

The specification confirms this point. It equates detecting SNVs with determining whether an SNV is present: “In certain aspects, provided herein are methods for detecting single nucleotide variants in a sample. Accordingly, provided herein is a method for **determining** whether a single nucleotide variant is present at a set of genomic positions in a sample from an individual, the method comprising . . .” ’596 patent at 5:4-9 (emphasis added). The specification then describes the method as including a step of “receiving observed nucleotide identity information for each genomic position in the sample[.]” *Id.* at 5:14-15. A skilled scientist understands that this step refers to using the information

from both what the base is (*i.e.*, “nucleotide identity information”) and where it is located in the genome (*i.e.*, “for each genomic position”). Lennon Decl. ¶ 35. The next two steps of the method describe data processing steps to “**determine** the most-likely real variant percentage and confidence from the set of probabilities for each genomic position.” ’596 patent at 5:16-26 (emphasis added). This refers to determining whether an SNV mutation (*i.e.*, “variant”) is present at each genomic position by accounting for noise. Lennon Decl. ¶ 35. The patent equates “detecting” an SNV with “determining whether a single nucleotide variant is present” in other places as well. *See, e.g., id.* at 65:14-67 (describing “Exemplary Embodiments for Detecting Single Nucleotide Variants” as involving “**determining** whether a single nucleotide variant is present at a set of genomic positions in a sample from an individual . . .”) (emphasis added).

To be clear, NeoGenomics is not arguing that the claims are limited to any specific way to detect SNVs. But the specification is consistently clear that in order to detect an SNV, you need to know that an SNV is present rather than “noise,” and some data processing is required to figure that out.

The patent’s file history further confirms that both the inventors and the examiner understood the claim language to require a determination about the presence of an SNV mutation from sequence reads. Specifically, Natera added the underlined language below in response to a prior art rejection:

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.

(Ex. 9 at 2, Jun. 1, 2021 OA Response.) Natera then argued that the amended language distinguished the invention from the prior art because Diehn (which the examiner found disclosed high-throughput sequencing) and another prior art reference (Murtaza) were not able to detect the presence of an SNV mutation at or below the added 0.015% sensitivity limitation:

Diehn also fails to teach or suggest “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.” In contrast to the presently claimed invention, Diehn discloses “NSCLC DNA were accurately detected at fractional abundances between 0.025% and 10%” (paragraph 0792) and “fractions of tumor-derived DNA detected in plasma by SNV and/or indel reporters ranged from ~0.02% to 3.2%” (paragraph 0797). Further, Murtaza discloses detection of mutant allele frequency (AF) between 3% to 34% in patient plasma samples (Table 1).

Ex. 9 at 7, Jun. 1, 2021 OA Response. The Examiner agreed and allowed the claims on that basis. Ex. 12, Mar. 14, 2022 Notice of Allowance.

A scientist would understand that this portion of the file history confirms that the added language—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—means that an SNV mutation is determined to be present at a level lower than 0.015%. *See* Lennon Decl. ¶¶ 40-44. This prosecution history also confirms that the added wherein clause does not simply “inform[s] the mechanics of how the high-throughput sequencing is performed.”

See, e.g., Mayne Pharma Int'l Pty Ltd. v. Merck & Co., No. CV 15-438-LPS, 2016 WL 7441069, at *5 (D. Del. Dec. 27, 2016), *aff'd sub nom. Mayne Pharma Int'l Pty. Ltd. v. Merck Sharp & Dohme Corp.*, 927 F.3d 1232 (Fed. Cir. 2019) (finding “‘wherein’ clauses . . . material to patentability” and noting that “[d]uring prosecution, the specific parameters were used to distinguish the claimed invention from the prior art”).

2. Natera’s construction is contrary to the purpose of the claimed invention, which is detecting cancer

Natera’s proposed construction for this term does not require a determination that an SNV mutation is present and contravenes the entire purpose of the purported invention claimed in the ’596 patent, which is to “monitor[] the progression of cancer.” ’596 patent at claim 1. “A patent’s statement of the described invention’s purpose informs the proper construction of the claim terms.” *KEYnetik, Inc. v. Samsung Elecs. Co.*, 837 F. App’x 786, 793 (Fed. Cir. 2020) (denying “a construction that is inconsistent with—and indeed, would eviscerate—the purpose of the invention”). For instance, in *KEYnetik*, the patent’s stated purpose was to provide a “sleep period” for a handheld device. *Id.* The court rejected an “open-ended construction [that] would encompass a sleep command that is sent days, hours, months, or even years after the executed command” because it conflicted with the specification that “implied an immediacy that simply precludes that construction.” *Id.* at 792.

Here, it makes no sense that a method of monitoring the progression of cancer would not require a determination that cancer is present. But Natera’s construction would yield exactly this result. Instead of making a determination that an SNV signifying cancer is

present, Natera's construction would only require obtaining sequence reads with zero understanding as to what those sequence reads mean and zero information as to whether an SNV (and thus cancer) is present. *See* Lennon Decl. § IV-V. Claim 12 further illustrates this point. It requires "detecting recurrence and/or metastases of the cancer from the tumor-specific mutations detected in the cell-free DNA." '596 patent at 172:44-47. Detecting recurrence and/or metastasis of cancer from mutations in the cell-free DNA requires that the "mutations" have actually been determined to be present. *See* Lennon Decl. ¶¶ 38-39. Natera's proposed construction is contrary to the stated purpose of the purported invention and should be rejected.

3. Natera's construction conflicts with the plain and ordinary meaning of detect an SNV mutation

Natera's position on this term is also at odds with what a skilled scientist would have understood detecting an SNV mutation to mean at the time of the alleged invention. As Dr. Lennon explains, a skilled scientist "would have understood the term 'wherein an SNV mutation . . . is detected from the sequence reads,' in claim 1 of the '596 patent to mean 'wherein an SNV mutation is determined to be present from the sequence reads.'" Lennon Decl. ¶ 31.² Determining whether an SNV is present involves several data processing steps that use the obtained sequence reads to determine the presence of an SNV. Lennon Decl. § IV, ¶¶ 31-32.

² At the time of the purported invention Dr. Lennon was a Senior Director of Translational Genomics at the Broad Institute of MIT and Harvard.

Specifically, a skilled scientist would have understood that sequencing to obtain sequence reads and detecting an SNV mutation from the sequence reads requires at least sequencing to obtain sequence reads (also referred to as “base calling”) and alignment or mapping of sequence reads to the correct loci on the reference genome and finally SNV detection (also referred to as variant calling). Lennon Decl. § IV. NeoGenomics’ proposed construction of this term reflects its plain and ordinary meaning to a scientist in the field in view of the patent’s intrinsic evidence. Sequence reads alone do not detect SNVs, and no scientist would understand otherwise.

Natera’s proposal that this term is “part of the ‘performing high-throughput sequencing . . . to obtain sequence reads’ step” and that “the ‘wherein’ clause informs the mechanics of how the high-throughput sequencing is performed” is designed to sidestep the plain language of the claim (SNVs are detected “from” sequence reads), the specification (confirming that detecting an SNV requires a determination that it is present), and the basic science (a sequence read alone cannot detect an SNV).

For these reasons, the Court should adopt NeoGenomics’ proposal.

**D. “performing high-throughput sequencing of the amplified DNA”
(’596 Patent, Claim 1)**

Natera’s Proposed Construction	NeoGenomics’ Proposed Construction
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 parties dispute whether the term “*the* amplified DNA” in claim 1 of the ’596

patent excludes PCR amplification steps that generate new amplicons (and thus different amplified DNA) between the claimed targeted multiplex amplification step and the claimed high-throughput sequencing step. Critically, the PTAB's denial of NeoGenomics' *inter partes* review of the related '454 patent based on Natera's statements is new evidence showing that NeoGenomics' construction is correct.³

There is no dispute that “the amplified DNA” finds its antecedent basis in the preceding targeted multiplex amplification step:

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...

'596 patent at 172:1-15 (emphases added). “[T]he amplified DNA” to be sequenced thus refers back to amplified DNA generated by the preceding amplifying step. *Id.* at 172:5-12. The plain language of the claim supports NeoGenomics' understanding of this term that would preclude intermediate PCR amplification steps that create new, different amplified DNA to be sequenced.

NeoGenomics filed an IPR petition on the related '454 patent to which Natera responded. The '454 patent's “sequencing the amplicons” limitation mirrors the '596 patent's “performing high-throughput sequencing of the amplified DNA” limitation.

³ NeoGenomics filed a Motion to Modify the Court's Construction of the Claim Term “Sequencing the Amplicons” in the '454 patent. *See* Dkt. 364-366.

Those proceedings are thus properly considered here. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1343 (Fed. Cir. 2015) (“A statement made during prosecution of related patents may be properly considered in construing a term common to those patents”).

NeoGenomics raised an invalidity challenge in its IPR petition based on the Forshew prior art reference. Natera responded that Forshew did not invalidate the ’454 patent because Forshew “plainly did consider and reject use of multiplex amplification alone[.]” Dkt. 366-2 at 22. Natera distinguished Forshew’s two amplification steps that occurred after the targeted multiplex amplification step and before amplicon sequencing: a “single-plex PCR,” and “additional PCR steps” for adding “additional sequencing adaptors and a barcode.” *Id.* at 13, 23. Natera argued that as a result of those intervening steps, the DNA sequenced in Forshew was not “the amplicons” of the targeted multiplex amplification.

The PTAB accepted Natera’s arguments and denied institution of NeoGenomics’ IPR, resting specifically on the fact that the amplicons in Forshew obtained from the targeted multiplex amplification step are not the same amplicons generated in subsequent amplification steps. Dkt. 366-3 at 12-13 (“Forshew teaches the barcoding PCR step, and also the single-plex amplification step, which is after the multiplex amplification step. Thus, even under Petitioner’s proposed claim construction in the North Carolina case, we are not persuaded that the examiner materially erred because, in Forshew, the amplicons sequenced are not those obtained from the targeted multiplex amplification step.”) (internal

citation omitted). Natera thus disclaimed methods including intervening PCR amplification steps following targeted multiplex amplification prior to sequencing. *See Aylus Networks, Inc.*, 856 F.3d at 1362 (finding prosecution disclaimer based on patentee's statements made in its preliminary response to IPR petition which led the PTAB to deny institution).

The same logic applies here. The language and structure of the claim are directed to targeted multiplex amplification alone, and additional PCR amplifications that create new amplified DNA to be sequenced are excluded. NeoGenomics' proposed construction of "performing high-throughput sequencing of the amplified DNA obtained from the targeted multiplex PCR amplification step" flows from the claim language and properly accounts for Natera's efforts to distinguish its claims from prior art disclosing intermediate PCR amplification steps.

V. CONCLUSION

NeoGenomics' proposed constructions resolve the parties' disputes about claim scope in a manner that appropriately reflects the plain and ordinary meaning of the disputed terms and will best assist the jury in understanding them. For the foregoing reasons, NeoGenomics submits that its proposed constructions should be adopted.

This the 21st day of January, 2025

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83.1(d)

CERTIFICATE OF WORD COUNT

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

Dated: January 21, 2025

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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on January 21, 2025, I electronically filed the foregoing **DEFENDANT NEOGENOMICS, LABORATORIES, INC.'S OPENING CLAIM CONSTRUCTION BRIEF** with the Clerk of Court using the CM/ECF System.

Dated: January 21, 2025

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