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, INC.'S OPENING CLAIM CONSTRUCTION BRIEF

TABLE OF CONTENTS

Page

I. INTRODUCTION 1

II. BACKGROUND ON THE ’035 AND ’454 PATENTS 1

III. DISPUTED CLAIM TERMS 4

A. “SNP [single nucleotide polymorphism] loci . . . associated with cancer” (’035 Patent, Claim 1) 4

B. “amplifying the tagged products . . . wherein one of the amplification steps comprises targeted amplification” (’035 Patent, Claim 1) 7

C. “sequencing the amplicons” (’454 Patent, Claims 1, 14) 11

1. NeoGenomics’ Construction is Supported By the Antecedent Basis 11

2. Natera Disclaimed Intermediate Steps Between Targeted Amplification and Sequencing 13

D. “sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads” (’454 Patent, Claims 1, 14) 16

E. “clonal” / “subclonal” (’454 Patent, Claims 3-5) 18

F. “present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus” / “present in 0.005% to 0.015% of the cell-free DNA comprising the SNV locus” (’454 Patent, Claims 14, 28) 22

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page i
Case 1:23-cv-00629-CCE-JLW Document 264 Filed 04/08/24 Page 2 of 32

TABLE OF AUTHORITIES

Page(s)

Cases

Amgen Inc. v. Sandoz Inc.,
923 F.3d 1023 (Fed. Cir. 2019)..... 7, 8, 9, 10

BookIT Oy v. Bank of Am. Corp.,
817 F. App'x. 990 (Fed. Cir. 2020) 4

Dow Chem. Co. v. NOVA Chems. Corp. (Canada),
803 F.3d 620 (Fed. Cir. 2015)..... 22

Eastman Chem. Co. v. Aktiengesellschaft,
47 F. App'x. 566 (Fed. Cir. 2002) 12

Function Media, LLC v. Google, Inc.,
708 F.3d 1310 (Fed. Cir. 2013)..... 8, 17

G.W. Aru, LLC v. W.R. Grace & Co.-Conn.,
No. CV JKB-22-2636, 2023 WL 7170356 (D. Md. Oct. 31, 2023) 6

Guardant Health, Inc. v. Found. Med., Inc.,
No. CV 17-1616-LPS-CJB, 2019 WL 5677748 (D. Del. Nov. 1, 2019),
report and recommendation adopted, No. CV 17-1616-LPS-CJB, 2020
WL 1329513 (D. Del. Mar. 23, 2020) 11, 12, 13

Halliburton Energy Servs., Inc. v. M-I LLC,
514 F.3d 1244 (Fed. Cir. 2008)..... 21

HZNP Meds. LLC v. Actavis Lab'ys UT, Inc.,
940 F.3d 680 (Fed. Cir. 2019)..... 22

Icon Health & Fitness, Inc. v. Polar Electro Oy,
656 F. App'x 1008 (Fed. Cir. 2016)..... 19, 21

Invitrogen Corp. v. Clontech Lab'ys, Inc.,
429 F.3d 1052 (Fed. Cir. 2005)..... 15

Kyocera Senco Indus. Tools Inc. v. Int'l Trade Comm'n,
22 F.4th 1369 (Fed. Cir. 2022) 5

Media Rights Techs., Inc. v. Cap. One Fin. Corp.,
800 F.3d 1366 (Fed. Cir. 2015)..... 24

Meds. Co. v. Mylan, Inc.,
853 F.3d 1296 (Fed. Cir. 2017)..... 5

Mformation Techs., Inc. v. Research in Motion, Ltd.,
764 F.3d 1392, 1398-99 (Fed. Cir. 2014) 17

Nautilus, Inc. v. Biosig Instruments, Inc.,
572 U.S. 898 (2014)..... 18

NTP, Inc. v. Research in Motion, Ltd.,
418 F.3d 1282 (Fed. Cir. 2005)..... 14

Omega Eng'g, Inc, v. Raytek Corp.,
334 F.3d 1314 (Fed. Cir. 2003)..... 13

Optima Tech Corp. v. Roxio Inc.,
2004 WL 5029231 (C.D. Cal. Oct. 1, 2004)..... 5

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005)..... 6

Teva Pharms. USA, Inc. v. Sandoz, Inc.,
789 F.3d 1335 (Fed. Cir. 2015)..... 14

Other Authorities

Manual of Patent Examining Procedure § 2173..... 18

I. INTRODUCTION

Natera asserts against NeoGenomics U.S. Patent Nos. 11,519,035 ("the '035 patent") and 11,530,454 ("the '454 patent"), both directed to methods for analyzing DNA using amplification and sequencing. For three of the four claim terms where the parties seek competing constructions, Natera proposes "plain and ordinary meaning" without further clarification of what that meaning is. Natera does not believe there is no dispute about what those terms should mean. Rather, Natera seeks to obscure meanings it intends to later pursue under the guise of "plain and ordinary." But Natera's intended meanings conflict with the plain text of the claims, the specification, and the basic science a person of ordinary skill would have understood. For the fourth term, Natera still does not propose a construction of the term but attempts to collapse the recited sequencing and detecting steps by stating "[t]he terms are part of one sequencing step." Here too, Natera's construction is in direct conflict with the plain text of the claims and contravenes the basic science of how the claimed method is performed. Finally, NeoGenomics seeks a finding of indefiniteness for two sets of terms regarding tumor clonality and the sensitivity of the claimed methods in the '454 patent.

The Court should adopt NeoGenomics' proposed constructions and indefiniteness arguments, each of which clarifies to the Court, the parties, and most importantly, the jury, the metes and bounds of Natera's asserted claims.

II. BACKGROUND ON THE '035 AND '454 PATENTS

The basic steps to perform DNA sequencing have long been well-known. At a

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 1

high level, DNA is isolated from a sample such as blood or tissue, the DNA is amplified in a polymerase chain reaction (PCR) using primers, sequencing tags made up of short sequences of nucleotides are added, and the tagged DNA is run on a sequencer to "read" out the base pairs that make up the DNA sequences. Once the DNA sequences are obtained, the sequenced data can be analyzed. Both patents claim these basic, well-known laboratory techniques for DNA sequencing, but do so with particular requirementsand in a particular order for their desired outcomes.

The '035 patent is directed to amplifying and sequencing cell-free DNA to identify single nucleotide polymorphisms that are associated with cancer. *See, e.g.*, '035 patent, claim 1. The definitions section of the '035 patent states, "Single Nucleotide Polymorphism (SNP) refers to a single nucleotide that may differ between the genomes of two members of the same species." *Id.*, 34:46-48. SNPs at certain locations in a person's genome may indicate an increased risk of cancer. *Id.*, 8:38-43. When a person's cells die, they release their contents into the blood stream. DNA released by this process is called cell-free DNA. *Id.*, 110:64-111:1. Thus, SNPs in a person's genome can be found in a person's cell-free DNA when the person's cells die. In order to detect and identify SNPs associated with cancer in a person's cell-free DNA, the '035 patent recites a specific series of steps. Illustrative claim 1 is shown below with its disputed terms emphasized.

> 1. A method for amplifying and sequencing DNA, comprising:
>
> tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products, wherein the isolated cell-free DNA is

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 2

> isolated from a blood sample collected from a subject who is not a pregnant women;
>
> ***amplifying the tagged products*** *one or more times to generate final amplification products,* ***wherein one of the amplification steps comprises targeted amplification*** *of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume*, wherein one of the amplifying steps introduces a barcode and one or more sequencing tags; and
>
> sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products, wherein the plurality of ***SNP loci*** comprises 25-2,000 loci ***associated with cancer***.

The '454 patent is directed to a two-part test for identifying the presence of cancer DNA in the bloodstream. In the first part, the entire genome or exome of a tumor sample is sequenced to identify single nucleotide variant (SNV) mutations that are specific to the tumor. *See, e.g.*, '454 patent, claims 1, 14. Unlike SNPs, SNVs are not present in a person's genome but rather arise spontaneously after birth and so can be used, for example in the case of a patient with cancer, to detect the presence of circulating tumor DNA in a person. *Id.*, 4:55-62. In the second part, cell-free DNA from the blood is analyzed to determine whether any of those tumor specific SNV mutations are present. *Id.* Illustrative claim 14 is shown below with its disputed terms emphasized.

> 14. A method for preparing a plasma sample of a subject having cancer or suspected of having cancer useful for detecting one or more single nucleotide variant (SNV) mutations in the plasma sample, the method comprising:
>
> performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations;
>
> performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from

cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons, wherein the target loci are amplified together in the same reaction volume; and

sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads, wherein the method is capable of detecting an SNV mutation that is ***present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus***.

III. DISPUTED CLAIM TERMS

A. "SNP [single nucleotide polymorphism] loci . . . associated with cancer" ('035 Patent, Claim 1)

Natera's Proposed Construction	NeoGenomics' Proposed Construction
Plain and ordinary meaning	"A single nucleotide that may differ between the genomes of two members of the same species and is associated with cancer."

NeoGenomics' proposed construction combines the specification's express definition of "single nucleotide polymorphism" with the plain language of the claim—"associated with cancer." Under black letter claim construction law, that should be the end of the inquiry, and NeoGenomics' proposed construction should be adopted.

Natera cannot credibly dispute that the specification expressly defines SNP. *BookIT Oy v. Bank of Am. Corp.*, 817 F. App'x. 990, 994 (Fed. Cir. 2020) ("There can be no clearer definitions than those expressly recited in the patent."). The "Definitions" section of the specification states: "Single Nucleotide Polymorphism (SNP) refers to a single nucleotide that may differ between the genomes of two members of the same species." '035 patent, 34:46-48; *id.*, 34:63-65 (defining "polymorphism locus" as "locus where the genotype varies between individuals within a given species"). The location of

this statement in the "Definitions" section shows that it is definitional and should govern the construction of the claim term SNP. *Optima Tech Corp. v. Roxio Inc.*, 2004 WL 5029231, at *4–5 (C.D. Cal. Oct. 1, 2004) (ruling that patentee acted as lexicographer by including a definition of term under a heading labeled "Definitions"). The statement's use of "refers to" also confirms that this is an express definition. *Meds. Co. v. Mylan, Inc.*, 853 F.3d 1296, 1306 (Fed. Cir. 2017) (finding "refers to" to be definitional); *Kyocera Senco Indus. Tools Inc. v. Int'l Trade Comm'n*, 22 F.4th 1369, 1378 (Fed. Cir. 2022) (finding "referred to herein" to be definitional). In adopting that definition, the inventors distinguished inherited mutations (also called germline mutations), which "differ between the genomes of two members of the same species" and are within the claims' scope, from acquired mutations (also called somatic mutations), which fall outside the claims. "Polymorphisms are inherited." Ex. A, Buckingham & Flaws, *Molecular Diagnostics Fundamentals Methods and Clinical Applications* (2007) at 228; '035 patent, 143:30-32 ("inheritance patterns between SNPs"), 238:20-26 ("[B]ecause this method targets SNPs, this method will also facilitate parental haplotype reconstruction, allowing for detection of fetal inheritance of individual disease-linked loci."). The Court should adopt the definition of SNP provided by the inventors.

The term SNP appears as part of the claim limitation "SNP loci … associated with cancer. The specification defines "locus" (plural "loci") as "a particular region of interest on the DNA (or RNA) of an individual, ***which may refer to an SNP***, the site of a possible insertion or deletion, or the site of some other relevant genetic variation." '035 patent,

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 5

34:58-61(emphasis added). In the context of the claim, the word "loci" is referring to SNPs, so the Court should simply take the express definition of SNP and plug it into the claim.

Instead, Natera asks the Court to adopt a non-construction of "plain and ordinary meaning." To the extent the plain and ordinary meaning differs from the specification's express definition, however, the express definition must govern. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) ("[O]ur cases recognize that the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs."). And this Court should not adopt a construction of "plain and ordinary meaning" without resolving this dispute. "[T]he Federal Circuit has [] made clear that when the claim term is disputed, 'it is the court's duty to resolve it' . . . simply declaring that the claim 'needs no construction' or has the 'plain and ordinary meaning' is not enough." *G.W. Aru, LLC v. W.R. Grace & Co.-Conn.*, No. CV JKB-22-2636, 2023 WL 7170356, at *8 (D. Md. Oct. 31, 2023) (citing *O2 Micro Intern. Ltd. V. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1361-62 (Fed. Cir. 2008)).

For present purposes, the claim construction dispute ends here. The express definition in the specification controls. To be sure, the parties may dispute how that construction applies to the RaDaR product, and thus whether RaDaR infringes. But any dispute about infringement should be left for another day. Accordingly, the Court should adopt NeoGenomics' proposed construction.

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

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

NeoGenomics seeks a construction clarifying that "tagging isolated cell free DNA" recited in claim 1 of the '035 patent is a separate process step from "amplifying the tagged products." The parties agree that the claim requires tagging before amplifying. Dkt. 145 (Metzker Decl. ISO Pl.'s PI Reply) ¶ 62. But clarification from the Court is necessary because Natera's application of the claim improperly collapses the claimed tagging and amplifying steps into a single process step in contravention of the claim language and Federal Circuit precedent.

Amgen Inc. v. Sandoz Inc., 923 F.3d 1023 (Fed. Cir. 2019), is instructive. The claim at issue in *Amgen* recited a series of method steps including "(f) washing the separation matrix; and (g) eluting the protein from the separation matrix. . . ." *Id.*, 1026. The Federal Circuit rejected Amgen's broad reading that the claimed washing and eluting

[1] This Court's preliminary injunction order addressed infringement related to this term, but did not expressly resolve the parties' dispute about whether the claims encompass a single PCR using a single set of primers to perform the claimed steps of tagging to generate tagged products and targeted amplification to generate amplification products. Dkt. 169 at 5-7.

could overlap in a single process step "as long as the functions of washing and eluting happen in sequence." *Id.*, 1028. The court held that the washing and eluting steps required "***distinct solutions added to the matrix at different times***." *Id.* (emphasis added). To reach that conclusion, the Court found that "expressing the protein in a non-mammalian cell (limitation (a)) obviously must occur before the step of lysing that cell (limitation (b))."[2] *Id*. And it found "no indication . . . that the washing and eluting steps are any different." *Id.* The specification reinforced that the claims required separate process steps because washing and eluting were "consistently described in the specification as ***separate steps performed by different solutions***." *Id.* (citing "four exemplary purification methods using separate washing and eluting steps and discrete solutions").

Claim 1 here is even clearer than *Amgen* that the tagging and amplifying steps do not overlap. The claim begins with the tagging step, which "generate[s] tagged products." The amplifying step is then performed on the "tagged products" that were generated in the tagging step. Similarly, the amplifying step "generate[s] final amplification products," and the subsequent sequencing step is performed on "the final amplification products" generated by the amplifying step. By reciting the product of the previous step, the text of the claim instructs that each subsequent step is separate from the previous step. *See Function Media, LLC v. Google, Inc.*, 708 F.3d 1310, 1319-21 (Fed. Cir. 2013) (where the claim recited an inputting step for creating an electronic

[2] The act of lysing breaks cells open and inhibits protein expression.

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 8

advertisement and a processing step for processing the electronic advertisement, the creation of the advertisement must be completed before the processing of the advertisement could begin). Because amplifying occurs separate from and after the completion of tagging, the PCR reaction in the claimed amplifying step would necessarily use distinct primers in "distinct solutions added . . . at different times." *Amgen*, 923 F.3d at 1028.

That claim 1 is directed to distinct process steps is buttressed by the dependent claims. The parties agree that claim 1 recites tagging and amplifying. Ex. B, Natera Appeal Resp. Br. at 5-6. The parties also agree that the claims recite two ways of tagging: (1) ligation and (2) amplifying by PCR. Dkt. 162-3 (Nov. 27, 2023 PI Hrg. Tr.) at 17:14-16 (Natera's expert explaining the universal tail adaptors in the '035 patent can be attached "by either ligation—which is a technical term that just means gluing two pieces of DNA together—or by PCR"). Dependent claim 2 recites the former: "The method of claim 1, wherein ***tagging*** the cell free DNA ***comprises ligating*** the one or more universal tail adaptors to the cell free DNA" (emphasis added). Dependent claim 13 recites the latter: "The method of claim 12, wherein ***tagging*** the cell free DNA ***comprises amplifying*** the cell free DNA with a first primer comprising the first universal tail adaptor and a second primer comprising the second universal tail adaptor" (emphasis added). As Natera's expert explained, ligating is a different chemical process than PCR that is necessarily separate. And the parties agree that the process of "tagging . . . comprising amplifying" recited in claim 13 is "separate and apart" from the "amplifying"

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 9

step in claim 1. Ex. B, Natera Appeal Resp. Br. at 39 (Claim 13 "illustrates that ***the tagging in claim 1's tagging step*** may be performed by its own amplification process, ***separate and apart*** from the amplification that occurs in the amplification step."). Claims 2 and 13 thus confirm that any "tagging" within claim 1, whether done by ligation or PCR, is a separate process step from the claimed "amplifying" step.

As in *Amgen*, tagging separately from amplifying is also "consistently described in the specification." 923 F.3d at 1028. The patent describes universal tail adaptors being added during the tagging step so they can be used in a subsequent amplification. *See, e.g.*, '035 patent, 84:51-53; 86:26-29, 61-66 (performing a universal amplification using the universal tail adaptors to increase the starting amount of DNA where DNA in the sample is limited); *id.*, 21:12-27, 85:53-55 (performing a targeted amplification using a forward targeted primer and a reverse primer complementary to the universal tail adaptors). Natera intends to argue its claims cover the addition of universal tail adaptors during the first PCR cycle of the targeted amplification step, but the patent provides no working examples of performing both steps in one PCR reaction.

Although the claim language itself is enough to defeat Natera's expansive reading of the claim, the intrinsic and extrinsic evidence further confirm that tagging and amplifying in claim 1 are separate and distinct process steps. The Court should adopt NeoGenomics' proposed construction.

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 10

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

Natera's Proposed Construction	NeoGenomics' Proposed Construction
Plain and ordinary meaning	"Sequencing the amplicons obtained from the targeted multiplex amplification step."

NeoGenomics' proposed construction for "sequencing the amplicons" in claims 1 and 14 of the '454 patent clarifies that "***the*** amplicons" refers to the amplicons obtained from the preceding step: "performing targeted multiplex amplification . . . to obtain amplicons." This understanding flows directly from the antecedent basis and should not be controversial.

Natera nevertheless refuses to agree, and again offers "plain and ordinary" meaning without saying what the claims actually mean. Natera intends to argue that RaDaR infringes even where intervening steps are performed such as size selection or barcoding which mean that the amplicons being sequenced are not the amplicons obtained from performing the targeted multiplex amplification. Natera's reading should be rejected because it flies in the face of the claim language and the inventors' statements during prosecution.

1. NeoGenomics' Construction is Supported By the Antecedent Basis

Here, the patentee's use of "the" before "amplicons" instructs that the amplicons being sequenced are those obtained from the targeted multiplex amplification step. "[U]se of definite articles such as 'the' and 'said' . . . refer[s] to the initial antecedent phrase.'" *Guardant Health, Inc. v. Found. Med., Inc.*, No. CV 17-1616-LPS-CJB, 2019 WL 5677748, at *10 (D. Del. Nov. 1, 2019), *report and recommendation adopted*, No.

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 11
Case 1:23-cv-00629-CCE-JLW Document 264 Filed 04/08/24 Page 15 of 32

CV 17-1616-LPS-CJB, 2020 WL 1329513 (D. Del. Mar. 23, 2020) (quotations and citations omitted); *see also Eastman Chem. Co. v. Aktiengesellschaft*, 47 F. App'x. 566, 573-74 (Fed. Cir. 2002) (construing "the salt" to refer to the "product of step(a)" because "[a] plain reading of the claims shows that the term refers to the salt earlier described" and "the word 'the' must have an antecedent basis"). NeoGenomics' proposal to construe this phrase as "sequencing the amplicons obtained from the targeted multiplex amplification step" gives effect to the claim language as written and no more.

Guardant Health is directly on point. There, the disputed claim recited:

> (d) sequencing . . . to produce ***a plurality of sequence reads*** . . . ; and
>
> (e) grouping ***the plurality of sequence reads*** . . . into families[.]

Guardant Health, 2019 WL 5677748, at *10 (emphasis added). Like Natera here, Guardant argued that the claim permitted an intervening step of filtering out certain sequence reads before the claimed grouping step. *Id.*, *11. The court rejected those arguments, holding that the use of "the" before "sequence reads" meant the claim required "grouping of '*the*' sequence reads referred to in the prior step," not simply "any" or "some" of the plurality of sequence reads. *Id.*, *10. The court stated, "The possibility of additional unclaimed steps, [such as filtering,] cannot alter the express limitations of the claims" and accordingly construed the claim as "'grouping ***every one*** of the sequence reads generated in step (d) into a family . . ..'" *Id.*, *11-12 (emphasis added). The '454 patent's use of "***the*** amplicons" similarly refers to the amplicons generated in the prior targeted multiplex amplification step, and not to the amplicons remaining after size

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 12

selection or those generated by different amplification steps.

To the extent Natera argues that claim 11, which depends on claim 1 and recites "performing barcoding PCR prior to the sequencing," permits intervening steps, *Guardant* rejected that argument too. Guardant pointed to dependent claims that recited filtering out sequence reads that failed to meet a quality threshold. *Id.* The court found the claims "d[id] not actually speak to when the sequence reads must be filtered out, and thus [did] not seem to 'preclude filtering sequence reads after grouping.'" *Id.* As in *Guardant*, claim 11 speaks to barcoding PCR before sequencing but does not preclude barcoding PCR prior to targeted amplification, as described in the specification. *See, e.g.*, '454 patent, 99:12-22; 99:47-49.

2. Natera Disclaimed Intermediate Steps Between Targeted Amplification and Sequencing

Natera's apparent construction should be rejected for the additional reason that Natera disclaimed "intermediate steps between the multiplex amplification and sequencing step from the scope of the claims" in order to overcome prior art during prosecution of the related U.S. Patent No. 11,486,008 ("the '008 patent") and cannot reclaim that disclaimed scope here. Ex. C, '008 Patent File History, May 18, 2020 Interview Summ. at 2. "[S]tatements made during prosecution [that are] both clear and unmistakable" will "preclude patentees from recapturing through claim interpretation specific meanings disclaimed during prosecution." *Omega Eng'g, Inc, v. Raytek Corp.*, 334 F.3d 1314, 1323-26 (Fed. Cir. 2003). "A statement made during prosecution of related patents may be properly considered in construing a term common to those patents

. . . ." *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1343 (Fed. Cir. 2015); *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.").

The '454 patent and Natera's related '008 patent are part of the same family, share an identical specification, and recite very similar claims. Both patents recite "performing multiplex targeted amplification" directly followed by "sequenc[ing] the amplicons":

'454 Patent, Claim 14	**'008 Patent, Claim 1**
performing targeted multiplex amplification to amplify 10 to 500 target loci . . . **to obtain 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, **wherein the method is capable of detecting an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus.**	**performing multiplex targeted amplification** to amplify at least 100 target loci . . . **to obtain amplicons**, …; **performing high-throughput sequencing to sequence the amplicons obtained in the multiplex targeted amplification reaction to obtain sequence reads**; and detecting one or more of the mutations or genetic variations present in the cell-free DNA from the sequence reads, **wherein an SNV mutation that is present in less than or equal to 0.015% of cell-free DNA molecules having the SNV locus in the biological sample is detected**.

During prosecution of the '008 patent, the Examiner rejected claim 1 in view of Forshew et al., *Sci. Transl. Med.* (2012). Ex. C, '008 Patent File History, Appl. Rem. at 6. To overcome the rejection, Natera argued:

> Forshew requires a ***subsequent and separate*** targeted amplification step (i.e., parallel single-plex PCR) to generate amplicons for sequencing, and therefore Forshew' s amplicons for sequencing are not obtained from the alleged multiplex targeted amplification.

Id., 7 (emphasis added). It further distinguished Forshew by adding an alleged "highly accurate mutation detection" limitation that "wherein an SNV mutation that is present in less than or equal to 0.015% of cell-free DNA molecules having the SNV locus in the biological sample is detected." *Id.* at 7, 9. When the examiner questioned whether the "claim as amended still permits additional method steps," Bernhard Zimmermann—Natera employee and named inventor of both asserted patents—removed any doubt by representing that "the highly accurate mutation detection obtained" by the claimed methods of the '008 patent was "due to lack of intermediate steps between the multiplex amplification and sequencing step." Ex. C, '008 Patent File History, May 18, 2020 Interview Summ. at 2. That is a clear and unmistakable disclaimer of claim scope, which Natera expressly conceded at the preliminary injunction hearing. Dkt. 162-3 (Nov. 27, 2023 PI Hrg. Tr.) at 56:4-6 ("Claim '008 says: 'To sequence the amplicons obtained in the multiplex targeted amplification reaction.' That in the '008 is a disavowal.").

Natera is wrong to argue prosecution disclaimer from the '008 patent does not apply to the '454 patent simply because the words "obtained in the multiplex targeted amplification reaction" do not appear in the '454 patent claims. This minor difference in language is beside the point. *See Invitrogen Corp. v. Clontech Lab'ys, Inc.*, 429 F.3d 1052, 1078 (Fed. Cir. 2005) (recognizing disclaimer may apply "where an amendment to

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 15

a related limitation in the parent application distinguishes prior art and thereby specifically disclaims a later (though differently worded) limitation in the continuation application") (citing *Elkay Mfg. Co. v. EBCO Mfg. Co.*, 192 F.3d 973, 978–79 (Fed. Cir. 1999)). Claim 14 of the '454 patent was also rejected over Forshew, and Natera relied on the same "highly accurate mutation detection" limitation—"detecting an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus"—to distinguish Forshew. Ex. D, '454 Patent File History, July 28, 2022 OA Resp. at 8. Thus, Mr. Zimmermann's statement that this limitation is possible "due to lack of intermediate steps between the multiplex amplification and sequencing step" is equally applicable to disclaim intermediate steps from the claims of the '454 patent.

The Court should adopt NeoGenomics' proposed construction.

D. "sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads" ('454 Patent, Claims 1, 14)

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

NeoGenomics' proposed construction clarifies that "sequencing the amplicons to obtain sequence reads" and "detecting . . .from the sequence reads" are separate steps that must be performed separately and in sequence. Natera's proposal, an ambiguous statement that "[t]he terms are part of one sequencing step," ignores the explicit language

and structure of the claim, as well as the basic science that would inform a scientist's understanding of the claim.

The claim language here recites "sequencing" and "detecting" as sequential steps and further delineates between the two with a comma. The claim recites that sequencing is performed to obtain sequence reads and then any SNV mutations are detected "***from*** the sequence reads." '454 patent, claim 1 (emphasis added). Thus, the claim "requires an ordering of steps . . . as a matter of logic or grammar." *Mformation Techs., Inc. v. Research in Motion, Ltd.*, 764 F.3d 1392, 1398-99 (Fed. Cir. 2014). As in *Function Media* discussed above, claiming "detecting . . . from the sequence reads" means that "the creation of the [sequence reads] must happen before the [detecting] begins." 708 F.3d at 1319-21. The two are not one undifferentiated step.

The specification reinforces the discrete nature of these steps. It defines "sequence" as "a DNA sequence or a genetic sequence" and states that "sequencing" "refers to data representing a sequence of nucleotide bases that were measured, e.g., using a clonal sequencing method . . . [to] produce sequence data representing single, or clones, or clusters of one original DNA molecule." '454 patent, 28:19; 31:17-21. By contrast, the patent describes "detecting" using computer algorithms to analyze raw sequence data—"nontransitory computer readable medium comprising computer readable code that, when executed by a processing device, causes the processing device to carry out the methods for detecting SNVs." *Id.*, 65:20–33; 67:52-56 ("identifying using a computer, one or more single nucleotide variant positions with a statistically significant

depth of read . . . thereby detecting the one or more single nucleotide variants"); *see also id.*, 5:63–67; 43:15-35; 60:21–63:49; 147:49–151:42; & Figs. 69, 70. Sequencing generates DNA sequence data and detecting analyzes that sequence data to determine if any SNVs are present.

These are separate steps that must be performed in the order written. The plain and ordinary meaning of this limitation makes this apparent, but NeoGenomics requests this construction to resolve the parties' dispute and make clear that the two steps are not one step.

E. "clonal" / "subclonal" ('454 Patent, Claims 3-5)

Natera's Proposed Construction	NeoGenomics' Proposed Construction
Not indefinite; plain and ordinary meaning.	Indefinite.

A patent is invalid for indefiniteness if its claims, read in light of the patent's specification and prosecution history, fail to inform those skilled in the art about the scope of the invention with reasonable certainty. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898 (2014). The indefiniteness requirement "ensure[s] that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent." Manual of Patent Examining Procedure § 2173. A patent must be "precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them," so as to avoid "a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Nautilus*, 572 U.S. at 909-10 (cleaned up).

An ambiguous distinction between two claim terms "renders them incapable of construction." *Icon Health & Fitness, Inc. v. Polar Electro Oy*, 656 F. App'x 1008, 1014, 1016 (Fed. Cir. 2016). In *Icon Health*, the Federal Circuit affirmed a finding of indefiniteness where the terms "in-band" and "out-of-band" were relative terms and "only ha[d] meaning in a given context with a defined reference," but there was "no reference provided in the specification to teach a person of ordinary skill what constitutes an in-band communication versus an out-of-band communication (other than the fact that they are different)." *Id.*, 1014-15.

Tumor clonality is a term used to refer to the genetic origins of a tumor. Decl. David Smith, Ph.D. ("Smith Decl.") ¶ 21. Mutations shared by all cells in a tumor are referred to as clonal, while mutations that differ, due to further mutation as cancer develops, are referred to as subclonal. *Id.*, ¶¶ 21-22. Scientists in this field understand the distinction between "clonal" and "subclonal" to be inherently vague such that the terms do not provide reasonable certainty as to what methods would or would not infringe the claims. For example, the "illusion of clonality" is a well-known phenomenon where mutations that might seem clonal using one frame of reference might also appear subclonal using a different frame of reference. *Id.*, ¶ 36. A mutation might be classified as "clonal" if present in two out of three tumor sites, and only the two sites with the mutation were sampled. *Id*. The same mutation in the same patient might be classified as "subclonal" if a biopsy happened to include a tumor site that lacked the mutation. *Id.*

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 19
Case 1:23-cv-00629-CCE-JLW Document 264 Filed 04/08/24 Page 23 of 32

And one would run into the same issue if only a portion of a single site were sampled that was not representative of the entire site. *Id.*

The specification provides no guidance as to how to choose the frame of reference to differentiate between a clonal and subclonal mutation. Smith Decl. ¶ 37. It does not describe how many samples should be taken, where those samples should be taken from, or what proportion of those samples must share the mutation for it to be deemed clonal. *Id.* For instance, Dr. Smith (an eminent scientist with decades of experience in the field) describes two articles that discuss two different frames of reference for determining clonality—one using cells within a single biopsy and making determinations of clonality based on a single statistical confidence level, and one using multiple sampled tumor regions to construct a tree to assess the branched evolutionary pattern. *Id.* The '454 patent specification does not provide any such method for classifying mutations as clonal or subclonal. Nor does the specification discuss how one should deal with issues of contamination when ascertaining the scope of the claims. *Id.*, ¶ 38. The presence of non-cancerous cells in tumor biopsies is inevitable. These cells act as contaminants in the biopsy sample and can dramatically change determinations of clonality and subclonality. *Id.*

During prosecution, the examiner purported to interpret "clonal SNV mutations" and "subclonal SNV mutations," "as discussed in the specification at paragraphs 111 [31:17-24] and 748 [168:20-26]." Ex. D, '454 patent file history, Jul. 7, 2022 Non-Final Rejection at 2. Neither of those paragraphs cures the indeterminate differentiation of the

NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 20
Case 1:23-cv-00629-CCE-JLW Document 264 Filed 04/08/24 Page 24 of 32

terms. Paragraph [0111] (now '454 patent 31:17-24) refers to "clones," or copies, of DNA; it does not refer to "clonality" of cancer cells, *i.e.*, whether tumor cells share genetic makeup with other tumor cells, and thus cannot provide any guidance as to the scope of claims 3-5. Smith Decl. ¶ 39.

The Examiner's citation to Paragraph [0748] is similarly unhelpful. Paragraph [0748] (now '454 patent 168:20-26) merely states, "Clonal populations had VAF [variant allele frequency] allele calls in all biopsied samples assayed and in plasma, while subclonal populations had VAF allele calls in at least one biopsy sample, but not all biopsy samples." This single sentence description suffers from the same ambiguities discussed above and does not provide sampling or statistical protocols for distinguishing between clonal and subclonal mutations. Smith Decl. ¶ 40.

The claims and specification of the '454 patent thus do not provide adequate guidance of the metes and bounds of clonal and subclonal, and the claims areindefinite. *See Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1251 (Fed. Cir. 2008) ("Even if a claim term's definition can be reduced to words, the claim is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully precise claim scope."). As in *Icon Health*, the "ambiguous nature of the distinction" between clonal and subclonal renders both claim terms incapable of construction. 656 F. App'x at 1016.

F. "present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus" / "present in 0.005% to 0.015% of the cell-free DNA comprising the SNV locus" ('454 Patent, Claims 14, 28)

Natera's Proposed Construction	NeoGenomics' Proposed Construction
Not indefinite; plain and ordinary meaning.	Indefinite.

Claims 14 and 28 of the '454 patent conclude by reciting a method "capable of detecting an SNV mutation that is present" in a certain percentage of cell-free DNA comprising the SNV locus. These claims are indefinite because there are multiple methods and statistical representations for determining and representing the limits of detection that lead to different results, and the patent does not provide guidance as to which should be used.

A claim is indefinite where multiple tests for a claimed property are known in the art, but those "tests do not provide consistent results" such that a skilled person "would not know under what standard to evaluate" the claimed property. *HZNP Meds. LLC v. Actavis Lab'ys UT, Inc.*, 940 F.3d 680, 696–99 (Fed. Cir. 2019); *see also Dow Chem. Co. v. NOVA Chems. Corp. (Canada)*, 803 F.3d 620, 634–35 (Fed. Cir. 2015). In *Dow Chemical*, the term "slope of strain hardening coefficient" was indefinite because the patent provided no guidance on which of four slope calculation methods known in the art to use, and the different methods did not always produce the same result. 803 F.3d at 633-635.

Here, the ’454 patent describes a metric known as the “limit of detection” or “LOD,” which scientists understand describes the lowest levels of variants that a sequencing method is capable of identifying consistently. Smith Decl. ¶ 43. But the ’454 patent specification identifies three different methods for determining LOD:

1. LOD-mr5: “based on a minimum of 5 reads being chosen as the minimum number of times a SNV is observed in the sequencing data to have sufficient confidence the SNV is actually present.” ’454 patent, 157:56-60.
2. LOD-zs5.0: “based on the z-score,” which is “the number of standard deviations an observed error percentage is away from the background mean error.” *Id.*, 158:1-5.
3. LOD-zs5.0-mr5: based on the maximum value of the two metrics above. *Id.*, 93:35-37.

Smith Decl. ¶¶ 44-47. Figure 35 (annotated below) of the patent shows that these three methods yield different LOD results.

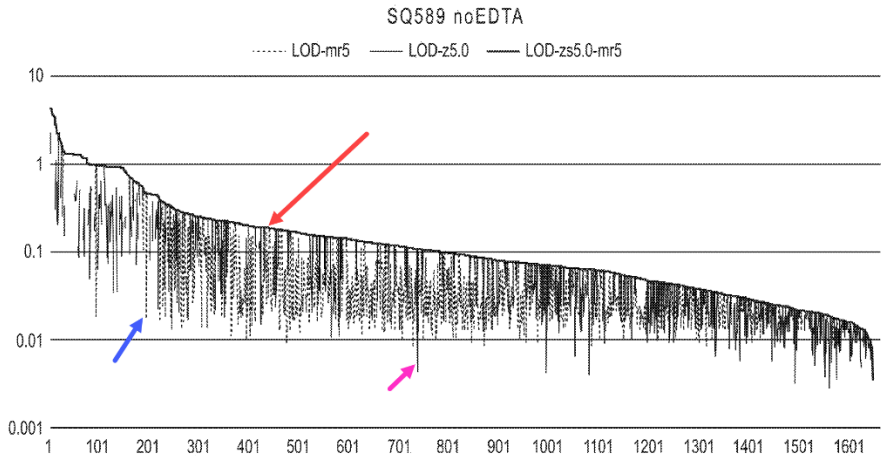

FIG. 35

At various points denoted by colored arrows, the selection of one method versus another shows as much as "a ten-fold difference between the different methods"—a difference that can affect whether a process practices the claims. *Id.* ¶¶ 48-50. The specification and prosecution history contain no corresponding disclosure of how to choose among different methods. *Id.* ¶ 51.

Compounding this problem, multiple different statistical representations of LOD are disclosed, which also yield different results. Smith Decl. ¶ 51 (noting that "Example 6 describes mean and median LODs that differ by more than a factor of 2);'454 patent, 158:32-34 ("For the analysis of cDNA in a plasma sample shown in FIG. 35, the mean limit of detection was 0.24%, and the median limit of detection was 0.09%."). The specification fails to inform a POSA about which statistical representation of LOD should be used. Smith Decl., ¶¶ 51-52.

For the reasons discussed above, a POSA reading the specification "would not know under what standard to evaluate" the claimed LOD or whether a particular method's LOD falls within the scope of the claims. *Media Rights Techs., Inc. v. Cap. One Fin. Corp.*, 800 F.3d 1366, 1371 (Fed. Cir. 2015).

This the 8th day of April, 2024

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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, the undersigned, hereby certify that on April 8, 2024, I electronically filed the foregoing **DEFENDANT NEOGENOMICS, INC.'S OPENING CLAIM CONSTRUCTION BRIEF** with the Clerk of Court using the CM/ECF System.

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NATERA EX2030
NeoGenomics v. Natera, IPR2024-00812
Page 28