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|---------------------------|---|----------------------------|
| NATERA, INC.              | ) |                            |
|                           | ) |                            |
| Plaintiff,                | ) |                            |
|                           | ) |                            |
| v.                        | ) | C.A. No. 1:23-cv-629       |
|                           | ) |                            |
| NEOGENOMICS LABORATORIES, | ) | <b>JURY TRIAL DEMANDED</b> |
| INC.                      | ) |                            |
|                           | ) |                            |
| Defendant.                | ) |                            |

NATERA EX2014  
NeoGenomics v. Natera, IPR2024-00346  
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Pursuant to Federal Rules of Civil Procedure 12(b) and 12(c), NeoGenomics Laboratories, Inc. (“NeoGenomics”) respectfully moves to dismiss this patent infringement case. As described below, this motion is warranted because U.S. Patent No. 11,530,454 (“the ’454 Patent”) and U.S. Patent No. 11,519,035 (“the ’035 Patent”) (collectively, “Asserted Patents”) are invalid under 35 U.S.C. § 101.

## **I. SUMMARY OF THE ARGUMENT**

Natera’s ’454 and ’035 Patents are invalid because they claim ineligible subject matter. Specifically, the claimed inventions are the generic detection of tumor mutations or cancer-associated DNA code using conventional DNA technology.

Given that patents and their claims are usually the central evidence to resolve § 101 disputes, and that such evidence is properly considered on FRCP 12(b)(6) motions, courts frequently invalidate patents on such motions. *See, e.g., PersonalWeb Technologies LLC v. Google LLC*, 8 F.4th 1310, 1314 (Fed. Cir. 2021) (patent eligibility “may be, and frequently has been, resolved on a Rule 12(b)(6)”).

Moreover, the Federal Circuit has repeatedly invalidated patents claiming the detection of DNA characteristics because it amounts to the detection of natural phenomena. *CareDx, Inc. v. Natera, Inc.*, 40 F.4th 1371, 1377 (Fed. Cir. 2022) (collecting cases). In *CareDx*, it was Natera itself that successfully argued before the district court, and on appeal, that the detection of DNA characteristics was an ineligible natural phenomenon and DNA amplification and sequencing steps used to identify genetic code were conventional in 2009 (before the claimed inventions here). *CareDx, Inc. v. Natera, Inc.*, 563 F. Supp. 3d 329 (D. Del. 2021), *aff’d*, 40 F.4th 1371.

Natera's Complaint appears to bank on its mere relabeling of the claims of the '454 Patent as a "method for preparing" changed from a "method for detecting." The earliest application on the face of the '454 Patent was filed on April 21, 2014. Ex. 1. Eight years later, the preamble to the claims of the '454 Patent was still labeled a "method for detecting." Just last year, however, Natera changed the preamble to relabel it a "method for preparing" unprovoked by the Patent Office right before issuance, without explanation. Ex. 2 at 2, 3. But the steps of the claims, despite the relabeling, still include detection in multiple places, including the third and final step which requires generically "detecting" tumor mutations. Natera's relabeling lacks substance and was merely intended to exploit a 2020 Federal Circuit decision finding a true method of preparation patent eligible. *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 967 F.3d 1319, 1327 (Fed. Cir. 2020). The claimed methods here are methods of detecting a natural phenomenon and Natera's relabeling does not change that.

The claims of the '454 Patent cover a three-step process involving sequencing DNA, amplifying DNA, and detecting tumor mutations. But the Patent does not describe the claimed detection techniques as themselves inventive. Instead, the 173 columns of the Patent describe extensive math and a litany of unclaimed techniques as its invention. The claimed sequencing and amplification techniques are described in the Patent as well known, not inventive. High-throughput sequencers have been commercially available for many years and amplification (making copies of DNA) dates back to the 1980s.

This motion is especially ripe because Natera previously argued – and thus cannot deny plausibly – that DNA amplification and sequencing techniques were conventional by

2009 in a successful effort to invalidate CareDx's patents. Here, the earliest application on the face of the '454 Patent was filed in 2014. Ex. 1. If such techniques in this fast-moving field were conventional in 2009, they were surely conventional by 2014. Natera should be legally precluded from disputing the positions it successfully advanced in *CareDx*.

Similarly, the '035 Patent should also be invalidated. The Patent Office allowed the claims because they detect DNA code "associated with cancer" rather than DNA of a fetus in a mother's blood as you might for prenatal diagnostics. Detecting DNA because it correlates with cancer, however, is a natural phenomenon that is ineligible subject matter. The amplification methods and other conventional steps in the claims are not inventive and thus cannot save the claims from invalidation.

Therefore, this motion should be granted and both Asserted Patents invalidated.

## **II. STATEMENT OF FACTS**

### **A. The '454 Patent**

The claims of the '454 Patent describe the detection of tumor mutations to help with the detection of cancer. The claims exclude most of the technology described in the lengthy specification and instead reference only conventional DNA techniques.

To detect a DNA mutation, a researcher needs to find a location in DNA where the DNA code (a series of A, C, G and T nucleotide bases) differs from normal. As an example, where the DNA code at a particular location might be the sequence TAGC in a healthy person, someone with cancer might instead have TACC in that location. At the third position in this strand, the cancer patient has a "C" base whereas a healthy person has a "G" base. Each DNA base (A, C, G, or T) is a nucleotide and when there is only a variant

at one position, it is known as a single nucleotide variant (SNV) or single nucleotide polymorphism (SNP). This base alteration at the third position is called a SNV. The detection of one or more SNVs to distinguish tumor DNA is the subject of the claims.

Conventional techniques to detect an SNV include amplifying DNA, which allows you to select a region of DNA and create many copies of it (called amplicons because they are the product of amplification). Then, the amplicons can be sequenced to see if the DNA code matches that of a healthy person or one with cancer, for example.

Using amplification and sequencing to detect the DNA code of a sample has been the subject of two Federal Circuit decisions finding such a process patent ineligible. These examples help explain the technology. In *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015), amplification was used to determine which part of the DNA in the mother included a “Y” chromosome that is associated with male DNA. If the DNA has a “Y” chromosome, you know that it is associated with a male fetus. The Federal Circuit ruled that detecting whether the DNA code was that of a “Y” chromosome was patent ineligible because amplification was conventional and the detection itself is patent ineligible. *Id.* at 1376-78.<sup>1</sup>

In *CareDx*, the invalidated patents related to monitoring an organ transplant patient for organ rejection. To do so, the patents described evaluating how much of the donor’s DNA (from the transplanted organ) was in the transplant patient’s blood compared to their own DNA. When an organ undergoes distress (such as during rejection), it releases more

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<sup>1</sup> *Ariosa* involved the DNA that circulates in blood outside an intact cell, which is known as cell free DNA (cfDNA).

DNA and the ratio of donor DNA can spike. To distinguish the donor DNA from the organ recipient's own DNA the patents use amplification and sequencing techniques. Both the District Court and the Federal Circuit concluded that using these known amplification and sequencing techniques to differentiate DNA between the donor and recipient based on a SNV were patent ineligible because they involved the use of conventional techniques to detect a natural phenomenon. *CareDx*, 563 F. Supp. 3d 329, *aff'd*, 40 F.4th 1371. Like *Ariosa*, *CareDx* involved the detection of cfDNA.

Here, the claims describe a method of detecting whether the DNA code of the cfDNA of a patient suspected of having cancer is that of a tumor mutation. To do so, it describes using known amplification and sequencing techniques. To differentiate the DNA code the method looks for SNVs.

The '454 Patent offers a method to detect DNA characteristics generically. It is generic because the claims do not identify particular SNVs to detect or what SNVs are associated with cancer tumors. The user needs to determine what SNVs they want to detect. The claims simply define a general procedure for looking for DNA mutations, but the user needs to know what DNA code they actually want to detect.

#### **B. The '035 Patent**

The claims of the '035 Patent similarly include three steps: (1) tagging DNA, (2) amplifying the tagged DNA, and (3) sequencing the tagged DNA. Tagging DNA involves adding nucleotides (i.e., tags) to the DNA, which are used to identify the DNA. The Patent Office allowed these claims over the prior art because the DNA locations are "associated with cancer" and the claimed method excludes samples "obtained from a pregnant female."

Ex. 3 at 3 (“The amendment to the claim requires the claimed method excludes samples of cell free nucleic acid obtained from a pregnant female and that the plural 25-2000 loci are associated with cancer. The amendment is sufficient to overcome the rejection of record and over any other references in the prior art which are focused on multiplex amplification and sequencing of 25 to 2000 SNP targets in a sample.”).

Multiplex amplification is the amplification of multiple DNA samples in the same container, and Natera has suggested that part of the inventive concept of these claims is “multiplexing” so that multiple DNA locations (“loci”) are amplified in one container. But the claims only require multiplexing 25 or more loci. The ’035 Patent itself, however, explains that multiplexing up to 100 loci was well-known before the claimed inventions. Ex. 4 at 48:25-27 (“the general belief in the art is that multiplexing PCR for sequencing is limited to about 100 assays in the same well”). And prior art cited and incorporated by reference in the patent plainly identifies multiplexing more than 25 loci. Ex. 5 (describing amplifying 90 exons from genomic DNA); Ex. 6 (disclosing amplifying more than 1000 SNPs).

### III. LEGAL STANDARD

Patentability under 35 U.S.C. § 101 is a threshold legal issue. *Bilski v. Kappos*, 561 U.S. 593, 602 (2010). And it “may be, and frequently has been, resolved on a Rule 12(b)(6).” *PersonalWeb*, 8 F.4th at 1314.

The *Alice* two-step inquiry governs this motion. *Alice Corp. Pty. Ltd. v. CLS Bank Intern.*, 573 U.S. 208 (2014). “In the first step, the court must determine whether the claims at issue are directed to a patent ineligible concept.” *Int’l Bus. Machines Corp. v. Zynga*

*Inc.*, No. 22-590-GBW, 2022 WL 17177735, at \*3 (“*Alice* Step One”). “In other words, are the claims directed to a law of nature, natural phenomenon, or abstract idea?” *Id.* “If the answer to the question is ‘yes,’ then the court proceeds to step two, where it considers ‘the elements of each claim both individually and as an ordered combination’ to determine if there is an ‘inventive concept—i.e., an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.’” *Id.* (quoting *Alice*, 573 U.S. at 217-18) (“*Alice* Step Two”).

#### IV. ARGUMENT

“[W]here a patent claims a method for detecting a natural phenomenon, the dispositive inquiry [to determine patent eligibility] is whether the asserted method uses more than standard or conventional techniques of detection.” *CareDx*, 563 F. Supp. 3d at 341, *aff’d*, 40 F.4th 1371. More generally, evaluation of *Alice* Step One and Two is focused on the conventionality of the techniques used to detect the natural phenomenon. *Id.*

##### A. The ’454 Patent Is Invalid

###### 1. *Alice* Step One Is Satisfied Because The Claims Of The ’454 Patent Are Directed To A Natural Phenomenon

Asserted claim 1 of the ’454 Patent reads as follows:

1. 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 having a length of 50-150 bases, 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 sequencing has a depth of read of at least 50,000 per target locus.<sup>2</sup>

The claims of the '454 Patent are directed to detecting a natural phenomenon: the presence in a blood (plasma) sample of DNA mutations associated with a cancerous tumor. For example, Claim 1 culminates in “detecting one or more of the tumor-specific SNV mutations.” An “SNV” is a location in the genome where a single nucleotide base is a variant, indicating the presence of a tumor.

Federal Circuit law holds that patent claims that involve detecting a natural phenomenon (e.g., DNA characteristics) with known laboratory methods satisfy *Alice* Step One. *See, e.g. Ariosa Diagnostics, Inc.*, 788 F.3d at 1376. Indeed, Natera successfully argued exactly this point in *CareDx* to both the District Court and Federal Circuit. *CareDx*, 563 F. Supp. 3d at 340 (“Thus, under binding Federal Circuit case law, ***methods-of-detection claims are directed to a patent-ineligible concept if they ‘only involve detecting a natural law with no meaningful non-routine steps.’*** *Athena*, 915 F.3d at 752”), *aff’d CareDx*, 40 F.4th at 1377 (“Natera adds that the district court properly applied *Alice* step one and relied on the ***express use of the word ‘detecting’ in the claims***, and our case law

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<sup>2</sup> Emphasis supplied throughout.

addressing similar ‘detecting’ claims, to conclude that the claims are directed to a natural phenomenon.”).

To try to avoid patent ineligibility, Natera’s Complaint relies on a patent drafting artifice by attempting to camouflage that the ’454 Patent in fact claims a method of ***detecting*** a natural phenomenon. Late last year, after eight years of patent prosecution, Natera amended its preamble to the claims of the ’454 Patent to try to relabel the claimed method from a “method for detecting” to a “method for ***preparing***” even though the method steps are basically the same. Ex. 2 at 2, 3. The timing of this maneuver explains a lot. Natera is trying to exploit that, although the case law does not protect methods of detection, there is a 2020 Federal Circuit case, *Illumina, Inc.*, 967 F.3d at 1326, that upheld a true “method of preparation” patent. However, in *Illumina*, the Federal Circuit only upheld the method of preparation claims because they were true methods of preparing a physical composition – that plainly were not methods of detection. *Id.* (“[t]he claimed methods achieve more than simply observing that fetal DNA is shorter than maternal DNA or detecting the presence of that phenomenon. The claims include physical process steps that change the composition of the mixture, resulting in a DNA fraction that is different from the naturally occurring fraction in the mother’s blood.”).

Natera’s attempt to rely on manipulative claim drafting fails legally. The Supreme Court has sternly warned against allowing mere “patent drafting” techniques to avoid patent ineligibility. *Alice Corp.*, 573 U.S. at 226 (“This Court has long ‘warn[ed] ... against’ interpreting § 101 ‘in ways that make patent eligibility depend simply on the draftsman’s art.’”) (internal citations omitted).

The claims in the '454 Patent explicitly are directed to a method of detecting. The method includes three steps. First, performing DNA sequencing of a tumor sample “to identify a plurality of tumor-specific SNV mutations.” This, on its face, is detection of mutations. Second, amplifying DNA strands with “tumor-specific SNV mutation(s)” to generate copies of DNA (“amplicons”) containing those mutations. Third, “sequencing the amplicons” and “**detecting** one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads.” The claimed method culminates in this **detection** of tumor-specific mutations, a natural phenomenon – not the sample preparation, as stated by the modified preamble.

The preamble cannot change the actual detection required by the three method steps. It is termed a “method for preparing” a blood sample of a cancer patient “useful for detecting one or more single nucleotide variant (SNV) mutations in the plasma sample.” But the method steps do not prepare for detection of such mutations, they actually **require** it in the last step, as explained above.

The '454 Patent itself confirms that the supposed invention is a method of detection, not a method of preparation. The Title states it is a method of detection. Ex. 1 (“Detecting mutations and ploidy in chromosomal segments”). The Abstract states the invention is a method “for detecting single nucleotide variants.” *Id.*, Abstract. The Field of the Invention is “detecting single nucleotide variants.” *Id.* at 1:28-31. The Patent references detection dozens of times, including references to detecting SNVs for tumor mutation detection. *See, e.g., id.* at 5:32-45 (“In certain embodiments of this method for detecting one or more SNVs . . .”), 6:1-2 (“In certain embodiments of this method for detecting one or more SNVs the

sample is a plasma sample”), 44:6-8 (“In another aspect, the present invention generally relates, at least in part, to improved methods of detecting single nucleotide variations (SNVs).”).

The '454 Patent mentions “preparation” as an individual step for treating the sample that *precedes* both the sequencing and detection steps. Figure 63(a) exemplifies this:

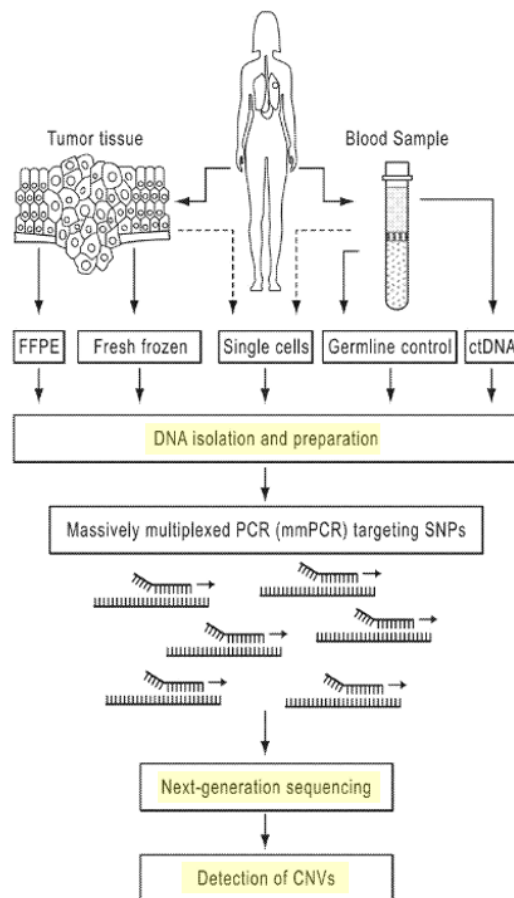


FIG. 63A

*Id.*, Fig. 63A (highlights added). Yet, Claim 1 does not just recite preparation, but instead requires the detection of tumor-specific SNVs – directing the claim towards the detection of a natural phenomenon, and satisfying *Alice* Step One.<sup>3</sup>

**2. *Alice* Step Two Is Satisfied Because The Claimed Method Of Detection Does Not Include Inventive New Detection Techniques**

*Alice* Step Two addresses whether the steps used to detect the natural phenomenon (SNV tumor mutations) are themselves inventive. *CareDx*, 40 F.4th at 1380 (“We have repeatedly held that applying standard techniques in a standard way to observe natural phenomena does not provide an inventive concept... Each of the methods in the recited steps was already being performed by those in the art.”); *Ariosa Diagnostics, Inc.*, 788 F.3d at 1377 (“Because the method steps were well-understood, conventional and routine, the method of detecting paternally inherited cfDNA is not new and useful.”).

The ’454 Patent, and Natera, have acknowledged that each claim step is conventional. The preamble of claim 1 states 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.” Obtaining a blood plasma sample was well known and is not even described with detail in the Patent. This is a step that the Delaware court, at Natera’s behest, found conventional in 2009. *CareDx*,

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<sup>3</sup> Insofar as Natera argues that the claims are directed to the detection techniques themselves, that argument fails because all those techniques are conventional as explained below. See *CareDx*, 40 F.4th at 1379 (“claims applying conventional methods ‘directed to’ natural phenomena satisfy *Alice/Mayo* step one”).

563 F.3d at 336 (“to obtain cfDNA samples ‘any technique known in the art may be used, e.g. a syringe or other vacuum suction device’”).

The first step of Claim 1 is “performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations.” Both whole exome and whole genome sequencing were well known by 2014 and either one would satisfy the sequencing requirement. The Patent states “whole exome sequencing” could be performed on commercial equipment available long before 2014. Ex. 1 at 168:13-15 (“Each biopsied sample was assayed by whole exome sequencing (Illumina HiSeq2000; Illumina, San Diego, Calif.)”). “Whole genome sequencing” was so well-known that the Patent mentions it in passing once without describing what it is. *Id.* at 41:59-61.

In *CareDx*, Natera successfully argued based on its expert’s declaration that whole genome sequencing to identify an SNV was routine and conventional by 2009. Ex. 7 ¶ 93 (describing that determining SNPs (SNVs) by “whole genome sequencing or exome sequencing” in 2009 was routine and conventional by reference to patents predating 2009). The District Court found multiple claim elements in multiple patents that require sequencing to identify SNPs (SNVs) were conventional by 2009. *CareDx*, 563 F. Supp. 3d at 333-36.

The second step of Claim 1 is “multiplex amplification” to amplify 10-500 loci of the DNA to result in amplified DNA for each such location that are 50-150 bases long, which was conventional in 2014 with numerous descriptions in the literature. Indeed, the ’454 Patent does not purport to include this as part of its inventive concept. Rather, it refers

to prior art patent publications to describe such multiplex amplification, including U.S. Patent Application No. 13/300,235 (Ex. 8) (supposedly invented in 2010 and published in 2012).<sup>4</sup> Ex. 1 at 97:52-65; Ex. 8 at 78:19-21 (“Whereas traditional multiplex PCRs evaluate up to fifty loci simultaneously, the approach described herein may be used to enable simultaneous evaluation of more than . . . 500 loci simultaneously . . .”), 92:23-28 (“Prior art demonstrates that ordinary people skilled in the art typically design 100+ bp amplicons . . . In an embodiment, the amplicons may be designed to be less than 50 bp.”). Because these prior disclosures of multiplex amplification resulting in amplified DNA that was 50-150 bases long occurred years before the claimed inventions of the ’454 Patent, it cannot possibly be the inventive concept of this patent.

Indeed, Natera successfully argued that selective multiplex amplification was conventional at least by 2009 when it challenged CareDx’s patents. Ex. 7 ¶ 8. The District Court agreed that multiplex amplification was conventional. *CareDx*, 563 F. Supp. 3d at 334 (finding ’607 patent, claim 1 step (c) conventional). On appeal, Natera again successfully argued selective (targeted) amplification was conventional by 2009. Ex. 9 at 50 (“There is a good reason for this: the patentee admitted selective amplification was routine and conventional—so much so that it was unnecessary to provide any guidance on how to apply it to 1,000 SNPs.”) (citations omitted).

The third step of Claim 1 is “sequencing” the amplicons (DNA copies) from step 2 to “detect[] one or more of the tumor-specific SNV mutations” using a “sequencing depth

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<sup>4</sup> U.S. Publication No. 2013/0123120 is also cited.

of at least 50,000 per target loci.” Sequencing to detect SNVs was conventional. The ’454 Patent describes commercially available Illumina sequencers to accomplish that. Ex. 1 at 96:18-22, 152:43-48, 163:52-59. Natera successfully argued that advanced sequencing was conventional in 2009 to the Delaware court. Ex. 7 ¶ 93. And the Court found that it was. *CareDx*, 563 F. Supp. 3d at 345 and n.5 (D. Del. 2021), *aff’d*, 40 F.4th 1371.

Natera’s inclusion of a sequencing depth of “50,000 per target loci” simply does not add an inventive concept. The ’454 Patent does not describe sequencing depth as inventive and gives it little attention. Ex. 1 at 68:33-40 (referencing a laundry list of sequencing depths, only one of which includes 50,000). For good reason. In *CareDx*, Natera successfully explained to the District Court that sequencing depth was well-known in 2009 and that ordinary artisans knew that to improve sensitivity the sequencing depth (i.e., the number of copies of the same DNA molecules sequenced) should be increased. *See* Ex. 7 ¶ 119 (citing literature and explaining: “POSA’s prior to November 6, 2009, were well aware that sequencing more molecules, of increasing sequencing depth, improves sensitivity.”).

Claim 1 does not add an inventive concept to the detection of SNV tumor mutations, which is a natural phenomenon. Sequencing a sample, amplifying DNA and detecting SNV tumor mutations were known techniques by 2014, and as early as 2009 – as Natera successfully argued. Ex. 7 ¶ 8. The ’454 Patent did not invent these standard techniques.

### **3. Natera Should Be Collaterally Estopped Based On *CareDx***

Natera should be collaterally estopped from relitigating the invalidity issues that were raised and finally decided by the Federal Circuit in *CareDx* as described in this brief

and insofar as Natera denies its prior positions. Collateral estoppel is properly considered, and courts may take judicial notice of facts from a prior proceeding, on a Rule 12(b)(6) motion. *In re Lee*, 461 F. App'x 227, 234 (4th Cir. 2012) (“A court may consider collateral estoppel at the motion to dismiss stage of litigation.”); *Briggs v. Newberry Cnty. Sch. Dist.*, 838 F. Supp. 232, 234 (D.S.C. 1992), *aff'd*, 989 F.2d 491 (4th Cir. 1993) (“Facts subject to judicial notice may be considered by a court on a motion to dismiss. When entertaining a motion to dismiss on the ground of res judicata or collateral estoppel, a court may judicially notice facts from a prior judicial proceeding.”) (internal citations omitted).

In *CareDx*, Natera acknowledged that in 2009 every claim step was well known in the art and conventional. Natera successfully asserted that detection of DNA characteristics was an ineligible natural phenomenon and obtaining a blood plasma sample, amplifying DNA including by selective (targeted) multiplex amplification, sequencing techniques including whole genome sequencing to identify an SNV, and detecting SNV tumor mutations were conventional. Natera asserted that sequencing depth was well-known and ordinary artisans knew that to improve sensitivity the sequencing depth should be increased. And Natera successfully argued that Federal Circuit precedent holds that claims that involve detecting a natural phenomenon (e.g., DNA characteristics) with known laboratory methods satisfy *Alice* Step One. *See CareDx*, 563 F. Supp. 3d at 340; *aff'd CareDx*, 40 F.4th at 1377. Yet now, Natera may take the opposite position in an effort to enforce its own ineligible patents. This Court should take judicial notice of the *CareDx* opinions and related Natera submissions, and collateral estoppel should prevent Natera

from relitigating the invalidity issues considered and decided in *CareDx*, as explained above and insofar as Natera attempts to contravene such positions in this case.

#### 4. Claim 1 Is Representative

Natera's Complaint vaguely alleges that NeoGenomics infringes "more than one" claim of the '454 Patent, failing to specifically identify which claims are at issue. ECF 1 ¶ 38. Exhibit 3 to Natera's Complaint is a claim chart describing alleged infringement only with respect to Claim 1. As the Federal Circuit recently explained in *Hantz Software, LLC v. Sage Intacct, Inc.*, No. 2022-1390, 2023 WL 2569956, at \*1 (Fed. Cir. Mar. 20, 2023), where a complaint only identifies a particular claim as infringed, the other claims are not at issue. Claim 1 is accordingly all that needs to be addressed to resolve this motion with respect to the '454 Patent. Regardless, Claim 1 is representative such that a separate patentability analysis is not necessary for the other claims. *See Wireless Discovery LLC v. Coffee Meets Bagel, Inc.*, No. 22-cv-478-GBW, 2023 WL 1778638, at \*3-5 (D. Del. Feb. 6, 2023) (rejecting arguments that a claim is not representative where the additional claims do not add different elements that warrant a separate patentability analysis).

The other claims do not add an inventive concept. They are either patent ineligible themselves or add a conventional step. Many dependent claims merely describe known features of the detected DNA, which is part of the natural phenomenon. *See* Claims 2 and 16 (from circulating tumor DNA), Claims 3 and 17 (clonal SNV mutations), Claims 4 and 18 (subclonal SNV mutations), Claims 5 and 17 (both clonal and subclonal SNV mutations). Other claims merely describe the generic detection of cancer from mutations.

See Claims 12 and 26 (detecting cancer from the detection of mutations), Claims 13 and 27 (detecting different types of cancer).

Claims 8, 9, 22, and 23 merely identify numbers of target loci also described in prior patent applications. See, e.g., Ex. 8 at 78:17-21 (“Whereas traditional multiplex PCRs evaluate up to fifty loci simultaneously, the approach described herein may be used to enable simultaneous evaluation of more than . . . 100 loci simultaneously . . .”).

Claims 10 and 24 add only the conventional step of selecting the primers used for PCR or using hybrid capture probes, which are both so conventional they are described in prior published patent applications cited in the Patent. For example, primer design is so basic that the ’235 application contains a definition of primer that includes designing the primer. Ex. 8 at 31:22-26 (“Primer, also ‘PCR probe’ refers to a single DNA molecule (a DNA oligomer) or a collection of DNA molecules (DNA oligomers) where the DNA molecules are identical, or nearly so, and where the primer contains a region that is *designed* to hybridize to a targeted polymorphic locus, and m contain a priming sequence *designed* to allow PCR amplification.”). Hybrid capture is also described in prior published patent applications referenced in the ’454 Patent. See, e.g., *id.* at 70:8-9 (“Hybrid capture involves hybridizing probes that are complementary to the targets of interest to the target molecules.”)

Claims 11 and 25 add only the conventional step of barcoding, which is mentioned in passing in the ’454 Patent and described in prior published patent applications cited in the Patent. See, e.g., Ex. 8 at 31:26 (“A primer may also contain a molecular barcode.”), 91:30-31 (“Primers may contain additional functional sequences, e.g. barcodes”).

Claim 15 includes the same sequencing depth as in Claim 1, which thus adds nothing.

Claim 14 is the only independent claim other than Claim 1. It is near identical. It only adds the degree of detection, but does not claim how that is accomplished other than by use of the claimed conventional steps. This outcome is the product of conventional steps and not any inventive concept.

## **B. The '035 Patent Is Invalid**

### **1. *Alice* Step One Is Satisfied Because The Claims of the '035 Patent Are Directed To A Natural Phenomenon**

Asserted claim 1 of the '035 Patent reads as follows:

#### **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 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 claims of the '035 Patent are directed to detecting a natural phenomenon: the presence of SNPs (DNA code variants) “associated with cancer.” To be sure, the Patent is generic in that it does not purport to teach anything about how to determine which DNA

code variants are associated with particular types of cancer or even which DNA code indicates healthy cells and which indicates cancerous cells. The claimed inventions merely propose amplifying and sequencing DNA that is not from a fetus but that the user is somehow able to associate with cancer.

The reasons for allowance confirm that the claims of the '035 Patent are directed to generically detecting DNA code “associated with cancer.” During prosecution, the Examiner issued a final rejection of all of the pending claims (1-15), rejecting Claims 1-5 and 10-15 as anticipated by U.S. Patent No. 8,318,430 (“Chuu”), Claim 6 as obvious over Chuu in view of Wright et al. 2009, and Claims 7-9 as obvious over Chuu in view of Cronn et al. 2008. Ex. 10. In response, Claim 1, which all of the other claims depend on, was amended to recite sequencing SNP loci comprising 25-2000 loci “associated with cancer.” Ex. 11 at 2. Moreover, the Applicant asserted that “Chuu fails to teach or suggest targeted amplification of 25-2,000 target loci associated with cancer in a single reaction volume.” Ex. 11 at 5. The '035 Patent was subsequently allowed, and the reasons for allowance explain that the amendment to add the DNA “associated with cancer” rather than the DNA of a fetus requirement is what caused the allowance. Ex. 3 at 3. This confirms that the claims of the '035 Patent are directed to a natural phenomenon, satisfying *Alice* Step One.

**2. *Alice* Step Two Is Satisfied Because The Claimed Method Of Detection Does Not Include Inventive New Detection Techniques**

The issue under *Alice* Step Two is whether the claims of the '035 Patent describe an “inventive concept” that is not a natural phenomenon. As explained above in connection with the '454 Patent, the basic techniques of amplifying and sequencing were well known

by the filing date as described by Natera itself. Collateral estoppel applies to this patent too – if Natera attempts to contradict its prior positions. And, importantly, the '035 Patent never states that these prior art techniques were somehow the inventive concept of *this* patent.

The claims of the '035 Patent include three steps, all of which were well known in the art: (1) tagging DNA, (2) amplifying the DNA, and (3) sequencing the DNA. For example, the patent incorporates by reference prior art from 2008 titled “Nested Patch PCR enables highly multiplexed mutation discovery in candidate genes,” authored by Varley et al. (“Varley”). Ex. 4 at 93:41-58 (citing Ex. 5), 250:9-11. Varley demonstrates that the three steps of the '035 Patent were known before the claimed inventions. Ex. 5 at Abstract (“This is the first method that couples *multiplex PCR with sample-specific DNA barcodes and next-generation sequencing* to enable highly multiplex mutation discovery in candidate genes for multiple samples in parallel.”), 1845 (“Sample-specific DNA barcodes are then incorporated into the primers used for the final universal PCR by tailing the 5’ end with sample-specific DNA sequences and 454 sequencing primers”).

As explained, the '035 Patent claims were allowed because they were amended to add that the DNA code being detected was not from a fetus (as would be for fetal diagnostics) but instead is “associated with cancer.” Ex. 3. However, when prosecuting another patent application, Natera inventor Bernhard Zimmermann (who is also an inventor of both the Asserted Patents) submitted an affidavit to the Patent Office stating that detecting cell-free DNA of a cancer tumor is an “equivalent condition” to detecting it from a fetus. Ex. 12 ¶ 10 (“Lastly, it should be noted that cfDNA from a fetus in the plasma or

serum is considered by a person of ordinary skill in the art as an ‘equivalent condition’ to the presence of ctDNA in the relevant art.”). This is not an isolated incident. Rather, Natera has asserted similar arguments on numerous occasions. As another example, when prosecuting another patent that has some of the same inventors as the Asserted Patents (Matthew Rabinowitz, Zachary Demko, and Milena Banjevic) Natera argued that “the same lab techniques including extraction of cell-free DNA, amplification of targeted loci, and sequencing of the amplicons can be used in both the fetal DNA context and cancer DNA context.” Ex. 13 at 5; Ex. 14 at 1, 3, 6. Thus, even if detecting DNA code variants “associated with cancer” instead of from a fetus were eligible subject matter, it is the same thing according to Natera and its inventor and cannot be the basis for finding an inventive concept.

Insofar as Natera again attempts to assert that multiplexing more than 25 locations (loci) of DNA code (sometimes called a 25-plex) in one container is an inventive concept, that is disproven by the ’035 Patent itself. The Patent acknowledges that it was generally known how to perform plexes up to 100. Ex. 4 at 85:14-16 (“Methods described in the prior art used to multiplex more than 50 or 100 reactions in one reaction volume followed by sequencing . . .”). The Patent also admits that the Patent is built on prior art and “fundamental methods” in the prior art “underlie the methods disclosed herein.” Ex. 4 at 93:41-58 (citing Ex. 5, Ex. 6, and Ex. 15).

As one example, the ’035 Patent states that Varley teaches fundamental multiplexing methods underlying the claimed inventions. Ex. 4 at 93:41-58 (citing Ex. 5). The Patent states that the multiplexes in Varley average 9-plexes. Ex. 4 at 53-58 (“A

method comprising *multiplexing of an average of 9 assays* for sequencing is described in” Varley). But that is wrong. Varley teaches **90**-plexes. Ex. 5 at 1845 (“we designed oligonucleotides for **94 exons** from six genes that cause cancer when mutated in the germline (TP53, APC, MLH1, RB1, BRCA1, VHL)”). That is more than the claimed 25-plexes. Because the ’035 Patent acknowledges that the inventors took multiplexes larger than 25-plexes from the prior art, this cannot be an inventive concept. There is no inventive concept that can save the ’035 Patent and it should be invalidated.

### 3. Claim 1 Is Representative

Similarly to the ’454 Patent, the Complaint merely alleges that NeoGenomics infringes “more than one” claim of the ’035 Patent, but does not specifically identify which claims are at issue, and Natera only provided a claim chart for Claim 1 describing alleged infringement. ECF 1 ¶ 38. Thus, Claim 1 of the ’035 Patent, which is the only independent claim and representative, is all that needs to be addressed to resolve this motion. *See Hantz Software*, 2023 WL 2569956, at \*1. The other claims do not add an inventive concept and are also patent ineligible.

## V. CONCLUSION

For the foregoing reasons, NeoGenomics respectfully requests that Plaintiff’s complaint be dismissed.

### **CERTIFICATE OF WORD COUNT**

Pursuant to Local Rule 7.3(d), I certify that this document contains fewer than 6,250 words, excluding the parts of the document that are exempted by Rule 7.3(d). This certificate was prepared in reliance on the word count feature of the word processing software used to prepare this document.

/s/ John F. Morrow, Jr.

John F. Morrow, Jr. (N.C. Bar No.  
23382)

WOMBLE BOND DICKINSON (US)  
LLP

One West Fourth Street  
Winston-Salem, NC 27101

Telephone: 336.721.3584

Facsimile: 336.733.8429

John.Morrow@wbd-us.com

September 5, 2023

Respectfully submitted,

WOMBLE BOND DICKINSON (US)  
LLP

/s/ John F. Morrow, Jr.

John F. Morrow, Jr. (N.C. Bar No.  
23382)

WOMBLE BOND DICKINSON (US)  
LLP

One West Fourth Street  
Winston-Salem, NC 27101

Telephone: 336.721.3584

Facsimile: 336.733.8429

John.Morrow@wbd-us.com

Edward R. Reines\*

Derek C. Walter\*

WEIL, GOTSHAL & MANGES LLP

201 Redwood Shores Parkway

Redwood Shores, CA 94065

Tel: (650) 802-3000

Fax: (650) 802-3100

edward.reines@weil.com

derek.walter@weil.com

*Counsel for Defendant NeoGenomics  
Laboratories, Inc.*

*\* Special Appearance Under Local Rule  
83.1(d)*

## CERTIFICATE OF SERVICE

I hereby certify that I caused the foregoing document to be electronically filed with the Clerk of Court using the EM/ECF system, which will give notice of such filing to all attorneys currently of record in the above-captioned case.

Dated: September 5, 2023

/s/ John F. Morrow, Jr.

John F. Morrow, Jr. (N.C. Bar No. 23382)