

**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

**CONTAINS HIGHLY
CONFIDENTIAL OUTSIDE
ATTORNEYS' EYES ONLY
MATERIAL¹**

DEFENDANT’S FINAL INVALIDITY CONTENTIONS (REDACTED)

Pursuant to Local Rules for Patent Cases LR 103.6, Defendant NeoGenomics Laboratories, Inc. (“NeoGenomics” or “Defendant”) provides the following final invalidity contentions and narrowing of invalidity theories for claims 1, 2, 12, and 13 of U.S. Patent No. 11,519,035 (“the ’035 patent”); and claims 1–28 of U.S. Patent No. 11,530,454 (“the ’454 patent”) (collectively, the “Asserted Patents” and the “Asserted Claims”) that Plaintiff Natera, Inc. (“Natera”) has asserted in its initial infringement contentions, served on February 5, 2024. Defendant reserves all rights with respect to these contentions.

Although the Court has issued a claim construction order, Defendant does not agree with Natera's apparent interpretation of that order as reflected in Natera's infringement contentions. Accordingly, these invalidity contentions do not represent an agreement of view as to either the proper construction of any term in any of the asserted claims or the proper application of the Court's claim construction order to the same. Similarly, nothing herein shall be construed as an admission regarding the application of the Asserted Claims to the accused products or an

¹ Contains Plaintiff-designated material under the Protective Order (Doc. 47). Defendant-designated material originally appearing in these contentions has been redacted.

admission as to claim scope.

Pursuant to the Federal Rules of Civil Procedure, the Local Rules, and Court Orders, Defendant also reserves the right to amend or supplement these invalidity contentions as additional research is conducted, prior art is discovered, discovery is obtained, supplements or modifications are made to the infringement theories advanced by Natera, claim construction positions are taken or subsequent orders are issued, expert discovery is obtained, and for any other reason permitted under the Federal Rules of Civil Procedure, the Local Rules, or Court Orders.

I. INTRODUCTION AND BACKGROUND

The following patents and claims were elected by Natera in its Preliminary Infringement Contentions served on February 5, 2024.

<u>Patent No.</u>	<u>Asserted Claims Against NeoGenomics</u>
US 11,519,035	1, 2, 12, and 13
US 11,530,454	1-28

A. The Asserted Claims of the '035 Patent

Natera asserts claims 1, 2, 12, and 13 of the '035 patent.

Asserted Claim 1 of the '035 patent recites:

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.

Asserted Claim 2 of the '035 patent recites:

2. 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.

Asserted Claim 12 of the '035 patent recites:

12. The method of claim 1, wherein the one or more universal tail adaptors comprise a first universal tail adaptor and a second universal tail adaptor.

Asserted Claim 13 of the '035 patent recites:

13. 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.

B. The Asserted Claims of the '454 Patent

Natera asserts claims 1–28 the '454 patent.

Asserted Claim 1 of the '454 patent recites:

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.

Asserted Claim 2 of the '454 patent recites:

2. The method of claim 1, wherein the cell-free DNA comprises circulating tumor DNA.

Asserted Claim 3 of the '454 patent recites:

3. The method of claim 1, wherein the SNV mutations comprise one or more clonal SNV mutations.

Asserted Claim 4 of the '454 patent recites:

4. The method of claim 1, wherein the SNV mutations comprise one or more subclonal SNV mutations.

Asserted Claim 5 of the '454 patent recites:

5. The method of claim 1, wherein the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations.

Asserted Claim 6 of the '454 patent recites:

6. The method of claim 1, wherein the tumor sample of the subject is a tumor tissue sample.

Asserted Claim 7 of the '454 patent recites:

7. The method of claim 1, wherein the method further comprises determining clonal heterogeneity of the tumor sample.

Asserted Claim 8 of the '454 patent recites:

8. The method of claim 1, wherein the targeted multiplex amplification amplifies 20 to 50 target loci each encompassing a different tumor-specific SNV mutation.

Asserted Claim 9 of the '454 patent recites:

9. The method of claim 1, wherein the targeted multiplex amplification amplifies 50 to 100 target loci each encompassing a different tumor-specific SNV mutation.

Asserted Claim 10 of the '454 patent recites:

10. The method of claim 1, wherein the method further comprises designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample.

Asserted Claim 11 of the '454 patent recites:

11. The method of claim 1, wherein the method further comprises performing barcoding PCR prior to the sequencing.

Asserted Claim 12 of the '454 patent recites:

12. The method of claim 1, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the SNV mutations detected in the cell-free DNA.

Asserted Claim 13 of the '454 patent recites:

13. The method of claim 1, wherein the cancer is colorectal cancer, lung cancer, bladder cancer, or breast cancer.

Asserted Claim 14 of the '454 patent recites:

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.

Asserted Claim 15 of the '454 patent recites:

15. The method of claim 14, wherein the sequencing has a depth of read of at least 50,000 per target locus.

Asserted Claim 16 of the '454 patent recites:

16. The method of claim 14, wherein the cell-free DNA comprises circulating tumor DNA.

Asserted Claim 17 of the '454 patent recites:

17. The method of claim 14, wherein the SNV mutations comprise one or more clonal SNV mutations.

Asserted Claim 18 of the '454 patent recites:

18. The method of claim 14, wherein the SNV mutations comprise one or more subclonal SNV mutations.

Asserted Claim 19 of the '454 patent recites:

19. The method of claim 14, wherein the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations.

Asserted Claim 20 of the '454 patent recites:

20. The method of claim 14, wherein the tumor sample of the subject is a tumor tissue sample.

Asserted Claim 21 of the '454 patent recites:

21. The method of claim 14, wherein the method further comprises determining clonal heterogeneity of the tumor sample.

Asserted Claim 22 of the '454 patent recites:

22. The method of claim 14, wherein the targeted multiplex amplification amplifies 20 to 50 target loci each encompassing a different tumor-specific SNV mutation.

Asserted Claim 23 of the '454 patent recites:

23. The method of claim 14, wherein the targeted multiplex amplification amplifies 50 to 100 target loci each encompassing a different tumor-specific SNV mutation.

Asserted Claim 24 of the '454 patent recites:

24. The method of claim 14, wherein the method further comprises designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample.

Asserted Claim 25 of the ’454 patent recites:

25. The method of claim 14, wherein the method further comprises performing barcoding PCR prior to the sequencing.

Asserted Claim 26 of the ’454 patent recites:

26. The method of claim 14, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the SNV mutations detected in the cell-free DNA.

Asserted Claim 27 of the ’454 patent recites:

27. The method of claim 14, wherein the cancer is colorectal cancer, lung cancer, bladder cancer, or breast cancer.

Asserted Claim 28 of the ’454 patent recites:

28. The method of claim 14, wherein the method is capable of detecting an SNV mutation that is present in 0.005% to 0.015% of the cell-free DNA comprising the SNV locus.

II. PRIORITY DATES

A. ’035 Patent

The ’035 patent issued from U.S. Patent Application No. 16/934,407 (filed on July 21, 2020), which purports to be a continuation of application No. 16/743,724, filed on Jan. 15, 2020, now Pat. No. 10,731,220, which is a continuation of application No. 16/399,268, filed on Apr. 30, 2019, now Pat. No. 10,538,814, which is a continuation of application No. 16/140,298, filed on Sep. 24, 2018, which is a continuation of application No. 14/918,544, filed on Oct. 20, 2015, now Pat. No. 10,316,362, which is a continuation-in-part of application No. 14/877,925, filed on Oct. 7, 2015, now abandoned, and a continuation-in-part of application No. 14/692,703, filed on Apr. 21, 2015, now Pat. No. 10,179,937, and a continuation-in-part of application No. 14/538,982, filed on Nov. 24, 2014, now Pat. No. 9,677,118, said application No. 14/877,925 is a

continuation-in-part of application No. 14/225,356, filed on Mar. 25, 2014, now abandoned, and a continuation-in-part of application No. 13/780,022, filed on Feb. 28, 2013, now abandoned, and a continuation of application No. 13/683,604, filed on Nov. 21, 2012, now abandoned, said application No. 14/225,356 is a continuation of application No. PCT/US2012/058578, filed on Oct. 3, 2012, said application No. 13/780,022 is a continuation-in-part of application No. 13/683,604, filed on Nov. 21, 2012, now abandoned, and a continuation-in-part of application No. PCT/US2012/058578, filed on Oct. 3, 2012, and a continuation-in-part of application No. 13/335,043, filed on Dec. 22, 2011, now Pat. No. 10,113,196, and a continuation-in-part of application No. 13/300,235, filed on Nov. 18, 2011, now Pat. No. 10,017,812, and a continuation-in-part of application No. 13/110,685, filed on May 18, 2011, now Pat. No. 8,825,412, said of application No. 13/300,235, filed on Nov. 18, 2011, now Pat. No. 10,017,812, and a continuation-in-part of application No. 13/110,685, filed on May 18, 2011, now Pat. No. 8,825,412, said application No. PCT/US2012/058578 is a continuation-in-part of application No. 13/300,235, filed on Nov. 18, 2011, now Pat. No. 10,017,812, said application No. 13/335,043 is a continuation-in-part of application No. 13/300,235, filed on Nov. 18, 2011, now Pat. No. 10,017,812, and a continuation-in-part of application No. 13/110,685, filed on May 18, 2011, now Pat. No. 8,825,412, said application No. 13/300,235 is a continuation-in-part of application No. 13/110,685, filed on May 18, 2011, now Pat. No. 8,825,412, which claims priority to provisional application No. 62/148,173, filed on Apr. 14, 2015, provisional application No. 62/146,188, filed on Apr. 10, 2015, provisional application No. 62/147,377, filed on Apr. 14, 2015, provisional application No. 62/066,514, filed on Oct. 21, 2014, provisional application No. 61/994,791, filed on May 16, 2014, provisional application No. 61/987,407, filed on May 1, 2014, provisional application No. 61/982,245, filed on Apr. 21, 2014, provisional application No.

61/634,431, filed on Feb. 29, 2012, provisional application No. 61/675,020, filed on Jul. 24, 2012, provisional application No. 61/683,331, filed on Aug. 15, 2012, provisional application No. 61/542,508, filed on Oct. 3, 2011, provisional application No. 61/426,208, filed on Dec. 22, 2010, provisional application No. 61/571,248, filed on Jun. 23, 2011, provisional application No. 61/516,996, filed on Apr. 12, 2011, provisional application No. 61/448,547, filed on Mar. 2, 2011, provisional application No. 61/462,972, filed on Feb. 9, 2011, provisional application No. 61/398,159, filed on Jun. 21, 2010, provisional application No. 61/395,850, filed on May 18, 2010.

In its Preliminary Infringement Contentions, Natera contends the Asserted Claims of the ’035 patent are entitled to a priority date of “no later than May 18, 2011.”² Preliminary Infringement Contentions at 9.

NeoGenomics contends that no Asserted Claim of the ’035 patent is entitled to a priority date earlier than October 20, 2015. The ’035 patent is part of a chain of continuation and continuation-in-part applications spanning over a decade. Several of those applications were not issued as patents and were abandoned, but served the purpose of keeping the application “alive,” allowing Natera to seek claims—and add new subject matter to the specification—at a later date, for instance, after later publications including Forshew et al., *Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA*, Sci Transl Med 4 (136) (2012). As such, the claims issued in the ’035 patent are not supported by the original

² Natera contends in its second supplemental response to Interrogatory No. 1 that the conception date for the ’035 is “no later than May 18, 2010, the filing date of U.S. Provisional App. No. 61/395,850 to which the ’035 Patent claims priority.” Natera’s Second Suppl. Resp. and Obj. to NeoGenomics Interrogatory No. 1, at 3. Natera has not met its burden to demonstrate the ’035 Patent is entitled to a priority date of May 18, 2010 nor shown diligence from the alleged conception to the alleged reduction to practice date. NeoGenomics accordingly provides these contentions based on the alleged priority date in Natera’s infringement contentions of April 21, 2015, but reserves the right to amend should Natera meet its burden to prove up an earlier priority date.

applications to which they purport to claim priority.

For instance, none of the parent applications that predate U.S. Patent Application No. 14/918,544 filed on October 20, 2015 provide adequate written description or enablement support for the cancer-related limitations requiring that the cell-free DNA is isolated from a blood sample collected “from a subject who is not a pregnant women” and that the SNP loci are “associated with cancer” (the “Cancer Limitations”). To the extent Natera contends such support is provided by, for example, Examples 23, 26, 27, 28, and/or 29, none of those examples were added to the specification until the filing of Application No. 14/918,544 on October 20, 2015.

The Patent Office specifically determined that before those examples were added, the specification lacked written description for cancer detection. During prosecution of U.S. Patent Application No. 14/877,925, to which the '035 patent purports to be a child patent, the applicant proposed claims directed to determining a ploidy status of a chromosome or chromosome segment of a cancer in a plasma sample. The Examiner issued a final rejection under Section 112(a) for lack of written description because “review of the specification did not reveal support for ‘measuring free-floating DNA in a plasma sample of the host that comprises both DNA from normal cells and DNA from cancer’.” 6/6/2018 Final Rejection at 7. The applicant did not respond and the application was abandoned.

Indeed, Natera relied on the Cancer Limitations to overcome the prior art. In the Examiner’s final rejection during prosecution of the '035 patent, the Examiner rejected the claims as anticipated by U.S. 8,318,430 (“Chuu”). Natera overcame Chuu by amending claim 1 to include the Cancer Limitations. 3/3/2021 Amendment and Reply Under 37 CFR 1.116. As support for those amendments, Natera relied on Examples 26-29 including paragraph [0956] of Example 27 (corresponding to 244:52–58 of the '035 Patent).

Other disclosures in the specification confirm that the inventors did not possess the Cancer Limitations before Examples 23, 26, 27, 28, and 29 were added. Claim 1 is directed to single nucleotide polymorphisms (SNPs), which the patent defines as “a single nucleotide that may differ between the genomes of two members of the same species.” ’035 patent at 34:46–50. Accordingly, a POSA reading the specification at the time of Natera’s claimed priority date would have understood the term SNP as not encompassing mutations associated with cell free tumor DNA. The specification confirms that distinction by consistently distinguishing between polymorphisms and “other mutations.” *See, e.g.*, ’035 patent at 8:41–43 (“wherein one or more of the target human loci comprises a polymorphism or other mutation associated with an above normal risk for cancer or associated with cancer”); 10:62–66 (“a sequence (e.g., a polymorphism or other mutation) associated with an increased risk”); 18:29–36 (same). Indeed, the terms “SNV” and “single nucleotide variant” were not added to the specification until the filing of provisional application No. 61/982,245 on April 21, 2014.

This is consistent with documents showing that Natera was only in the initial ideation stages for cancer-related applications in March to May 2013 and did not begin research and development efforts into cancer applications, and particularly those based on nucleotide variants, until after December 2013. For example, Natera was initially considering using loss of heterozygosity to detect cancer in March 2013 but concluded that a method based on loss of heterozygosity would be problematic, based on literature from 2005. NAT-NEO-00572482; NAT-NEO-00652098 at -116. Even by December 2013, Natera had not planned any oncology study design and had not even identified which tumor types to research. (NAT-NEO-00573800 at -804 (“[R]ight now we are in the R&D phase trying to understand what our methodology can

and can’t accomplish”) Only by February 2014 did Natera have a protocol to investigate SNP analysis of blood samples for a cancer-related application. NAT-NEO-00652418.

Separately, NeoGenomics contends that no Asserted Claim of the ’035 patent is entitled to a priority date earlier than July 21, 2020, the filing date of the application that led to the ’035 patent. The purported priority applications listed on the face of the ’035 patent do not provide written support for the Asserted Claims for at least the reasons set forth in section IV.B.1.

B. ’454 Patent

The ’454 patent issued from U.S. Patent Application No. 17/738,354 (filed on May 6, 2022), which is a continuation of U.S. Patent Application No. 17/692,469 (filed on Mar. 11, 2022), which is a continuation of U.S. Patent Application No. 15/898,145 (filed on Feb. 15, 2018, no U.S. Patent No. 11,319,595), which is a continuation of U.S. Patent Application No. 14/692,703 (filed on April 21, 2015, now U.S. Patent No. 10,179,937), which claims priority to U.S. Provisional Application No. 61/982,245 (filed on Apr. 21, 2014), U.S. Provisional Application No. 61,987,407 (filed on May 1, 2014), U.S. Provisional Application No. 62/066,514 (filed on Oct. 21, 2014), U.S. Provisional Application No. 62/146,188 (filed on Apr. 10, 2015), U.S. Provisional Application No. 62/147,377 (filed on Apr. 14, 2015), U.S. Provisional Application No. 62/148,173 (filed on Apr. 15, 2015).

In its Preliminary Infringement Contentions, Natera contends the Asserted Claims of the ’454 patent are entitled to a priority date of “by April 21, 2015.”³ Preliminary Infringement Contentions at 9.

³ Natera contends in its second supplemental response to Interrogatory No. 1 that the conception date for the ’454 is “no later than April 21, 2014, the filing date of U.S. Provisional App. No. 61/982,245 to which the ’454 Patent claims priority.” Natera’s Second Suppl. Resp. and Obj. to NeoGenomics Interrogatory No. 1, at 3. Natera has not met its burden to demonstrate the ’454 Patent is entitled to a priority date of April 21, 2014 nor shown diligence from the alleged conception to the alleged reduction to practice date. NeoGenomics accordingly provides these

To the extent Natera contends the ’454 application is entitled to a priority date earlier than April 21, 2015, the specification lacks adequate disclosure to support such a date. For instance, to the extent Natera contends the specification provides adequate support for “whole exome sequencing” or “whole genome sequencing” or a tumor-informed assay as claimed, for instance in Example 13, that example appeared for the first time in the priority chain in U.S. Patent Application No. 14/692,703 filed on April 21, 2015. Earlier disclosures of “long read sequencing” and “phasing” are unavailing because a POSA at the time of the claimed invention would have understood that “long read sequencing” and “phasing” could be, and often were, accomplished on smaller portions of genomic material than whole exomes or whole genomes.

III. THE ASSERTED CLAIMS ARE INVALID BASED ON THE PRIOR ART

The Asserted Patents are invalid under 35 U.S.C. § 102 and/or 35 U.S.C. § 103 for being anticipated and/or obvious over the prior art and the knowledge of a POSA.

Under 35 U.S.C. § 102, “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). “When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.” *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001).

The question of whether a claimed invention is obvious under § 103 considers the scope and content of the prior art as of the effective filing date of the claim, what the similarities are

contentions based on the alleged priority date in Natera’s infringement contentions of April 21, 2015, but reserves the right to amend should Natera meet its burden to prove up an earlier priority date.

between the claimed invention and the prior art, and what the level of ordinary skill in the art was at the effective filing date. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Where the claimed subject matter is no more than a predictable result of using known prior art elements according to their established functions, the claim is obvious and hence, invalid. *See id.* at 416. In determining whether there are known elements in the prior art, a court can “look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art.” *Id.* at 418. For example, obviousness can be demonstrated by showing “there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent’s claims.” *Id.* at 420. “[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* Common sense also teaches that “familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.” *Id.*

A. The Prior Art

In the accompanying exhibits, Defendant identifies specific exemplary portions of prior art references that disclose the elements of the Asserted Claims. Although Defendant has identified at least one citation per element for each reference, each and every disclosure of the same element in the reference is not necessarily identified. In an effort to focus the issues, Defendant identifies specific portions of the cited references.

It should be recognized that a person of ordinary skill in the art (“POSA”) generally would read a prior art reference as a whole. It should also be recognized that, when evaluating a

prior art reference, a POSA may consult multiple documents about that reference. One of ordinary skill in the art would read these prior art references in the context of other publications, literature, and general knowledge in the field available at the time of the invention described in the Asserted Claims. To understand and interpret any specific statement or disclosure in a prior art reference, a POSA would, when helpful, rely upon other information, including other publications and general scientific or engineering knowledge.

Defendant therefore reserves the right to rely upon other unidentified portions of the prior art references and on other publications and expert testimony to provide context and to aid understanding and interpretation of the identified portions. Defendant also reserves the right to rely upon other portions of the prior art references, other publications, and the testimony of experts to establish that the alleged invention is anticipated or would have been obvious to a POSA, including on the basis of modifying or combining certain cited references. Defendant also reserves the right to rely upon any admissions relating to prior art in the Asserted Patents or their prosecution histories.

Where Defendant identifies a particular figure in a prior art reference, the identification should be understood to encompass the caption and description of the figure, as well as any text relating to the figure, in addition to the figure itself. Similarly, where an identified portion of text refers to a figure or other material, the identification should be understood to include the referenced figure or other material as well.

To the extent that they constitute prior art, Defendant reserves the right to rely upon foreign counterparts of the U.S. Patents identified in these contentions; U.S. counterparts of foreign patents and foreign patent applications identified in these contentions; U.S. and foreign patents and patent applications corresponding to articles and publications identified in these

contentions; and any systems, products, or prior inventions that relate to any references identified in these contentions.

For the purposes of these contentions, the references are named with abbreviated nomenclature, but Defendant reserves the right to give references other nomenclature, labels or titles for expert discovery, trial, other proceedings, briefings, or uses in this litigation.

B. General Knowledge Of A POSA

1. Multiplex PCR

Performing multiplex PCR in a single reaction volume was well known in the art at the time of the claimed inventions. *See, e.g.,* Schochetman et al., *Polymerase Chain Reaction*, 158 J. of Infectious Diseases 6, 1154 (1988) (describing PCR generally); Varley et al., *Nested Patch PCR enables highly multiplexed mutation discovery in candidate genes* 18 GENOME RES. 1844, 1847–48 (2008) (teaching that “nested patch PCR” “should prove useful for the amplification of an intermediate number (100-1000) of candidate regions in a large number of samples” as it is “well suited to these applications because it incorporates sample-specific DNA barcodes, allows for the precise definition of the boundaries of targeted sequences, is reproducible, is highly specific, and uniformly amplifies different alleles at a given locus”); U.S. Patent Application Publication 2004/0126760 at 0025 (filed May 17, 2001) (“[t]he present invention is directed to a method for multiplex polymerase chain reaction (PCR), the simultaneous amplification of different target nucleic acid sequences in a single PCR reaction”), 0057 (“[t]he present invention is preferably used with 5 targets . . . and even more preferably with at least 100 targets”); U.S. Patent No. 7,790,393 at 25:7–14 (filed July 16, 2008) (explaining that the “highly multiplex PCR include[s] hundreds to thousands of products in a single reactions”), 26:63–27:3 (disclosing that in some embodiments “the number of PCR reactions is from about than [sic] 100 to 1,000”);

U.S. Patent Application Publication 2010/0285478 at 212–214 (filed March 26, 2010) (teaching a multiplex reaction with at least 100 targets and at least 100 primer pairs and “[t]he number of different amplification primer pairs utilized in the multiplex amplification is not critical and can range from as few as two, to as many as tens, hundreds, thousands or even more. Thus. . .the multiplex amplifications permit the simultaneous amplification of from as few as two to as many as. . .thousands, or even more polynucleotide sequences of interest”); U.S. Patent Application Publication 2012/0270212 at [0267] (filed No. 18, 2011) (“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 . . .”); *id.* at [0303] (“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.”); *id.* at [0515]–[0516] (teaching an example using 800-plex amplification of DNA); Kaper et al., *Parallel Preparation of Targeted Resequencing Libraries from 480 Genomic Regions Using Multiplex PCR on the Access Array System*, American Association for Cancer Research (AACR) 101st Annual Meeting (2010) (teaching use of an “Access Array” system for scaling up PCR capabilities by using 48 sample inputs with 48 primer sets, thus performing multiplex PCR); Wang et al., *A genotyping system capable of simultaneously analyzing >1000 single nucleotide polymorphisms in a haploid genome*, 15 Genome Research 276, 276–77 (2005) (demonstrating commercialization of systems wherein “universal sequences are attached to the amplicons with different approaches before PCR, allowing >1000 SNP-containing sequences to be amplified in a single reaction” and noting that such systems have “significantly facilitated high-throughput genotyping”).

The ‘035 patent itself describes “the general belief in the art” was that amplifying multiple targets with “multiplexing PCR” was already feasible up “to about 100 assays in the

same well.” ’035 patent at 48:25–29, 85:14–16 (similar), 87:29–57 (similar). *See also* ’035 patent at 2:65–3:4 (describing in the Background section how “simultaneous amplification of many target nucleic acids in a sample of interest can be carried out by combining many oligonucleotide primers with the sample and then subjecting the sample to polymerase chain reaction (PCR) conditions in a process known in the art as multiplex PCR.”); *id.* at 128:57–130:22 (disclosing that some embodiments utilize third-party “multiplex PCR kits”). *See also* ’454 patent at 44:40–42 (“The multiplex PCR and next generation sequencing that may be used increase throughput and reduces costs.”).

Further, Natera agrees multiplex PCR was known in the art at the time of the invention. Natera, Inc.’s Response to Emergency Mot. to Stay P.I. Pending Appeal, 2, *NeoGenomics Labs., Inc. v. Natera, Inc.*, No. 24-1324, 24-1409 (Fed. Cir.) (Dkt. 25-1) (explaining “[p]rior art amplification methods like Multiplex PCR”); Dkt. 145, Michael Metzker Decl. ISO Natera’s Reply ISO Mot. for P.I., ¶255 (“By 2011, one of ordinary skill in the art would have been familiar with multiplex PCR amplification.”); Michael Metzker Depo Trans. Nov. 14, 2023 at 27:9–17 (acknowledging a POSA would have been aware of methods to design primers for multiplex PCR amplification assays that would avoid primer dimers as of the Natera-asserted priority dates of the ’454 and ’035 patents).

Accordingly, performing multiplex PCR in a single reaction volume was routine and conventional at the time of the claimed inventions of the ’035 and ’454 patents.

2. Sequencing Technologies

The use of “next generation,” “high throughput,” and “massively parallel” sequencing for cell-free DNA was also well known in the art at the time of the claimed inventions. For instance, as early as 2000, Lynx Therapeutics (USA) Company had launched one of the first next

generation sequencing technologies, known as Massively Parallel Signature Sequencing (MPSS), which was later acquired by Illumina, Inc. *See* Marina Barba et al., *Historical Perspective, Development and Applications of Next-Generation Sequencing in Plant Virology*, 6 *Viruses* 106, 109 (2014). *See also* John R. ten Bosch & Wayne W. Grody, *Molecular Diagnostics: Techniques and Applications for the Clinical Laboratory* 59–67 (1 ed. 2010) (describing “the uses and potential uses of [massively parallel sequencing] technology in the clinical molecular diagnostic laboratory”); Mardis, *Next-Generation DNA Sequencing Methods*, 9 *Annu. Rev. Genomics Hum. Genet.* 387, 388 (2008) (explaining that, in 2008, “[t]hree platforms for massively parallel DNA sequencing read production are in reasonably widespread use at present: the Roche/454 FLX . . . the Illumina/Solexa Genome Analyzer . . . and the Applied Biosystems SOLiD System”); Shendure et al., *Next-generation DNA sequencing*, 26 *Nature Biotechnology* 10, 1136 (Oct. 2008) (teaching, in 2008, “[a]lternative strategies for DNA sequencing,” including “various implementations of cyclic-array sequencing that have recently been realized in a commercial product (e.g., 454 sequencing . . . Solexa technology . . . the SOLiD platform . . . and the HeliScope Single Molecule Sequencer technology”); Dawson et al., *Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer*, 368 *N. Engl. J. Med.* 13, 1200 (Mar. 28, 2013) (“Advances in sequencing technologies has enabled the rapid identification of somatic genomic alterations in individual tumors.”); Meyerson et al., *Advances in understanding cancer genomes through second-generation sequencing*, 11 *Nature Reviews* 685, Abstract (Oct. 2010) (explaining that the “application of second-generation DNA sequencing technologies (also known as next-generation sequencing)—through whole-genome, whole-exome and whole-transcriptome approaches—is allowing substantial advances in cancer genomics”).

The ‘035 patent itself describes “high throughput next-generation sequencing techniques” or “massively parallel” sequencing technology as known technologies. *See, e.g.*, ‘035 patent at 109:43-49 (describing an embodiment that “may be sequenced using any one of the previous, current, or next generation of sequencing instruments that sequences a clonal sample . . . examples include ILLUMINA GAIIx, ILLUMINA HISEQ, LIFE TECHNOLOGIES SOLiD, 550XL); 120:20-26 (“DNA sequencing techniques, particularly high throughput next-generation sequencing techniques (often referred to as massively parallel sequencing techniques) such as those employed in MYSEQ (ILLUMINA), HISEQ (ILLUMINA), ION TORRENT (LIFE TECHNOLOGIES), GENOME ANALYZER ILX (ILLUMINA), GS FLEX+(ROCHE 454) etc., can be used . . .”).

Further, Natera agrees that “high-throughput” sequencing was a “conventional technique” for cfDNA analysis since at least 2009. *See* Natera, Inc.’s Opening Brief ISO Mot. for Summary Judgment, 2, *CareDx, Inc. et al v. Natera, Inc.*, No. 1:19-cv-00567 (D. Del.) (ECF No. 101) (explaining that “the prior and contemporaneous scientific literature from 2009 and before confirms” that sequencing cfDNA “using ‘multiplex’ or ‘high-throughput’ sequencing” was a conventional technique); *see also* Natera, Inc.’s Concise Statement of Facts ISO Mot. Summary Judgment, 7, *CareDx, Inc. et al v. Natera, Inc.*, No. 1:19-cv-00567 (D. Del.) (ECF No. 102) (contending it was undisputed that “[b]y November 6, 2009 POSAs were using commercial laboratory instruments for high-throughput sequencing of samples comprising cell-free nucleic acids using sequencing-by-synthesis”).

3. Cell-Free DNA Technologies

Techniques for detecting and analyzing cell-free DNA were known in the art at the time of the claimed inventions, and it was known that such techniques could also be used with cell-

free tumor DNA. For instance, in 2006, Yu-Kwan Tong, and Y.M. Dennis Lo published a review paper titled “Diagnostic developments involving cell-free (circulating) nucleic acids” which surveys the history of analyzing cell-free nucleic acids encompassing both circulating tumor and circulating fetal DNA. Tong et al., *Diagnostic developments involving cell-free (circulating) nucleic acids*, Clinica Chimica Acta 363 (2006) 187–196. The paper discusses the “applications” of cancer testing and prenatal diagnosis and describes how “studies of circulating nucleic acids have opened up a new avenue for non-invasive prenatal diagnosis.” *Id.* at 188. *See also, e.g., id.* at Abstract (“Besides circulating DNA and RNA in plasma and serum, cell-free DNA in other body fluids, such as urine, has been detected in patients with different clinical conditions. Regardless of the sources of cell-free DNA for clinical use, the amount is frequently scarce.”); at 192 (“The discovery of circulating nucleic acids has opened up new possibilities for non-invasive detection and monitoring of various disease conditions. In cancer patients, detection and quantification of circulating nucleic acids have shown promise for cancer diagnosis and prognosis. Maternal plasma analysis can be used to detect or exclude certain diseases of the fetus, and quantification of fetal nucleic acids has the potential to be used to screen for certain pregnancy-associated complications. Other applications include monitoring following trauma and stroke, when circulating DNA level is correlated with the severity.”). *See also, e.g.,* Bischoff et al., *Cell-free fetal DNA in maternal blood: kinetics, source and structure*, Human Reproduction Update, Vol. 11, Issue 1 (2005), 59-67 (describing the study of ctDNA beginning in the early 1970s and parallel studies demonstrating fetal DNA in plasma and serum from healthy pregnant women in the 1990s) (citing Lo et al., Circulating DNA in plasma and serum: biology preanalytical issues and diagnostic applications, Clin Chem Lab Med. 40 (2002), 962-968); Swarup et al., Circulating (cell-free nucleic acids) – A promising, non-invasive tool for

early detection of several human diseases, *FEBS Lett.* (2007) (describing the use of quantitative PCR for quantifying circulating nucleic acids in cancer and prenatal contexts); Lo et al., *Next-Generation Sequencing of Plasma/Serum DNA: An Emerging Research and Molecular Diagnostic Tool*, *Clinical Chemistry*, Vol. 55, Issue 4 (2009), 607–608; Chiu et al., *Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma*, *PNAS*, Vol. 105, No. 51 (2008), 20458-20463; Korshunova et al., *Massively parallel bisulphite pyrosequencing reveals the molecular complexity of breast cancer-associated cytosine-methylation patterns obtained from tissue and serum DNA*, *Genome Res.* 18(1) (2008), 19-29; John R. ten Bosch & Wayne W. Grody, *Molecular Diagnostics: Techniques and Applications for the Clinical Laboratory* 59–67 (1 ed. 2010) (teaching methods of ligation- and PCR-mediated tagging of adapters to DNA fragments that can be used on fetal and tumor cfDNA).

4. Minimal Residual Disease Monitoring

Minimal residual disease (“MRD”) monitoring was known in the art at the time of the claimed inventions. MRD is the monitoring of residual cancer that remains after a patient has undergone treatment such as surgery, radiation, or chemotherapy. *See, e.g., Chan, Scanning for Cancer Genomic Changes in Plasma: Toward an Era of Personalized Blood-Based Tumor Markers*, 59 *Clinical Chemistry* 11, 1553 (July 2013) (“The analysis of circulating cell-free tumor DNA has remarkable potential for the detection and monitoring of cancers. Genetic alterations are present in virtually all types of cancers, allowing broad applicability of this approach regardless of the primary organ and histologic type of the cancer.”); Chan et al., *Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing*, 59

Clinical Chemistry 1, 222 (2013) (explaining that MRD monitoring was developed to provide patient-specific care by evaluating a specific individual’s tumor, that tumor’s susceptibility to different treatments, and the individual’s remission or likelihood of remission); Marzese et al., *Diagnostic and prognostic value of circulating tumor-related DNA in cancer patients*, 13 Expert Rev. Mol. Diagn. 8 (2013) (reviewing “the diagnostic and prognostic values of cfDNA in cancer patients”).

MRD monitoring generally involves whole genome sequencing or whole exome sequencing of cancerous DNA to identify cancer-related mutations, as well as follow-up monitoring (involving multiplex PCR and sequencing) of these mutations in cfDNA. *See generally* Forshew et al., *Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA*, 4 Sci. Transl. Med 136 (May 30, 2012); Bashashati et al., *Distinct evolutionary trajectories of primary high-grade serous ovarian cancers revealed through spatial mutational profiling*, 231 J Pathol 21 (2013); *see also* Dawson at 1200 (teaching use of whole genome sequencing for identification of somatic genomic alterations).

MRD monitoring was well known in the art and routinely conducted by at least 2013. *See, e.g.*, Chan at 223 (teaching an MRD approach called “shotgun sequencing”); Forshew at Abstract (teaching an MRD approach called “TAm-Seq”); Leary et al., *Development of Personalized Tumor Biomarkers using Massively Parallel Sequencing*, 2(20) Sci Transl Med, 2 (Feb. 24, 2010) (teaching an MRD approach called “chromosomal rearrangements”).

5. Clonal Heterogeneity

Clonal heterogeneity describes a tumor that includes cells with differing genetic makeup, resulting from continuing mutations as the cancer cells propagate. *See, e.g.*, Bashashati at 22 (“Rooted in the clonal evolution model of tumor progression, cancers are assumed to originate

from a monoclonal composition (the ancestral clone), with subsequent evolution leading to selective expansions of genomically distinct subclones with distinct phenotypic properties.”); Roberts et al., *A comparative analysis of algorithms for somatic SNV detection in cancer*, 29 Bioinformatics Review 18, 2223 (July 9, 2013) (“Cancers arise from a single ancestral cell that has acquired enough somatic mutations to deregulate its own proliferation and expand into a large cell population with clonal mutations matching the ancestral profile. Loss of function in genes for genome stability and repair establishes a mutator phenotype in which a greater rate of somatic mutation provides the cell population with a vast repository of mutations in low copy.”). Each time a cancerous cell divides and grows, there is a chance that it will accumulate more DNA mutations without undergoing apoptosis, a process of pre-programmed cell death. *See, e.g.,* Elmore, *Apoptosis: A Review of Programmed Cell Death*, 35(4) Toxicol Pathol. 495, 10 (Dec. 6, 2007) (describing apoptosis and explaining that “suppression of apoptosis during carcinogenesis is thought to play a central role in the development and progression of some cancers”); Roberts at 2223. A mutation present in the ancestor cancerous cell is a “clonal” mutation, while a mutation present in only a subpopulation of the cancer cells is a “subclonal” mutation. *Id.*

At the time of the claimed inventions, it was well known in the art that tumor heterogeneity is linked to treatment resistance and recurrence of cancer because one subclone of a cancer may be susceptible to a treatment while another may be resistant. *See, e.g.,* Bai et al., *Detection and Clinical Significance of Intratumoral EGFC Mutational Heterogeneity in Chinese Patients with Advanced Non-Small Cell Lung Cancer*, 8 PLOS ONE 2, 6 (Feb. 2013) (“[M]utational heterogeneity may be able to explain resistance mechanism of EGFR-TKI.”); Bashashati at 22 (“The concept of intratumoural heterogeneity has long been blamed for

treatment failure in ovarian carcinoma and other primary cancers.”). Furthermore, it was well known in the art at the time of the claimed inventions that tracking and measuring tumor heterogeneity can be done using the same techniques discussed above, including with cfDNA. *See, e.g.,* Bashashati at 22 (“[E]xamination of plasma cfDNA suggested that representative mutations in the ancestral clone and mutations present in subclones could be detected in ctDNA.”).

C. Prior Art to the '035 Patent⁴

1. Patent or Patent Application Prior Art

<u>Patent No. & Country of Origin</u>	<u>Filing or Priority Date</u>	<u>Date of Issue or Publication</u>	<u>Cited As</u>	<u>Prior Art Status⁵</u>	<u>Chart</u>
U.S. Patent Application Publication No. 2004/0110153	December 10, 2002	June 10, 2004	Dong	102(a), (b), (e)	Exhibit 1-A
U.S. Patent No. 8,318,434	September 22, 2008	November 27, 2012	Cuppens	102(e)	Exhibit 1-B
WO 2010/115154	April 2, 2009	October 7, 2010	May PCT	102(a), (e)	Exhibit 1-C
WO 2011/142836	May 14, 2010	November 17, 2011	Pieprzyk	102(e)	Exhibit 1-D
U.S. Patent Application No. 2010/0120038	January 22, 2009	May 13, 2010	Mir	102(a), (b), (e)	Exhibit 1-E

⁴ During the preliminary injunction briefing, Natera asserted a theory of infringement based on a reading of the Asserted Claims of the '035 Patent that the claimed tagging and amplification steps could be satisfied by a single round of PCR using a single set of primers. Neogenomics includes in the accompanying claim charts disclosures of the Asserted Claims under Natera's apparent construction, but reserves all rights to oppose that construction.

⁵ As explained above, NeoGenomics contends that the Asserted Claims are not entitled to an effective filing date earlier than October 20, 2015, such that the identified references are prior art under AIA-§102(a). For purposes of these contentions, NeoGenomics discloses the prior art status of the asserted references based on Natera's contention that the '035 Patent claims priority to no later than May 18, 2011. Thus, the table lists the references' prior art status under pre-AIA § 102.

<u>Patent No. & Country of Origin</u>	<u>Filing or Priority Date</u>	<u>Date of Issue or Publication</u>	<u>Cited As</u>	<u>Prior Art Status⁵</u>	<u>Chart</u>
WO 2010/126,614	April 30, 2009	November 4, 2010	Porreca	102(a), (e)	Exhibit 1-F
International Patent Publication No. 2007/18601	August 2, 2005	February 15, 2007	Makarov	102(a), (b), (e)	Exhibit 1-G
U.S. Patent Application No. 2013/0178371	January 25, 2011	July 11, 2013	Oliphant	102(a), (e)	Exhibit 1-H
International Patent Publication No. 2011/085491	January 15, 2010	July 21, 2011	Hansen	102(a), (e)	Exhibit 1-I
U.S. Patent No. 6,420,117	September 14, 1999	July 16, 2002	Wessler	102(a)	Various
International Patent Publication No. 2007/140417	May 31, 2006	December 6, 2007	Hoyal	102(a)	Various

2. Non-Patent Literature Prior Art

<u>Title</u>	<u>Date of Publication</u>	<u>Cited As</u>	<u>Prior Art Status</u>	<u>Chart</u>
MARA: a novel approach for highly multiplexed locus-specific SNP genotyping using high-density DNA oligonucleotide arrays, Nucleic Acids Research, Vol. 32, No. 22	December 15, 2004	Shapero	102(a), (b)	Exhibit 1-J
Parallel Preparation of Targeted Resequencing Libraries from 480 Genomics Regions Using	April 17-21, 2010 (AACR Annual Conference)	Kaper	102(a), (b)	Exhibit 1-K

<u>Title</u>	<u>Date of Publication</u>	<u>Cited As</u>	<u>Prior Art Status</u>	<u>Chart</u>
Multiplex PCR on the Access Array™ System				
Parallel Production of Barcoded Amplicon Libraries for 454 Sequencing using Individual an Multiplex PCR in Nanoliter Volumes	February 24-27, 2010 (ABGT Annual Conference)	May Poster	102(a), (b)	Exhibit 1-L
Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA, Science Translational Medicine, Vol. 4, Iss. 136	May 30, 2012	Forsheew	102(a), (b) (pre-AIA and AIA) ⁶	Exhibit 1-M

D. Prior Art to the '454 Patent

1. Patent or Patent Application Prior Art

<u>Patent No. & Country of Origin</u>	<u>Filing or Priority Date</u>	<u>Date of Issue or Publication</u>	<u>Cited As</u>	<u>Prior Art Status⁷</u>	<u>Chart</u>
U.S. Patent Application Publication No. 2010/0261189	April 15, 2009	October 14, 2010	Bentley	102(a)	Exhibit 2-F
WO 2013/138510	March 13, 2012	September 19, 2013	Patel	102(a)	Exhibit 2-A, 2-D

⁶ To the extent the Asserted Claims of the '035 patent are not entitled to Natera's claimed priority date asserted in Natera's Preliminary Infringement Contentions served February 5, 2024, NeoGenomics asserts Forsheew as prior art to the '035 patent and expressly reserves the right to amend these contentions to add additional prior art based on the accorded priority date. For instance, Natera touts having "a substantial intellectual property portfolio with over 150 issued patents and over 220 pending patent applications as of December 31, 2022." (D.I. 7, Malani Decl. ¶ 74). NeoGenomics's discovery into Natera's expansive patent portfolio is ongoing and NeoGenomics reserves the right to supplement its contentions based the results of such discovery pursuant to Local Rule 103.6(b).

⁷ For purposes of these contentions, NeoGenomics discloses the prior art status of the asserted references under the AIA based on Natera's contention that the '454 Patent claims priority to no later than April 21, 2015.

U.S. Patent No. 11,384,394	January 17, 2013	July 12, 2022	Bartha	102(a)	Exhibit 2-D
U.S. Patent Application Publication No. 2016/0032396	March 15, 2013	February 4, 2016	Diehn	102(a)	Exhibit 2-D

2. Non-Patent Literature Prior Art

<u>Title</u>	<u>Date of Publication</u>	<u>Cited As</u>	<u>Prior Art Status</u>	<u>Chart</u>
Detection and Clinical Significance of Intratumoral <i>ECFR</i> Mutational heterogeneity in Chinese Patients with Advanced Non-Small Cell Lung Cancer, PLOS One, Vol. 8, Iss. 2	February 13, 2013	Bai	102(a)	Exhibits 2-D, 2-E, and 2-F
Distinct evolutionary trajectories of primary high-grade serous ovarian cancers revealed through spatial mutational profiling, Journal of Pathology 2013; 231:21–34	June 7, 2013	Bashashati	102(a)	Exhibit 2-B, 2-E
Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA, Science Translational Medicine, Vol. 4, Iss. 136	May 30, 2012	Forsheew	102(a)	Exhibit 2-C, 2-D, 2-E, and 2-F
Ultrasensitive Measurement of Hotspot Mutations in Tumor DNA in Blood Using Error-Suppressed Multiplexed Deep Sequencing, Cancer Research, 72(14)	July 15, 2012	Narayan	102(a)	Exhibit 2-D, 2-F
Influence of Plasma Processing on Recovery and Analysis of Circulating Nucleic Acids, PLOS ONE, Vol. 8, Iss. 10	Oct. 18, 2013	Page	102(a)	Exhibit 2-D, 2-E, and 2-F
Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer, N Engl J Med 368:13	Mar. 28, 2013	Dawson	102(a), (b)	Exhibit 2-D

E. Prior Art Combinations**1. '035 Patent**

As referenced and discussed in the claim charts attached as Exhibits 1-A to 1-M, multiple prior art references teach or suggest the concepts claimed in the '035 patent. To the extent Natera argues that any concepts claimed in the '035 patent were not contained in any prior art reference, it would, at a minimum, have been obvious to adapt each reference to include the concept or combine it with other references that disclose the concept. In addition, each of the constituent techniques required to carry out the steps of the claimed methods were well-known to those of skill in the art. The reasons for modifying or combining references and for a reasonable expectation of success include at least those identified in Exhibits 1-A to 1-M.

The Asserted Claims of the '035 patent are obvious in light of at least the following combination(s) of prior art:

- Dong on its own or in view of Cuppens, May PCT, Pieprzyk, Shapero, Mir, Porreca, Kaper, Oliphant, Hansen, May Poster or the knowledge of a POSA. (*See* Ex. 1-A)
- Cuppens on its own or in view of Pieprzyk, Mir, May PCT, Makarov, Shapero, Porreca, Dong, Hansen, or the knowledge of a POSA. (*See* Ex. 1-B)
- May PCT on its own or in view of Makarov, Porreca, Shapero, Dong, or the knowledge of a POSA. (*See* Ex. 1-C)
- Pieprzyk on its own or in view of Makarov, Porreca, Shapero, Dong, or the knowledge of a POSA. (*See* Ex. 1-D)
- Mir on its own or in view of Makarov, Shapero, Porreca, Dong, or the knowledge of a POSA. (*See* Ex. 1-E)

- Porreca on its own or in view of Makarov, Hansen, Pieprzyk, or the knowledge of a POSA. (*See* Ex. 1-F)
- Makarov on its own or in view of Cuppens, May PCT, Pieprzyk, Shapero, Mir, Porreca, Kaper, Oliphant, Hansen, May Poster or the knowledge of a POSA. (*See* Ex. 1-G)
- Oliphant on its own or in view of Makarov, Shapero, Porreca, Dong, Pieprzyk, May PCT, Hansen, or the knowledge of a POSA. (*See* Ex. 1-H)
- Hansen on its own or in view of Makarov, Shapero, Porreca, Dong, Hoyal, Wessler, or the knowledge of a POSA. (*See* Ex. 1-I)
- Kaper on its own or in view of Pieprzyk, Hansen, Makarov, Shapero, Porreca, Dong, Hoyal, Wessler, or the knowledge of a POSA. (*See* Ex. 1-K)
- May Poster on its own or in view of Pieprzyk, Makarov, Shapero, Porreca, Dong, Hoyal, Wessler, or the knowledge of a POSA. (*See* Ex. 1-L)
- Forshew on its own or in view of Dong, Cuppens, Shapero, Porreca, Oliphant, Makarov, Hoyal, Wessler, or the knowledge of a POSA. (*See* Ex. 1-M)

2. '454 Patent

As referenced and discussed in the claim charts attached as Exhibits 2D, 2E, and 2F, multiple prior art references teach or suggest the concepts claimed in the '454 patent. To the extent Natera argues that any concepts claimed in the '454 patent were not contained in any prior art reference, it would, at a minimum, have been obvious to adapt each reference to include the concept or combine it with other references that disclose the concept. In addition, each of the constituent techniques required to carry out the steps of the claimed methods were well-known to those of skill in the art. The reasons for modifying or combining references and for a reasonable

expectation of success include at least those identified in Exhibits 2D, 2E, and 2F, which are incorporated by reference into this section.

The Asserted Claims of the ’454 patent are obvious light of at least the following combination(s) of prior art:

- Patel on its own or in view of Bai, Bashashati, Forshew, Page, Dawson, Diehn, Bartha, or the knowledge of a POSA. (See Exs. 2-A, 2-D)
- Bashashati on its own or in view of Forshew, Bai, Patel, Page, or the knowledge of a POSA (See Exs. 2-B, 2-E)
- Forshew on its own or in view of Bai, Bashashati, Patel, Bentley, Narayan, Page, or the knowledge of a POSA, including as evidenced by NEOGEN00275278–NEOGEN00275334 and NEOGEN00275270–NEOGEN0027527. (See Exs. 2-C, 2-F)

F. Objective Indicia of Non-obviousness

Evidence of objective indicia must be considered in conducting an obviousness analysis. *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1080 (Fed. Cir. 2012). However, with any such showing, evidence of objective indicia of non-obviousness must be commensurate in scope with the claims. There must be a nexus between the asserted indicia, such as unexpected results, and the claimed invention. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 963 (Fed. Cir. 2014). “For objective evidence of secondary considerations to be accorded substantial weight, its proponents must establish a nexus between the evidence and the merits of *the claimed invention*.” *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quoting *Wyers*, 616 F.3d at 1246 (emphasis added)). Where objective indicia “result[] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention.” *Id.* “We have repeatedly held that evidence of commercial success must have

a nexus to the claims to be given weight in an obviousness analysis. In other words, there must be a legally and factually sufficient connection between the evidence and the patent claims. . . . Simply speaking, there may be many reasons a product is commercially successful; it is only where the success is due to the claimed invention that commercial success can show nonobviousness.” *UCB, Inc. v. Actavis Lab'ys UT, Inc.*, 65 F.4th 679, 695 (Fed. Cir. 2023).

Plaintiff has not provided evidence or analysis of how Signatera practices the Asserted Claims on a limitation-by-limitation basis for either of the Asserted Patents. With respect to the ’454 patent, Plaintiff has not provided evidence, for example, that Signatera achieves sequencing with a depth of read of at least 50,000 per target locus (claim 1); or that Signatera is capable of detecting an SNV mutation that is present in less than 0.015% of the cell-free DNA comprising the SNV locus (claim 14, claim 28); or that Signatera achieves targeted multiplex amplification of 20 to 50 target loci each encompassing a different tumor-specific SNV mutation (claim 8, claim 22); or that Signatera achieves targeted multiplex amplification of 50 to 100 target loci each encompassing a different tumor-specific SNV mutation (claim 9, claim 23). With respect to the ’035 patent, Plaintiff has not provided evidence, for example, that Signatera sequences 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 (claim 1); or that Signatera uses a first universal tail adaptor and a second universal tail adaptor (claim 12, claim 13); or that Signatera achieves tagging cell free DNA with a first primer comprising a first universal tail adaptor and a second universal tail adaptor (claim 13).

Plaintiff alleges that Signatera has received industry praise, awards, and is commercially successful. *See* Natera’s Response to Interrogatory No. 13. But Plaintiff has not shown that the alleged commercial success, industry praise, or awards relating to Signatera are due to the “novel features” of any Asserted Claim of any of the Asserted Patents. For example, FDA Breakthrough Device Designation eligibility is based in part on the disease or condition that the product intends to

treat rather than the product itself, and a product does not require breakthrough technology to be eligible. Nor has Plaintiff shown that Signatera is coextensive with any, let alone all, of the Asserted Claims. The specifications of the Asserted Patents describe many alternative methods and techniques for amplifying, sequencing and detecting cfDNA, none of which are actually required by the Asserted Claims. Natera has not demonstrated a sufficient nexus between the alleged secondary considerations and the Asserted Claims.

NeoGenomics reserves all rights to respond to any objective indicia of non-obviousness that Plaintiff may later assert. Should Plaintiff identify any additional objective indicia of non-obviousness, NeoGenomics reserves all rights to respond to and rely upon further references not cited herein to rebut those objective indicia of non-obviousness.

As another example, simultaneous invention, when it occurs within a short space of time from the alleged date of invention, “is strong evidence of what constitutes the level of ordinary skill in the art” and may demonstrate the obviousness of an invention. *Ecolochem v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000). For instance, Natera has argued that NeoGenomics’s RaDaR product infringes the ’035 patent based on Forshew, describing use of Access Array with cell-free DNA. Forshew et al., *Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA*, Sci Transl Med 4 (136) (2012). That article was submitted for publication just months after the alleged priority date of the ’035 patent and before the application was public, and so supports a finding that Forshew independently developed use of Access Array with cell-free DNA contemporaneously with the purported 2011 priority date. Moreover, as discussed above, the work that ultimately led to the publication of Forshew began around December 2010 and included the detection of mutations in cfDNA of a cancer patient using the methods described in Forshew around March 2011. *See, e.g.*, NEOGEN00275278–NEOGEN00275334 and NEOGEN00275270–NEOGEN00275277. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Such “independent” actions “within a comparatively short space of time” are “persuasive evidence” of obviousness. *Concrete Appliances Co. v. Gomery et al.*, 269 U.S. 177, 185 (1925).

G. The Asserted Claims are Invalid for Obviousness-Type Double Patenting

The doctrine of obviousness-type double patenting was created by the courts to “prevent claims in separate applications or patents that do not recite the ‘same’ invention, but nonetheless claim inventions so alike that granting both exclusive rights would effectively extend the life of patent protection.” *In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013) (quoting *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1373 (Fed. Cir. 2005)). Obviousness-type double patenting “prevent[s] the extension of the term of a patent . . . by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent.” *Boehringer Ingelheim Int’l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1346 (Fed. Cir. 2010) (cleaned up). An obviousness-type double-patenting analysis, which “compares claims in an earlier patent to claims in a later patent or application,” requires that the court “construes the claims in the earlier patent and the claims in the later patent and determines the differences,” and then “determines whether those differences render the claims patentably distinct.” *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008). In considering whether the claims in the later patent are obvious, a court considers whether the claims are obvious in view of the prior art as a whole. *In re Longi*, 759 F.2d 887, 893 (Fed. Cir. 1985) (“Under that facet of the doctrine of double patenting, we must direct our inquiry to whether the claimed invention in the application for the second patent would have been obvious from the subject matter of the claims in the first

patent, *in light of the prior art.*”) (emphasis added). Patents may be shown to be invalid under statutory or non-statutory principles of obviousness-type double patenting. *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014). The Federal Circuit made “explicit what was implicit in *Gilead*: the doctrine of obviousness-type double patenting continues to apply where two patents that claim the same invention have different expiration dates.” *Id.* The Court noted the doctrine also prevents an inventor from securing a second, later expiring patent for the same invention. *Id.* at 1373. “Obviousness-type double patenting is a judicially created doctrine that ‘prohibit[s] a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent.’” *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008) (internal citation omitted). The same claims analyzed below are invalid under § 101 for statutory double patenting.

Natera touts having “a substantial intellectual property portfolio with over 150 issued patents and over 220 pending patent applications as of December 31, 2022.” (D.I. 7, Malani Decl. ¶ 74). On information and belief, the Asserted Claims are invalid for obviousness-type double patenting over certain of the vast number of claims of earlier-expiring patents commonly owned with the Asserted Claims and/or with overlapping inventors.

NeoGenomics’s discovery into Natera’s expansive patent portfolio is ongoing and NeoGenomics reserves the right to supplement its contentions based the results of such discovery pursuant to Local Rule 103.6(b). To the extent Plaintiffs contend any reference is disqualified under pre-AIA § 103(c), NeoGenomics may also rely on that reference as an OTDP patent if it is an earlier-expiring patent (or has an earlier-expiring U.S. Patent in the same family).

IV. THE ASSERTED CLAIMS ARE INVALID UNDER 35 U.S.C. § 112

Defendant contends that the Asserted Claims are invalid under 35 U.S.C. § 112 for lack of written description, lack of enablement, and/or indefiniteness. Defendant reserves the right to supplement these disclosures based on further investigation and discovery.

A. Indefiniteness

The following terms of the Asserted Claims fail to convey with reasonable certainty the scope of the claims in which the terms appear. Accordingly, the claims below and their dependent claims are invalid as indefinite.

Where the claims of a patent, read in light of its specification and prosecution history, fail to inform those skilled in the art about the scope of the invention with reasonable certainty, such claims are invalid under 35 U.S.C. § 112 for indefiniteness. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). Indefiniteness may exist where elements specified by the claim may be measured or assessed by a variety of means, none of which are written into the claim. In such instances, where something falls within the scope of the claim when assessed or measured by one means, but is excluded from the scope of the claim when assessed or measured by another means, the claim is invalid for indefiniteness. *Dow Chemical Co. v. NOVA Chemicals Corp. (Canada)*, 803 F.3d 620, 634–35 (Fed. Cir. 2015); *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1344–45 (Fed. Cir. 2015).

1. '035 Patent

a. “amplification steps”

Claim 1 of the '035 patent is directed to “amplifying the tagged products one or more times to generate final amplification products, wherein one of the amplification steps comprises targeted amplification.” All the Asserted Claims of the '035 patent depend, directly or indirectly, from claim 1.

Natera contends the “amplification step” of targeted amplification can include the “tagging” limitation of the claim. In its Preliminary Infringement Contentions, Natera contends RaDaR infringes because “common tail sequences (i.e., CS1 and CS2) are added to each end of a target sequence in a pre-amplification step via PCR to generate a tagged product” which one of ordinary skill in the art would have understood is a universal tail adaptor. Preliminary Infringement Contentions, Ex. 1 at 7. The specification however describes the universal amplification step as distinct from the targeted amplification step: “For example, a universal amplification step of the DNA prior to targeted amplification may confer several advantages, such as removing the risk of bottlenecking and reducing allelic bias.” ’035 patent at 105:60–63. As discussed above, the specification discloses no working examples of amplifying cfDNA where the universal tail adapters are added in the same PCR step as the targeted amplification, let alone doing so followed by massively parallel sequencing a plurality of 25-2,000 loci associated with cancer. Instead, the specification describes numerous embodiments of a two-step process involving (1) a universal amplification performed using universal priming sites that have been ligated to the cell free DNA, followed by (2) a targeted amplification using a distinct set of primers. *See, e.g.*, ’035 patent at 10:16–23, 15:52–60, 94:13–25, Example 27.

Accordingly, to the extent Natera contends that the targeted amplification “step” can include the “tagging” limitation, the specification fails to adequately explain how a POSA is to determine the claimed method of tagging. A POSA reading the claims in light of the specification would fail to understand the meaning of “step,” and would not understand the scope of the claimed invention with reasonable certainty. For at least these reasons, the claims are invalid for being indefinite.

b. “single nucleotide polymorphism (SNP)”

Claim 1 of the ’035 patent is directed to targeted amplification and sequencing of a “plurality of single nucleotide polymorphism (SNP) loci” on the cell free DNA. All the Asserted Claims of the ’035 patent depend, directly or indirectly, from claim 1. Natera alleges that NeoGenomics’s RaDaR product, which detects mutations in cell free tumor DNA, infringes these claims.

To the extent Natera contends the term SNP encompasses mutations associated with cell free tumor DNA, a POSA reading the specification would not understand the meaning of the term. The specification defines “Single Nucleotide Polymorphism (SNP)” as “a single nucleotide that may differ between the genomes of two members of the same species,” ’035 patent at 34:45–47. Natera’s apparent construction of SNP to include non-germline mutations conflicts not only with that express definition in the specification but also with a POSA’s understanding of the term in the art. Moreover, as discussed above, Examples 23, 26, 27, 28, and 29, the only examples arguably involving cell free tumor DNA, were not added to the specification until the filing of U.S. Patent Application No. 14/918,544 in October 2015. And the terms “SNV” and “single nucleotide variant” were not added to the specification until the filing of provisional application No. 61/982,245 on April 21, 2014. Accordingly, a POSA reading the specification at the time of Natera’s claimed priority date, prior to when those examples and disclosures were added, would not have understood the scope of the claims to include detection of SNVs from cell-free tumor DNA. The specification also confirms that distinction by consistently distinguishing between polymorphisms and “other mutations.” *See, e.g.*, ’035 patent at 8:41–43 (“wherein one or more of the target human loci comprises a polymorphism or other mutation associated with an above normal risk for cancer or associated

with cancer”); 10:62–66 (“a sequence (e.g., a polymorphism or other mutation) associated with an increased risk”); 18:29–36 (same).

To the extent Natera contends that the claimed methods involving amplifying and sequencing mutations in cell free tumor DNA, the claims are invalid as indefinite as a POSA would not understand the term SNP and would be unable to determine *a priori* what types of genetic variants fall within the claims. For at least these reasons, the claims are invalid for being indefinite.

2. ’454 Patent

a. **Multiplex amplification of “10 to 500 target loci each encompassing a different tumor-specific SNV mutation.”**

Claim 1 of the ’454 patent is directed to “performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation.” It is unclear, however, whether the claim requires “targeted multiplex amplification” with a different primer pair for each of the “target loci” (*i.e.*, 10 to 500 primer pairs), or whether only two or more primer pairs can be used for multiplex amplification of two or more regions encompassing 10 to 500 target loci. The specification does not provide any definition of loci “encompassing” tumor-specific SNVs. Further, the specification describes “a multiplex amplification reaction, wherein each amplicon of the series of amplicons spans at least one polymorphic loci of the set of polymorphic loci and wherein each of the polymorphic loci of the set is amplified.” ’454 patent at 58:36–40. The scope of the term “loci” is rendered even more unclear by Natera’s assertion in parallel Delaware district court proceedings regarding another patent in the same family that “each base” in any given amplicon is a “polymorphic locus relating to cancer-associated aneuploidy.” Natera’s Initial Claim Chart for U.S. Patent No. 10,262,755, *Natera, Inc. v. Inivata, Inc. et al*, Case No. 1:21-cv-00056-CBW (D. Del.), at 29. Accordingly, a POSA

reading the specification would not know whether there could be multiple target loci per amplicon.

Additionally, to the extent Natera contends that amplification of a tumor-specific SNV at each of the 10 to 500 target loci is not required by the claims, such a reading also supports a finding that the claim limitation is indefinite. For example, Figures 47–50 show the analysis of samples with tumor-specific SNVs and/or CNVs present, but some of those results did not show detectible amplification of such SNVs and/or CNVs. ’454 patent at Figs. 47–50 and accompanying text. A POSA would not know whether amplifying no tumor-specific SNVs or amplifying a single tumor-specific SNV would be within the scope of the claim.

b. Amplification of “a different tumor-specific SNV mutation.”

Claims 1 and 14 recite “performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations,” and then recite “performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation.” ’454 at 171:29–34. The phrase “a plurality of tumor-specific SNV mutations” does not provide antecedent basis for the phrase “a different tumor-specific SNV mutation. A POSA, therefore, would not be able to determine whether the “different tumor-specific SNV mutation” encompassed by the loci in the amplification step must be a tumor-specific SNV mutation *of the plurality of tumor-specific SNV mutations* identified in the whole exome sequencing or whole genome sequencing step, or if a “different tumor-specific SNV mutation” can be an SNV mutation not included in the “plurality of tumor-specific SNV mutations.”

c. “[D]esigning PCR primers or hybrid capture probes”

Claims 10 and 24 recite a method that comprises “designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample.” ’454 patent at 171:64–67, 172:54–57. For reasons similar to those set forth in subsection (a) above, it would not be clear to a POSA, however, whether the claims require designing a *different* PCR primer or hybrid capture probe for each of the plurality of SNV mutations identified in the tumor sample, or whether the claims encompass designing one or more PCR primer pairs or hybrid capture probes for a region encompassing the plurality of SNV mutations.

B. Lack of Written Description and Enablement

The Asserted Patents fail to convey that the inventor(s) were in possession of the claimed subject matter because the following terms are not described in the respective specifications. Accordingly, the claims below and their dependent claims are invalid for lacking written description support.

A patentee is required to provide a disclosure sufficient to convey with reasonable clarity to persons skilled in the art, as of the effective filing date, that the patentee in fact invented what is claimed. *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2014). That is, the patent specification, including its figures and claims, must allow a skilled artisan to easily recognize that the patentee was in possession of the claimed invention as of his/her asserted priority date. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Compliance with the written description requirement involves both an assessment of the scope of the claims and the adequacy of the specification to support claims of such scope. *See id.* The test requires an objective inquiry into the four corners of the

specification from the perspective of a person of ordinary skill in the art. *Id.* A description that merely renders the invention obvious does not satisfy the requirement. *Id.* at 1352.

If the claims of a patent cover generic-scope inventions, the specification is assessed for sufficient disclosure of species within the claimed genus. *See id.* at 1350. When a claim is phrased in functional language, a limited number of disclosed species may adequately support it if there is a known correlation between structure and function. *See id.* at 1350. However, where there is no known structure/function correlation, an appropriate number of species representative of the claimed genus across its scope must be disclosed. *Id.* Furthermore, numerous species that are closely related, i.e., derived from a common parent or the like, are not considered independently representative. *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300–01 (Fed. Cir. 2014). Their disclosure, thus, does not count as a disclosure of multiple representative species in the assessment of whether there is adequate support for the claim. *Id.*

Additionally, evidence showing that a claimed genus does not disclose a representative number of species may include evidence of species that fall within the claimed genus that are not disclosed by the patent, but, instead, postdate the priority date of the patent. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017).

The specification must “demonstrate that the patentee possessed the full scope of the invention recited in” the claims. *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). The claims may be no broader than the supporting disclosure, particularly where the patentee has indicated that a certain feature is an essential element of the invention. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) (“It is a truism that a claim need not be limited to a preferred embodiment. However, in a given case, the scope of the right to exclude may be limited by a narrow disclosure.”).

The Asserted Patents also fail to enable a POSA to practice the full scope of the Asserted Claims. Accordingly, the claims below are invalid for lack of enablement.

To satisfy the enablement requirement, a patent specification must teach a person of ordinary skill in the art how to make and use the claimed invention without undue experimentation. *Wyeth v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). The person of ordinary skill can draw upon what is already known in the art as of the effective filing date of the patent. Thus, the extent to which a patent enables its claims to be practiced without undue experimentation is based on the teachings of the specification and the knowledge of one of ordinary skill in the art. A patent specification is not enabling if it amounts to no more than an invitation to a person of ordinary skill to engage in research that may or may not result in the claimed invention. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374-75 (Fed. Cir. 1999). The degree to which a patent specification is enabling must be at least commensurate with the scope of the claims. *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012). If claims are not enabled across their scope, they are invalid for failure to comply with the enablement requirement of 35 U.S.C. § 112. *Id.*

The enablement requirement has both a “[how] to make” aspect and a “how to use” aspect. *Id.*; *see Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1322–23 (Fed. Cir. 2005). A person of ordinary skill in the art must be able to make the claimed invention across its scope without undue experimentation. *Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195–96 (Fed. Cir. 1999). Under the “how to use” prong of enablement, the specification must disclose a practical utility for the invention and the specification must also enable the skilled artisan to use the invention so as to achieve that utility. *Rasmusson*, 413 F.3d at 1322-23.

In determining whether the disclosure of a patent would require undue experimentation, several factors are considered, including: (1) the amount of experimentation necessary; (2) the amount of guidance presented in the patent; (3) whether the patent discloses specific working examples of the claimed invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the nature and predictability of the field; and (8) the breadth of the claims. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

In judging whether or not a patent specification is enabling, post-filing date references may be considered. Post-filing date references that show a claimed invention remained unknown or was never achieved after the filing date is evidence that the patent lacks an enabling disclosure. *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254–55 (Fed. Cir. 2004).

1. '035 Patent

The Asserted Claims of the '035 patent, claims 1, 2, 12, and 13, lack adequate written description and enablement.

a. Combination of Steps in Asserted Claims

The Asserted Claims of the '035 patent are invalid for lack of written description because the '035 patent specification does not disclose adequate support for the particular claimed combination of steps. Many of the individual concepts recited in the claims, such as multiplex PCR, molecular barcodes, and sequencing amplicons were known in the art and were routine and conventional at the time of the claimed invention such that a POSA would have known of and how to use those individual techniques. Therefore, to the extent there is anything inventive in the Asserted Claims, it must reside in the combination of recited elements. But none of the embodiments or other disclosures demonstrate that the inventors possessed the combination of all the elements in the manner claimed. For instance, the specification discloses no working

examples of performing tagging, amplification, and sequencing on isolated cell free DNA as claimed for 2,000 loci associated with cancer. Based on the disclosures in the specification, it would require undue experimentation for a POSA to combine all of those individual concepts in the claimed manner. Accordingly, to the extent Natera contends that disparate disclosures throughout the specification disclose each of the elements separately, such disclosure is insufficient on its own to satisfy the requirements for written description and enablement.

b. Tagging and Amplifying Using the Same Primers

The Asserted Claims of the ’035 patent are directed to a method of “tagging isolated cell free DNA with one or more universal tail adapters to generate tagged products” and “amplifying the tagged products one or more time to generate final amplification products, wherein one of the amplification steps comprises targeted amplification.”

Natera contends that the claimed tagging and amplification steps can be infringed by a single round of PCR using a single set of primers. The ’035 patent lacks adequate written description support such that a POSA reading the specification would not understand that the inventors were in possession of such a method. The patent contains 29 examples, none of which disclose tagging and targeted amplification performed by a single round of amplification using the same set of primers. In fact, the opposite is clear—the inventors were, at the time of this invention, focused exclusively on a universal amplification step that comes *before* targeted amplification. For example, the specification describes a workflow setting forth separate steps of universal pre-amplification followed by targeted amplification:

The workflow may entail (1) extracting DNA such as plasma DNA, (2) preparing fragment library with universal adaptors on both ends of fragments, (3) amplifying the library using universal primers specific to the adaptors, (4) dividing the amplified sample “library” into multiple aliquots, (5) performing multiplex (e.g. about 100-plex, 1,000, or 10,000-plex with one target specific

primer per target and a tag-specific primer) amplifications on aliquots, (6) pooling aliquots of one sample, . . .”

’035 patent at 86:61–87:10. The specification also discloses several embodiments comprising a universal amplification followed by a separate targeted amplification step. *See, e.g.*, ’035 patent at 10:16–23, 15:52–60, 33:12–21, 85:48–67.

A POSA reading the specification would have understood that the inventors sought out to address the problem of performing multiplex PCR where DNA molecules are limited by performing a separate universal amplification step before targeted amplification. For instance, the specification describes that “improved methods are needed to reduce the formation of non-target amplicons during multiplex PCR.” ’035 patent at 3:12–14. The specification describes solutions for samples with large quantities of DNA that can be “split among multiple sub-reactions and then recombined before sequencing.” ’035 patent at 84:49–51. The specification then describes that for samples where “either the overall sample or some subpopulation of DNA molecules is limited, splitting the sample would introduce statistical noise.” ’035 patent at 84:51–53. To solve that problem, the specification describes a universal pre-amplification to increase the overall sample quantity before splitting as a solution for analyzing samples where the DNA molecules are limited:

In these situations a universal pre-amplification step may be used to increase the overall sample quantity. Ideally, this pre-amplification step should not appreciably alter the allelic distributions. . . . Described herein are methods to first globally amplify the plasma DNA of a sample and then divide the sample up into multiple multiplexed target enrichment reactions with more moderate numbers of target sequences per reaction.

’035 patent at 84:62–65, 86:26–29.

The specification explains the benefits of that approach: “a universal amplification step of the DNA prior to targeted amplification may confer several advantages, such as removing the

risk of bottlenecking and reducing allelic bias.” ’035 patent at 105:60–63. A POSA at the time of the claimed invention would understand that statement to make no sense if the universal amplification step was simply performed as part of targeted amplification after splitting of the sample, as Natera contends, further confirming that the specification lacks adequate written description support for the claim as construed by Natera.

A POSA would also understand that the inventors possessed the claimed methods comprising tagging by ligation rather than by targeted PCR, as Natera contends. The specification describes ligation as part of the solution to the problem and discloses several embodiments of ligating universal tags. *See, e.g.*, 10:16–23, 15:52–60, 86:33–44, 86:46–60, 91:4–18, 92:4–15, 94:12–25. For instance, the specification describes use of “ligation mediated universal PCR amplification of fragmented DNA” where “the addition of tags to the fragments by ligation can enable detection of shorter fragments.” ’035 patent at 92:4–15. Moreover, the specification describes the challenges of amplifying short cfDNA fragments, specifically teaching away from using amplification for short DNA fragments. ’035 patent at 89:5–17.

A POSA at the time of the claimed invention likewise would be unable to perform the claimed method using PCR/primer-based amplification for the claimed tagging step. The specification provides no teaching of how to perform the claimed tagging and amplifying steps on cell free tumor DNA using a single round of PCR with a single set of primers. To the contrary, Example 27, the only example that even mentions ctDNA, describes that “[a]dapters were ligated to DNA fragments and the fragments were amplified,” followed by multiplexed PCR that “allows simultaneous amplification of many targets in a single reaction.” ’035 patent at 240:35–39. Therefore, even if a POSA understood the scope of the term to encompass tagging

by PCR/primer-based amplification, the POSA would be unable to make and use the invention as the relevant methodology was not disclosed.

For at least these reasons, the Asserted Claims of the '035 patent are invalid for lack of written description and non-enablement to the extent Natera contends the Asserted Claims encompass a method of tagging and targeted amplification in the same round of PCR using the same primers.⁸

c. The Cancer Limitations

The Asserted Claims of the '035 patent are limited to methods of amplifying and sequencing DNA from a blood sample collected from a subject “who is not a pregnant women” for SNP loci “associated with cancer” (hereafter “the Cancer Limitations”). A POSA reviewing the specification of the '035 patent at the time of the claimed invention would readily recognize that the inventors were not in possession of the claimed methods for purposes of cancer detection.

To the extent Natera contends written description support is present in Examples 23, 26, 27, 28, and/or 29, none of those examples were added to the specification until the filing of U.S. Patent Application No. 14/918,544 on October 20, 2015. In response to a Final Office Action dated March 3, 2021, Natera relied on Examples 26-29 including specifically paragraph [0956] of Example 27 (corresponding to 244:52-58 of the '035 Patent) as support for amending claim 1 to recite the Cancer Limitations. 03/03/2021 Response to Final Office Action. Moreover, the Patent Office determined that before those examples were added, the specification lacked written

⁸ To the extent Natera contends the specification discloses the claimed tagging and targeted amplification steps as occurring within the same PCR and therefore provides adequate support for written description and enablement purposes, similar disclosures in the prior art should be considered with equal force under Sections 102 and 103.

description for cancer detection. During prosecution of U.S. Patent Application No. 14/877,925, to which the '035 patent purports to be a child patent, the applicant proposed claims directed to determining a ploidy status of a chromosome or chromosome segment of a cancer in a plasma sample. The Examiner issued a final rejection under Section 112(a) for lack of written description because “review of the specification did not reveal support for ‘measuring free-floating DNA in a plasma sample of the host that comprises both DNA from normal cells and DNA from cancer’.” 6/6/2018 Final Rejection at 7. The applicant did not respond and the application was abandoned. The prosecution history accordingly demonstrates that specification does not provide adequate support for the Cancer Limitations. Indeed, the lack of adequate disclosure for this term is particularly salient because the applicant relied on the Cancer Limitations to overcome the prior art. In the Examiner’s final rejection during prosecution, the Examiner rejected the claims as anticipated by U.S. 8,318,430 (“Chuu”). The applicant overcame Chuu by amending claim 1 to include the Cancer Limitations and the phrase “in a single reaction volume.” 3/3/2021 Amendment and Reply Under 37 CFR 1.116.

For at least these reasons, the Asserted Claims of the '035 patent are invalid for lack of written description.⁹

d. Sequencing at Any Limit of Detection and/or Any Sensitivity

The Asserted Claims of the '035 patent are directed to “sequencing the plurality of SNP loci on the cell free DNA.” The claims do not specify a limit of detection (LOD), which refers to

⁹ To the extent Natera contends that the claims are adequately supported by the specification for written description based on the equivalence of cell free fetal DNA in maternal blood and other cell free DNA such as ctDNA in host blood, such implications of equivalence should equally apply to prior art disclosures regarding cell free fetal DNA in maternal blood under Sections 102 and 103.

the lowest levels of sequence variants that the method can sequence consistently in the background of wild-type sequences. Nor do the claims specify any limit or requirements on the sensitivity of the method. The claims therefore require support demonstrating that the inventors could perform sequencing at any level of detection or any level of sensitivity. For example, the specification would have to describe that the inventors were in possession of a method that could sequence SNP loci present at very low abundance, for example present in a single molecule of cfDNA, relative to wild-type sequences. A POSA reviewing the specification of the '035 patent at the time of the claimed invention would readily recognize that the inventors were not in possession of the claimed methods for sequencing at any limit of detection or at any level of sensitivity.

At best, Example 23 of the '035 specification describes a mean LOD of 0.24% and a median LOD of 0.09% for DNA in a plasma sample. '035 Patent at 234:55–59. The specification does not enable or demonstrate possession of a method for sequencing a plurality of SNP loci at any level of sensitivity, or even of a method with a lower limit of detection than a mean LOD of 0.24% and a median LOD of 0.09%. The lowest LOD for sequencing single nucleotide changes mentioned in the specification is 0.005%. '035 patent at 130:46–49. Because the claims of the '035 patent are not limited to any level of sensitivity or limit of detection, a POSA would understand that the inventors were not in possession of the full scope of the claimed subject matter.

A POSA at the time of the claimed invention likewise would be unable to perform the claimed method at all levels of sensitivity or with any limit of detection without undue experimentation. For instance, improved techniques for each step of the claimed methods would be necessary to achieve an LOD below 0.005%, and it would require undue experimentation for

a POSA at the time of the claimed invention to determine how, if it is even possible, to achieve such high sensitivity.

For at least these reasons, the full scope of the Asserted Claims of the '035 patent lack written description and are not enabled.

e. Failure to Claim an Essential Element of the Invention

The specification makes clear to the skilled artisan that the inventors were solely in possession of techniques that involved target loci selection and removal of primer pairs likely to form primer-dimers for targeted multiplex PCR amplification of more than 100 targets in a single reaction.

The specification explains that the inventors’ techniques used primer design for avoiding primer-dimers. The Background section of the patent describes the problem the inventors set out to solve:

Use of multiple PCR can significantly simplify experimental procedures and shorten the time required for nucleic acid analysis and detection. However, when multiple pairs are added to the same PCR reaction, non-target amplification products may be generated, such as amplified primer dimers. The risk of generating such products increases as the number of primers increases. These non-target amplicons significantly limit the use of the amplified products for further analysis and/or assays. Thus, improved methods are needed to reduce the formation of non-target amplicons during multiplex PCR.

'035 patent at 3:4–15.

The specification states:

The present invention is based in part on the surprising discovery that often only a relatively small number of primers in a library of primers are responsible for a substantial amount of the amplified primer dimers that form during multiplex PCR reactions. Methods have been developed to select the most undesirable primers for removal from a library of candidate primers. By reducing the amount of primer dimers to a negligible amount (~0.1% of the PCR products), these methods allow the resulting primer libraries

to simultaneously amplify a large number of target loci in a single multiplex PCR reaction.

’035 patent at 46:37–47.

The specification explains it is essential to remove such primer-dimers: “At high multiplexing it is not possible to eliminate all spurious interactions, but it is essential to remove the primers or pairs of primers with the highest interaction scores in silico as they can dominate an entire reaction, greatly limiting amplification from intended targets.” ’035 patent at 54:46–50. Over the span of several pages, the specification discusses “Exemplary Primer Design Methods” and “Exemplary Primers” at length. ’035 patent at 48:6–75:7. Additionally, the ’035 patent explains that without target loci selection and primer design techniques, the PCR reaction yields essentially nothing but primer dimer: “Sequencing of a 1042-plex without design and selection of assays resulted in >99% of sequences being primer dimer products.” ’035 patent at 96:28–30. Moreover, all of the working examples disclosed use techniques for targeted loci selection and primer design. Therefore, a POSA would understand that the Asserted Claims fail to recite essential steps involving target loci selection and removal of primer pairs likely to form primer-dimers for targeted multiplex PCR amplification of more than 100 targets in a single reaction.

For at least these reasons, the Asserted Claims of the ’035 patent lack an essential element of the invention and therefore lack adequate written description support. *See LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336 (Fed. Cir. 2005); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154 (Fed. Cir. 1998).

2. ’454 Patent

a. Combination of Steps in Asserted Claims

The Asserted Claims of the ’454 patent are invalid for lack of written description because the ’454 patent specification does not disclose adequate support for the particular claimed

combination of steps. Many of the individual concepts recited in the claims, such as multiplex amplification, molecular barcodes, and sequencing amplicons were known in the art and were routine and conventional as of Natera’s claimed priority date. Therefore, to the extent there is anything inventive in the Asserted Claims, it must reside in the combination of recited elements. But none of the embodiments or other disclosures demonstrate that the inventors possessed the combination of all the elements in the manner claimed. For instance, none of the embodiments disclose an example that discusses sequencing a tumor sample and then obtaining a depth of read of at least 50,000 for sequenced cell-free DNA. Based on the disclosures in the specification, it would require undue experimentation for a POSA to combine all of those individual concepts in the claimed manner. Accordingly, to the extent Natera contends that disparate disclosures throughout the specification disclose each of the elements separately, such disclosure is insufficient on its own to satisfy the requirements for written description and enablement.

b. Tumor-Informed Assay

In its infringement contentions, Natera contends the Asserted Claims of the ’454 patent cover a tumor-informed assay for single nucleotide variants in cell free DNA. Preliminary Infringement Contentions at 9–10. However, the ’454 patent specification does not disclose adequate support for a tumor-informed assay of cell free DNA, much less a tumor-informed assay for detecting minimal residual disease (MRD) after tumor resection or treatment. To the extent Natera contends Example 13 discloses a method for performing a tumor-informed assay, Example 13 performs sequencing on tumor biopsies and corresponding *pre-operative* blood plasma samples. ’454 patent at 167:66–168:6. Example 13 provides no support for using sequencing data from a tumor to design tumor-informed targeted assays for SNVs in *post-operative* plasma samples. And even for pre-operative plasma samples, Example 13 states that

“[n]ot all SNV's identified by sequencing were able to have corresponding PCR assays designed.” *Id.* at 168:28–30. Accordingly, the '454 patent lacks written description for methods of performing a tumor-informed assay as Natera purports to be claimed by the '454 patent.

A POSA reading the specification likewise would be unable to perform the claimed method for tumor-informed assays for all SNVs identified and/or on post-operative plasma samples without undue experimentation. The '454 patent does not disclose such methods, and it would require undue experimentation for a POSA in 2015 to determine how, if it is even possible, to achieve such tumor-informed assays for any given SNV or to detect minimal residual disease. sub

c. Whole Genome Sequencing

Claims 1 and 14 of the '454 patent recite the step of “performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations.” However, there is no adequate disclosure of “whole genome sequencing” in the '454 patent. The '454 patent’s single passing mention of “whole genome sequencing” in the description of Fig. 51B would not demonstrate to a POSA that the inventors were in possession of the method or how to perform the claimed whole genome sequencing without undue experimentation. '454 patent at 41:59–61. Accordingly, the specification of the '454 patent lacks adequate written description and enablement support this claim limitation.

d. Failure to Claim an Essential Element of the Invention

As with the '035 patent, discussed above, the '454 specification also makes clear to the skilled artisan that the inventors were solely in possession of techniques that involved target loci selection and primer design for highly multiplexed PCR.

Claims 1 and 14 of the ’454 patent recites steps related to performing PCR on multiple nucleic acid targets in the same reaction volume at the same time, a process referred to as “multiplex PCR.” In particular, claim 1 recites:

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.

The ’454 specification, however, shows that the inventors were only in possession of techniques involving target loci selection and primer design for highly multiplexed PCR in a single reaction volume. This is demonstrated by the specification’s disclosure that “it is essential to remove the primers or pairs of primers with the highest interaction scores in silico as they can dominate an entire reaction, greatly limiting amplification from intended targets.” ’454 patent at 108:19–22. Similarly, the specification discloses that “[o]ne way to identify the ‘bad’ primers is to look at the sequencing data of DNA that was amplified by targeted amplification; those primer dimers that are seen with greatest frequency can be removed to give a primer library that is significantly less likely to result in side product DNA.” *Id.* at 106:2–6. If the inventors were in possession of a method that did not require target loci selection and primer design for highly multiplex amplification, they would not have explained that such techniques were “essential.”

Further, the specification explains that removal of “problematic primers” is the element that “has unexpectedly enabled extremely high PCR multiplexing levels.” *Id.* at 105:58–61. According to the specification, “[e]mpirical data indicate that a small number of ‘bad’ primers are responsible for a large amount of non-mapping primer dimer side reactions. Removing these ‘bad’ primers can increase the percent of sequence reads that map to targeted loci.” *Id.* at 105:64–

106:1. In this way, the patentee distinguished the invention from the prior art by directly connecting the removal of the primers that cause primer dimers as something “unexpected.”

Accordingly, and because the specification does not disclose a method for carrying out the claimed multiplex PCR without primer design approaches, the ’454 patent lacks written description support for multiplex PCR amplification that does not utilize techniques for selection of primers to avoid primer side products. Therefore, a POSA would understand that the Asserted Claims fail to recite essential steps involving target loci selection and removal of primer pairs likely to form primer-dimers for targeted, highly multiplexed PCR amplification in a single reaction volume.

For at least these reasons, the Asserted Claims of the ’454 patent lack an essential element of the invention and therefore lack adequate written description support. *See LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336 (Fed. Cir. 2005); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154 (Fed. Cir. 1998).

e. Detection of SNVs at Any Limit of Detection and/or Any Sensitivity

Asserted Claim 1 of the ’454 patent requires “detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads.” The ’454 patent does not provide adequate written description and enablement support for the full scope of claim 1 and its dependents. For example, this claim does not specify a limit of detection (LOD), which refers to the lowest levels of sequence variants that the method can sequence consistently in the background of wild-type sequences. Nor does the claim specify any limit or requirements on the sensitivity of the method. Even if a POSA could understand how to calculate and measure a limit of detection, claim 1 purports to cover detecting *any* type of tumor-specific SNV at *any*

limit of detection (LOD). The claim and related dependent claims therefore require support demonstrating that the inventors could perform sequencing and detection at all levels of sensitivity and for any limit of detection. For example, the specification would have to demonstrate that the inventors could use the claimed method to detect tumor-specific SNV mutations at very low absolute and relative abundance, for example in a single molecule of cfDNA containing tumor-specific SNV mutations among many molecules of cfDNA not containing such mutations. A POSA reviewing the specification of the '454 patent at the time of Natera's claimed priority date would recognize that the inventors were not in possession of the claimed methods for detection at any limit of detection or at any level of sensitivity.

At best, Example 6 of the '454 specification describes a mean LOD of 0.24% and a median LOD of 0.09% for DNA in a plasma sample. '454 patent at 158:32–36. The specification does not enable or demonstrate possession of a method for sequencing a plurality of SNP loci at any level of sensitivity, or even a method with a lower limit of detection than a mean LOD of 0.24% and a median LOD of 0.09%. The lowest LOD for sequencing single nucleotide changes mentioned in the specification is 0.005%. '454 patent at 92:61–66. The specification provides no support for any higher sensitivity or lower limit of detection than the recited threshold. A POSA reviewing the specification of the '454 patent would readily recognize that the inventors were not in possession of the claimed methods for sequencing at any level of sensitivity or at any limit of detection. A POSA would understand that the inventors were not in possession of the full scope of the claimed subject matter.

Example 14 of the '454 specification similarly shows that the inventors were not in possession of the full scope of the claimed subject matter. For example, Fig. 59 illustrates “a plot of Limit of Detection (LOD) vs. Depth of Read (DOR) for detection of SNV Transition and

Transversion mutations in a 84-plex PCR reaction at 15 PCR cycles,” showing that a LOD lower than 0.01% was not achieved for *any* SNV at read depths lower than 100,000. ’454 patent at 42:15–18, Fig. 59. Figs. 60 and 61 similarly show that the LOD for SNVs was often greater than 0.01 or even 0.1 (meaning that an SNV present at lower frequencies could not be detected). *See* ’454 patent at 42:19–26, Figs. 60–61. Furthermore, Figs. 59–61 show that a LOD lower than 0.01% was not achieved for *any* SNV that was a transition mutation, regardless of read depth or number of PCR cycles. ’454 patent at Figs. 59–61.

Because the claims of the ’454 patent are not limited to any particular LOD or level of sensitivity and the specification does not describe performing the claimed methods at all LODs or levels of sensitivity, a POSA would understand that the inventors were not in possession of the full scope of the claimed subject matter. Nor are the claims limited to detecting transversion rather than transition mutations, which Example 14 shows could not be detected with a LOD lower than 0.01%.

A POSA reading the specification at the time of Natera’s claimed priority date likewise would be unable to perform the claimed method at all levels of sensitivity or with any limit of detection, or for any type of SNV mutation, without undue experimentation. For instance, improved techniques for each step of the claimed methods not disclosed in the ’454 patent would be necessary to sequence a particular tumor-specific SNV mutation present in less than 0.005% of the DNA molecules in a patient sample, and it would require undue experimentation for a POSA to determine how, if it is even possible, to achieve such high sensitivity.

f. “[E]ncompassing a different tumor-specific SNV mutation.”

Claims 1 and 14 recite “performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV

mutations,” and then recite “performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation.” ’454 at 171:29–34. The phrase “a plurality of tumor-specific SNV mutations” does not provide antecedent basis for the phrase “a different tumor-specific SNV mutation.” Natera may contend, therefore, that the phrase “different tumor-specific SNV mutation” refers to additional SNV mutations beyond the “plurality of tumor-specific SNV mutations” identified through whole exome sequencing or whole genome sequencing on a tumor sample of the subject. However, the specification does not disclose methods for identifying tumor-specific SNV mutations other than through whole exome sequencing or whole genome sequencing on a tumor sample of the subject. Accordingly, there is insufficient written description support to show that the inventors were in possession of a method comprising performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation beyond the plurality of tumor-specific SNV mutations identified after whole exome sequencing or whole genome sequencing on a tumor sample of the subject.

V. THE ASSERTED CLAIMS ARE INVALID UNDER 35 U.S.C. § 101.

The Asserted Patents are invalid under 35 U.S.C. § 101 for being directed to ineligible subject matter.

Under 35 U.S.C. § 101, “[l]aws of nature, natural phenomena, and abstract ideas are not patentable.” *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589 (2013) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 70 (2012)). Patent eligibility is assessed under the Alice/Mayo two-part test. First, it must be “determine[d] whether the claims at issue are directed to one of those patent-ineligible concepts.” *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 573 U.S. 208, 217 (2014). If the claims are directed to an ineligible

concept, then the inquiry is whether any additional elements of the claim “‘transform the nature of the claim’ into a patent-eligible application.” *Id.* (quoting Mayo, 566 U.S. at 78).

The Asserted Claims of the ’035 and ’454 patents are invalid under 35 U.S.C. § 101. Under *Alice* step 1, claims 1, 2, 12, and 13 of the ’035 patent and claims 1–28 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. Under *Alice* step 2, the Asserted Claims recite conventional steps, i.e., they lack an inventive concept, to carry out the detection of the natural phenomenon. NeoGenomics hereby incorporate by reference all the materials submitted in support of its Motion to Dismiss (D.I. 51, 52).

VI. THE ASSERTED PATENTS ARE INVALID DUE TO IMPROPER INVENTORSHIP.

“A patent is invalid if more or less than the true inventors are named.” *Trovan, Ltd. V. Sokymat SA, Irori*, 299 F.3d 1292 (Fed. Cir. 2002).

For purposes of determining the proper naming of inventors of a patent, as well as demarcating the exclusionary rights granted by a patent, the patented “invention” is defined by the subject matter set forth in the claims of the patent. “The claims of the patent provide the concise formal definition of the invention. They are the numbered paragraphs which “particularly [point] out and distinctly [claim] the subject matter which the applicant regards as his invention.” *Autogiro Co. of Am. v. United States*, 384 F.2d 391, 395 (Ct. Cl. 1967). The Supreme Court has ruled that the claimed invention consists of the entire subject matter specified in the individual claim, and that no part of the claim can be ignored in considering the scope of the invention. *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 29.

The ’454 patent claims a method based on whole exome sequencing of a tumor sample that was invented not by Natera alone, but rather in collaboration with researchers at University College London (“UCL”), including, for example, Dr. Miriam Jamal-Hanjani. Accordingly, the ’454 patent is invalid for improper inventorship by missing UCL inventors such as Dr. Miriam Jamal-Hanjani. NeoGenomics incorporates by reference its opposition brief to Natera’s preliminary injunction (Doc. 107), Van Ness declaration ISO NeoGenomics’ opposition (Doc. 116), Bernhard Zimmerman 10/4/2023 deposition transcript, and NeoGenomics’ opposition to Natera’s motion to dismiss NeoGenomics’ unenforceability counterclaim and strike related affirmative defenses (Doc. 147).

During prosecution of the ’035 patent, Natera initially named Joshua Babiarz, Tudor Constantin, Lane Eubank, Goergoe Gemelos, Matthew Hill, Huseyin Kirkizlar, Matthew Rabinowitz, Onur Sakarya, Styrmir Sigurjonsson, and Bernhard Zimmermann as inventors. Immediately before issuance of the ’035 patent, Natera removed Joshua Babiarz, Tudor Constantin, Lane Eubank, Huseyin Kirkizlar, Onur Sakarya from the inventorship. Natera further added Johan Baner, Milena Banjevic, Allison Ryan, and Zachary Demko as inventors. Natera has failed to explain how the associated claim amendments triggered this major inventorship reshuffle. Accordingly, the ’035 patent is invalid for improper inventorship.

ACCOMPANYING DOCUMENT PRODUCTION

Pursuant to Patent Local Rule 103.4(a), NeoGenomics is producing or has produced to Natera documents sufficient to show the operation of any aspects or elements of an Accused Instrumentality identified by Natera in its Preliminary Infringement Contentions. *See* NEOGEN00000125–NEOGEN00000981, NEOGEN00063691–NEOGEN00063849.

Pursuant to Local Rule 103.4(b), NeoGenomics is producing or has produced to Natera copies of the references mentioned above. *See* NEOGEN00063850–NEOGEN00123404.

Pursuant to Local Rule 103.6, NeoGenomics is producing or has produced to Natera additional documents in support of these Final Invalidity Contentions. *See* NEOGEN00275278–NEOGEN00275334 and NEOGEN00275270–NEOGEN0027527.

This the 11th day of July, 2024

/s/Aaron G. Fountain

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**Special Appearance under Local Civil Rule 83.1(d)*

CERTIFICATE OF SERVICE

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