Tracey B. Davies (*pro hac vice*)
tdavies@gibsondunn.com
Mark Reiter (*pro hac vice*)
mreiter@gibsondunn.com
GIBSON, DUNN & CRUTCHER LLP
555 Mission Street, Suite 3000
San Francisco, CA 94105-0921
Telephone: 415.393.8200
Facsimile: 415.393.8306

Karen I. Boyd, SBN 189808
boyd@turnerboyd.com
TURNER BOYD LLP
702 Marshall Street, Suite 640
Redwood City, CA 94063
Telephone: 650.521.5930
Facsimile: 650.521.5931

Attorneys for Defendant
NATERA, INC.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

ILLUMINA, INC.,

Plaintiff,

v.

NATERA, INC.,

Defendant.

Case No. 3:18-CV-01662-SI

NATERA INC.'S FIRST AMENDED ANSWER, AFFIRMATIVE DEFENSES AND COUNTERCLAIMS

[DEMAND FOR JURY TRIAL]

Pursuant to Federal Rule of Procedure 15(a)(1)(A), Defendant Natera, Inc. ("Natera"), by its attorneys, hereby answers the Complaint filed against it by Plaintiff Illumina, Inc. ("Illumina") on March 16, 2018 (Dkt. 1) and asserts affirmative defenses and counterclaims as follows. Natera states that anything in Illumina's Complaint to which Natera does not expressly admit is hereby denied.

NATURE OF THE ACTION

1. Natera admits that Illumina purports to bring an action for patent infringement arising under 28 U.S.C. § 1331 and the United States Patent Act, 35 U.S.C. § 100 *et seq*. Natera denies the legal sufficiency of Illumina's claims and allegations, and further denies that Illumina has any viable claim thereunder.

2. Natera denies Illumina's allegation of infringement and states further that it lacks knowledge or information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 2 of the "Nature of the Action" section of the Complaint, and therefore denies these allegations.

PARTIES

1. Natera lacks knowledge or information sufficient to form a belief about the truth of the allegations in Paragraph 1 of the "Parties" section of the Complaint, and therefore denies these allegations.

2. Natera lacks knowledge or information sufficient to form a belief about the truth of the allegations in Paragraph 2 of the "Parties" section of the Complaint, and therefore denies these allegations.

3. Natera admits that it is a company organized and existing under the laws of Delaware, with its principal place of business at 201 Industrial Road, San Carlos, California 94070. Natera admits that it provides a non-invasive prenatal screening test under the trade name "Panorama™ Natera Prenatal Screen," and that it performs the Panorama™ Natera Prenatal Screen at its facility in San Carlos, California. Natera otherwise denies the allegations in Paragraph 3.

JURISDICTION AND VENUE

4. To the extent Illumina purports to bring a civil action arising under the Patent Laws of the United States of America, 35 U.S.C. § 1 *et seq.*, Natera admits that this Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Natera denies the legal sufficiency of Illumina's claims and allegations, and further denies that Illumina has any viable claim thereunder.

5. Natera does not contest venue for purposes of this action.

BACKGROUND

6. Natera incorporates by reference its statements made in the foregoing paragraphs of this Answer as if fully and specifically set forth herein.

7. Denied.

8. Natera admits that the accused Panorama™ products relate to the analysis of cell-free fetal DNA present in maternal blood. Natera otherwise denies the allegations in Paragraph 8.

9. Natera admits that Paragraph 9 appears to accurately set forth claim 1 of the '831 patent. Natera otherwise denies the allegations in Paragraph 9.

10. Denied.

11. Natera admits that Exhibit 6 to the Complaint appears to be Illumina's chart of claims 1–3, 6–10, 13–22, and 24 of the '831 patent. With respect to the allegations of infringement Exhibit 6 purports to show, Natera denies that Exhibit 6 establishes infringement at any level. More specifically, Exhibit 6 relies on a collection of documents, *e.g.*, Exhibits 2–4, that neither represent individually nor collectively the accused Panorama™ Natera Prenatal Screen. Illumina, moreover, alleges infringement based on mixing and matching different, unrelated documents, while failing to explain how the documents fit together or relate to one another. For example, Exhibits 2 and 4, which are dated well before the '831 patent issued, do not even mention the accused Panorama™ Natera Prenatal Screen, while Exhibit 3 has no date at all. For at least this reason, Natera denies that the claim charts of Exhibit 6 detail infringement at any level. To the extent not already addressed, Natera otherwise denies the allegations in Paragraph 11.

12. Natera admits that in a December 20, 2016 letter, Illumina identified the '831 patent to Natera and stated that "according to information in Illumina's possession, at least the '831 patent is infringed by performance of Natera's NIPT method." In subsequent communications, Natera informed Illumina that the allegations contained in the December 20 letter were incorrect and that Natera does not infringe the '831 patent. Natera otherwise denies the allegations in that letter and in Paragraph 12.

13. Natera admits that it is aware that Illumina and ARUP communicated. Natera, however, denies that its awareness of those communications put Natera on notice of infringement or that Natera infringes. Natera lacks knowledge or information sufficient to form a belief about the truth of the remaining allegations in Paragraph 13 of the Complaint, and therefore denies these allegations.

ILLUMINA'S COUNT 1

14. Natera incorporates by reference its statements made in the foregoing paragraphs of this Answer as if fully and specifically set forth herein.

15. Natera admits that the '831 patent is entitled "Methods of Fetal Abnormality Detection" and that the face of the '831 patent states that it was issued November 15, 2016. As demonstrated by its petition for *inter partes* review filed June 29, 2018, IPR2018-01317, as well as its Motion to Dismiss because the '831 patent claims are based on patent ineligible subject matter, Natera denies that the '831 patent was "duly and legally issued." Natera lacks knowledge or information sufficient to form a belief about the truth of the remaining allegations in Paragraph 15 of the Complaint, and therefore denies these allegations.

16. Natera admits that Exhibit 6 purports to be a chart regarding alleged infringement of claims 1–3, 6–10, 13–22, and 24 of the '831 patent. Natera, however, expressly denies that it infringes any claim of the '831 patent, either literally or under the doctrine of equivalents. To the extent not already addressed, Natera otherwise denies the allegations in Paragraph 16.

17. Natera denies that Exhibit 6 establishes infringement at any level. More specifically, Exhibit 6 relies on a collection of documents, *e.g.*, Exhibits 2–4, that neither represent individually nor collectively the accused Panorama™ Natera Prenatal Screen. Illumina, moreover, alleges infringement based on mixing and matching different, unrelated documents, while failing to explain how the

documents fit together or relate to one another. For example, Exhibits 2 and 4, which are dated well before the '831 patent issued, do not even mention the accused Panorama™ Natera Prenatal Screen, while Exhibit 3 has no date at all. For at least this reason, Natera denies that the claim charts of Exhibit 6 detail infringement at any level. For at least this reason, Natera denies that the claim charts of Exhibit 6 detail infringement at any level. To the extent not already addressed, Natera otherwise denies the allegations in Paragraph 17.

18. Denied.

RESPONSE TO ILLUMINA'S JURY DEMAND

19. A response is not required to Illumina's demand for a jury trial in Paragraph 19 of the Complaint. To whatever extent a response is deemed required, Natera requests a jury trial for all issues so triable pursuant to Rule 38 of the Federal Rules of Civil Procedure.

RESPONSE TO ILLUMINA'S PRAYER FOR RELIEF

20. Illumina's prayer for relief does not require a response. To whatever extent a response is deemed required, Natera denies that Illumina is entitled to relief of any kind, including injunctive relief. Natera denies any and all factual allegations relating to Natera contained in Illumina's prayer. Natera has not infringed, directly or indirectly, any valid and enforceable claim of the '831 patent, and Illumina is not entitled to any remedy or recovery. Furthermore, Natera denies that this is an exceptional case such that an award of attorneys' fees to Illumina is appropriate. Illumina's prayer should therefore be denied in its entirety and with prejudice, and Illumina should take nothing therefor.

AFFIRMATIVE AND OTHER DEFENSES

21. Further answering the Complaint and as additional answers thereto, Natera asserts the following affirmative defenses, all of which are pled in the alternative, and none of which constitutes an admission that Natera is in any way liable to Illumina, that Illumina has been or will be injured or damaged in any way, or that Illumina is entitled to any relief whatsoever. By pleading these defenses, Natera does not in any way agree or concede that it has the burden of proof or persuasion on any of these issues. In addition to the defenses described below, Natera reserves all affirmative defenses under Rule 8(c) of the Federal Rules of Civil Procedure, the Patent Laws of the United States, and any other

defenses, in law or in equity, which may now exist or may in the future be available based on discovery and further investigation in this case.

FIRST AFFIRMATIVE DEFENSE – NON-INFRINGEMENT

22. Natera has not infringed and is not infringing directly, indirectly, contributorily, by inducement, or in any other manner any valid and enforceable claim of the '831 patent, either literally or by the doctrine of equivalents. Furthermore, Illumina is precluded under the doctrines of disclaimer and prosecution history estoppel from asserting a scope for any claim of the '831 patent that would encompass the accused Natera process.

SECOND AFFIRMATIVE DEFENSE – INVALIDITY

23. One or more claims of the '831 patent are invalid for failure to satisfy one or more of the requirements of the Patent Act, 35 U.S.C. § 1, *et seq.*, including, but not limited to, the conditions of patentability set forth in 35 U.S.C. §§ 101, 102, 103, and 112. For example, one or more claims of the '831 patent is ineligible under 35 U.S.C. § 101, including for the reasons set forth in Natera's Motion to Dismiss Under Federal Rule of Civil Procedure 12(b)(6) (Dkt. 24). In addition, one or more claims of the '831 patent are invalid in view of the prior art, including references cited on the face of the '831 patent, as well as the prior art and grounds set forth in Natera's Petition for Inter Partes Review of the '831 patent (IPR2018-01317), and articles, products, and processes that were publicly available or disclosed before the priority date of the '831 patent. In addition, one or more claims of the '831 patent are invalid because the full scope of those claims is not enabled, nor described, by the written description of the '831 patent, and those claims are indefinite.

THIRD AFFIRMATIVE DEFENSE – UNENFORCEABILITY

24. The '831 patent is unenforceable for failure to comply with the conditions required by the terminal disclaimer made during prosecution, which requires, among other things, co-ownership of the '831 patent and U.S. Patent No. 8,318,430 (the "'430 patent"). The '831 patent is owned by Illumina, while the '430 patent is owned by Verinata Health, Inc. ("Verinata").

FOURTH AFFIRMATIVE DEFENSE – PATENT EXHAUSTION

25. Illumina's claims are barred in whole or in part by the doctrine of patent exhaustion. Specifically, Illumina's sale of its sequencing systems and reagents to Natera under the August 26, 2013 Supply Agreement (TG Consumables) exhausts the claims of the '831 patent because it embodies or substantially embodies the claimed methods. *See LifeScan Scotland, Ltd. v. Shasta Techs.*, 734 F.3d 1361, 1366 (Fed. Cir. 2013) (citing *United States v. Univis Lens Co.*, 316 U.S. 241 (1942)); *Quanta Computer, Inc. v. LG Electronics, Inc.*, 128 S. Ct. 2109, 2119 (2008).

FIFTH AFFIRMATIVE DEFENSE – LICENSE

26. Illumina's claims are barred in whole or in part because Illumina has given Natera a license to use the claimed method, specifically the Supply Agreement (TG Consumables), effective August 16, 2013.

SIXTH AFFIRMATIVE DEFENSE – NO EQUITABLE RELIEF

27. Illumina has an adequate remedy at law and no basis exists for the grant of equitable relief. Illumina is a member of a patent pool, which includes the '831 patent. As a member of the patent pool, Illumina is a licensor of the '831 patent, and has offered to Natera a license to the patent. Indeed, there are multiple companies working in the NIPT industry to whom Illumina licenses its patents. Illumina also has conceded that it does not manufacture or sell a product covered by the '831 patent.

NINTH AFFIRMATIVE DEFENSE – FAILURE TO STATE A CLAIM

28. The Complaint fails to state any claim against Natera upon which relief can be granted pursuant to Rule 12(b)(6) of the Federal Rules of Civil Procedure.

TENTH AFFIRMATIVE DEFENSE – PATENT MISUSE

29. The '831 patent is unenforceable due to patent misuse by Illumina.

30. Illumina alleges that it is "a leading developer, manufacturer, and marketer of life science tools and integrated systems for large-scale analysis of genetic variation and function." Dkt. 1 at 2. At all relevant times, Illumina had and still has market power in the market for genetic sequencing platforms.

31. On its website, Illumina describes the workflow associated with non-invasive prenatal diagnosis (also called non-invasive prenatal testing or "NIPT"). https://www.illumina.com/clinical/reproductive-genetic-health/nipt.html In that description, Illumina states:

> A typical workflow starts with isolating plasma from maternal blood draw. Cell-free DNA (cfDNA) is then extracted from plasma and prepared for analysis. Data is generated from prepared cfDNA using sequencing, microarray, or other means. Sophisticated analysis is then applied to the data.

Id. In this case, Illumina has alleged that the method in the '831 patent provides a technique "for preparing DNA libraries for the specific technological realm of aneuploidy analysis in non-invasive prenatal diagnosis." Dkt. 32 at 18. Illumina has also alleged that the DNA library preparation method in Natera's Panorama™ Prenatal Screen test infringes certain claims of the '831 patent. Illumina further alleges that Natera is in the process of developing a genetic test (which has a different DNA library preparation method) for the Qiagen sequencing platform, and that if Natera's genetic test is operated on the Qiagen platform, Illumina will suffer irreparable harm. Dkt. 49 at 12. Thus, based on Illumina's allegations, the DNA library preparation method of the '831 patent is a part of the NIPT workflow and thus falls within the market for genetic sequencing platforms for which Illumina has market power. As such, Illumina has market power in the relevant market for the '831 patent.

32. In 2014, Illumina and Sequenom, Inc. executed a patent pool agreement ("the Illumina/Sequenom Patent Pool Agreement"), which granted Illumina exclusive rights to license the intellectual property rights in the patent pool, including the '831 patent, to third parties. Illumina, however, has improperly conditioned a license to the '831 patent in a manner that impermissibly broadens the scope of the '831 patent with anticompetitive effect.

33. For example, Illumina conditions the license of the '831 patent on the purchase of certain Illumina sequencing platforms and related sequencing reagents, which are not themselves covered by the '831 patent. In fact, Illumina itself has conceded that it neither makes nor sells a product

covered by the '831 patent. Moreover, Illumina's marketing materials denigrate the targeted sequencing technique claimed in the '831 patent.

> Illumina NIPT uses next-generation sequencing (NGS) to analyze cfDNA fragments across the whole genome, which has proved advantages over other NIPT methodologies such as targeted sequencing and array-based methods. Test failure rates are substantially lower with whole-genome sequencing versus other methodologies.

https://www.illumina.com/clinical/reproductive-genetic-health/nipt.html

34. In addition, Illumina coerces its customers exclusively to purchase Illumina's sequencers and sequencing reagents for NIPT by requiring such purchases as a condition to license the '831 patent and other patents in the Illumina/Sequenom Patent Pool Agreement. If a potential customer does not agree to buy (or an existing customer does not agree to continue to buy) Illumina's sequencing platforms and reagents, Illumina threatens that customer with a patent infringement suit. The resulting anticompetitive effect is the increased sales and market shares of Illumina's sequencing platforms and reagents for NIPT.

35. The DNA library preparation processes claimed in the '831 patent and Illumina's sequencers and sequencing reagents are entirely separate products, because the claims of the '831 patent do not recite any sequencing step and the libraries are prepared without any sequencers and related sequencing reagents. Moreover, Illumina's sequencers and related sequencing reagents are staple articles in commerce because they are used in a wide range of applications that utilize DNA sequencing.

36. Illumina has market power in the market for genetic sequencing platforms. Because of the '831 patent's DNA library preparation method is related to the use of Illumina's sequencing platforms, Illumina has market power in the relevant market for the '831 patent. Illumina's tying of the '831 patent rights to the purchase of certain Illumina sequencers and sequencing reagents impermissibly extended the scope of the '831 patent to these sequencers and reagents. Illumina's conduct constitutes misuse of the '831 patent.

NATERA'S COUNTERCLAIMS

In further response to Illumina's Complaint, pursuant to Federal Rule of Civil Procedure 13, Defendant and Counterclaimant Natera, Inc. ("Natera") hereby asserts these Counterclaims against Plaintiff and Counterclaim-Defendant Illumina, Inc. ("Illumina") and alleges as follows:

THE PARTIES

1. Natera is a company organized and existing under the laws of Delaware, with its principle place of business at 201 Industrial Rd, San Carlos, California 94070.

2. Natera is a leading developer of highly accurate solutions for non-invasive prenatal testing ("NIPT"), genetic-carrier screening, and miscarriage testing. Natera's Panorama™ Prenatal Screen test is a market-leading NIPT test that analyzes a fetus's risk for genetic disorders as early as nine weeks through a simple blood draw from the mother's arm.

3. On information and belief, Illumina is a company organized and existing under the laws of Delaware, with its principle place of business located at 5200 Illumina Way, San Diego, California 92122.

JURISDICTION AND VENUE

4. These counterclaims arise under federal law, and this Court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, and the Patent Laws of the United States, 35 U.S.C. § 1, *et seq.*

5. Illumina has voluntarily submitted to the personal jurisdiction of the United States District Court, Northern District of California, by virtue of, *inter alia*, bringing this present action in this Court. Illumina is also subject to personal jurisdiction in this judicial district for the purposes of Natera's Counterclaims.

6. Venue is proper under at least 28 U.S.C. §§ 1391 and 1400(b) because Illumina has consented to the propriety of venue in this Court by filing its Complaint for patent infringement in this Court, and these Counterclaims are filed in response to that Complaint.

BACKGROUND

General Background of the Invention

7. On March 25, 2014, the United States Patent Office duly and legally issued United States Patent No. 8,682,592 ("the '592 patent") (Ex. 1), which is entitled "System and Method for Cleaning Noisy Genetic Data from Target Individuals Using Genetic Data from Genetically Related Individuals," and which is assigned to Natera.

8. Since its issuance, Natera has owned the '592 patent.

9. As its Abstract explains, the '592 patent is directed to an improved and novel way of determining genetic data from a small set of cells or from fragmentary DNA where a limited quantity of genetic data is available. More specifically, the method claimed in the '592 patent permits the determination of a number of copies of a chromosome or chromosome segment of interest in the genome of an individual from only "fifty or fewer" cells, or from 0.3 ng or less of the individual's DNA, and/or extracellular DNA from the individual found in maternal blood. '592 patent, claim 1. Because the amount of genetic material obtained is small, the genetic data resulting from such a small amount of genetic material is noisy. By creating a set of hypotheses and determining probabilities given the noisy genetic data, the claimed method allows for accurate determination of the chromosome copy number in the genome of the embryo or fetus, *i.e.*, the "individual."

Improvements and Problems Solved by the '592 Patent Invention

10. The claimed invention of the '592 patent is an improvement over the prior art means of determining chromosome copy number where a limited quantity of genetic material is available. For example, such limited supply of genetic material arises in the context of prenatal diagnosis that can alert physicians and parents to abnormalities in growing fetuses. Rather than obtaining genetic material invasively from the fetus, it is possible to obtain fetal genetic information from cell-free fetal DNA and intact fetal cells in the maternal bloodstream. While such genetic information is present in the maternal blood stream, it is present only in a small amount; depending on the stage of pregnancy there may be only one fetal cell per 100,000 maternal cells. '592 Patent at 1:50-59. The methodology used to extract genetic data from a limited volume of fetal DNA results in "noisy" or incomplete genetic data. And

the noisy nature of the genetic data has created a "great need" for a method that increases "the fidelity of, or cleans, the primary data" for later analysis. *Id.* at 8:19-23.

11. As the '592 patent explains, the "system disclosed enables the cleaning of incomplete or noisy genetic data as a source of information" by "address[ing] [various] shortcomings of prior art" discussed in the patent. '592 Patent at 8:27–44. As the '592 patent states, prior art methods encountered several problems when measuring a small amount of genetic material:

> There are numerous difficulties in using DNA amplification in these contexts. Amplification of single-cell DNA (or DNA from a small number of cells, or from smaller amounts of DNA) by PCR can fail completely, as reported in 5-10% of the cases. This is often due to contamination of the DNA, the loss of the cell, its DNA, or accessibility of the DNA during the PCR reaction. Other sources of error that may arise in measuring the embryonic DNA by amplification and microarray analysis include transcription errors introduced by the DNA polymerase where a particular nucleotide is incorrectly copied during PCR, and microarray reading errors due to imperfect hybridization on the array. The biggest problem, however, remains allele drop-out (ADO) defined as the failure to amplify one of the two alleles in a heterozygous cell. ADO can affect up to more than 40% of amplifications and has already caused PGD misdiagnoses.

'592 Patent at 3:9–25.

12. The claimed invention of the '592 patent uniquely addresses, and solves, these problems associated with the small amount of genetic material from an embryo or fetus and the inherent noisiness of data extracted from that material. As such, the invention enables the user to reliably determine a number of copies of a chromosome or a chromosome segment of interest in the genome of an embryo or a fetus using only a small amount of genetic material from that embryo or fetus. Such ability is highly desirable, particularly in preimplantation or prenatal diagnosis, and an improvement over the prior art. For example, the '592 patent explains that:

> A need exists for a method for more extensive genotyping of embryos at the pre-implantation stage. The number of known disease associated genetic alleles is currently at 389 according to OMIM and steadily climbing. Consequently, it is becoming increasingly relevant to analyze multiple embryonic SNPs that are associated with disease phenotypes.

'592 patent at 2:12–16. The '592 patent further explains that "[t]he disclosed method is equally applicable to the context of Non-Invasive Prenatal Diagnosis (NIPD) where only a small number of fetal cells, or fragments of fetal DNA, have been isolated from the mother's blood." *Id*. at 8:58–61.

13. During an in vitro fertilization treatment, an accurate and comprehensive determination of embryo ploidy before implantation is critical to improve the rate of a successful pregnancy. Comprehensive screening of all 24 chromosomes is superior to other high-level karyotyping techniques, such as the 5-color fluorescent in situ hybridization for chromosomes 13, 18, 21, X and Y only, which was used at the time of the invention. The method of the '592 patent permits a more accurate determination of the copy numbers of all 24 chromosomes of the embryo, which improves glandthe rates of implantation and pregnancy outcomes.

14. Moreover, at the time of the invention, the conventional prenatal diagnostic test of chromosomal aneuploidy was the karyotyping of fetal cells collected through invasive procedures such as amniocentesis and chorionic villus sampling. The discovery of cell free fetal DNA in maternal blood opened up new opportunities for non-invasive prenatal diagnostic tests. However, the high background of maternal DNA and measurement bias pose challenges in developing a viable non-invasive fetal aneuploidy test. The method of the '592 patent enables the analysis of fetal aneuploidy with high accuracy despite the noisy data.

15. Specifically, using only a small amount of genetic material from an embryo or fetus, the claimed method of the '592 patent a) analyzes genetic data for some or all possible alleles at a plurality of at least 100 loci on the chromosome or chromosome segment of interest; b) creates a set of one or more hypotheses specifying the number of copies of the chromosome or chromosome segment of

interest; c) determines, on a computer, the probability of each of the hypotheses given the noisy genetic data; and d) uses the probabilities associated with each hypothesis to determine the most likely number of copies of the chromosome or chromosome segment of interest in the genome of that embryo or fetus.

16. It would not have been routine or conventional to analyze a plurality of at least 100 loci on the chromosome or chromosome segment of interest. It also would not have been routine or conventional to create a set of one or more hypotheses specifying the number of copies of the chromosome or chromosome segment of interest; determine, on a computer, the probability of each of the hypotheses given the noisy genetic data; and use the probabilities associated with each hypothesis to determine the most likely number of copies of the chromosome or chromosome segment of interest in the genome of an embryo or fetus, using only a small amount of genetic material and analyzing at a plurality of at least 100 loci on the chromosome or chromosome segment of interest.

17. As Natera explained during prosecution of the '592 patent application, "[p]roblems limiting the number of STR loci that could be analyzed as of the priority date of the present application include (1) overlapping ranges of alleles, (2) availability of only five dyes, (3) stutter artifacts that result from DNA polymerase slippage during DNA replication, and (4) unwanted primer interactions." Amendment and Response at 18.

18. Additionally, during prosecution of the '592 patent application, Natera discussed three references that underscored the problems limiting the number of STR loci that could be analyzed. First, Natera discussed that technology developed after the priority date of the '592 patent was required to address challenges with analyzing just 23 loci:

> To analyze 23 loci, Schellberg used a 6-dye chemistry that was developed several years after the priority date of the present application: "[t]o address these requirements and challenges, Life Technologies has developed a new, expanded STR multiplex configuration. To overcome the issue of size and spacing, the introduction of a novel, 6-dye chemistry enables all 23 of the loci listed in the CODIS recommendations to be incorporated into a single multiplex configuration."

Id. at 18 (quoting Schellberg).

19. Second, Natera discussed how Bacher and Schumm, Profiles in DNA 2(2):3–6 (1998) ("Bacher") "discusses two drawbacks that limit the number of STR loci that can be analyzed" (*id.*):

> The first problem is stutter artifacts that result from DNA polymerase slippage during DNA replication and complicate the determination of what alleles are present in a sample.
>
> …
>
> The second problem is the difficulty in physically separating DNA fragments so that different alleles can be distinguished.

Id. at 19.

20. Third, Natera discussed how Wallin et al., J. Forensic Sci 47(1):52–65 (2002) ("Wallin") discusses challenges associated with analyzing just 16 loci:

> Wallin describes six amplification kits that were each used to analyze only a subset of 16 loci that included 15 STR loci and amelogenin (see Table 1 of [Wallin]), submitted herewith as Exhibit C). Wallin teaches that unwanted primer interactions occur when attempting to make a large enough amount of the amplicons to detect on an electrophoresis system: "[w]ithout optimization, coamplification of several loci may introduce challenges for signal strength and amplification specificity. These challenges are due to potential competition for PCR building blocks and undesired complementarity both between primers (primer dimer) and between primers and genomic DNA template (mispriming)" (page 54, first full paragraph). Even in 2013, Zhang reported the analysis of only 18 loci (including 17 STR and amelogenin; Zhang et al., PLoS ONE 8(2): e57471, 2013. doi:10.1371/joumal.pone.0057471, submitted herewith as Exhibit D).

Id. at 19–20.

21. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the amount of genetic material measured is from twenty or fewer of the individual's cells, from one of the individual's cell[s], from 0.3 ng or less of the individual's DNA, and from

extracellular DNA from the individual found in maternal blood.

22. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the genetic data analyzed is noisy and the noisy data comprises allege drop out errors, measurement bias, and incorrect measurements.

23. Another advantage of the present invention is that it allows for the computation of a confidence for the determination of the number of copies of the chromosome or chromosome segment of interest in the individual's genome.

24. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where that determination is used to make a clinical decision on the individual.

25. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the individual is a fetus, and where the sample is a maternal blood sample comprising DNA from the fetus and DNA from the mother of the fetus.

26. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the individual's genetic data has been obtained by amplifying and/or measuring the individual's genetic material using tools and/or techniques selected from the group consisting of Polymerase Chain Reaction (PCR), Ligation-mediated PCR, degenerative oligonucleotide primer PCR, Multiple Displacement Amplification, allele-specific amplification techniques, and combinations thereof, and wherein one or more of the individual's genetic data has been measured using tools and or techniques selected from the group consisting of MOLECULAR INVERSION PROBES (MIPs) circularizing probes, other circularizing probes, Genotyping Microarrays, the TAQMAN SNP Genotyping Assay, other hydrolysis probes, the ILLUMINA Genotyping System, other genotyping assays, Sanger DNA sequencing, pyrosequencing, other methods of DNA sequencing, other high throughput genotyping platforms, fluorescent in-situ hybridization (FISH) and combinations thereof.

27. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, wherein the individual's genetic data has been obtained by amplifying and/or measuring the individual's genetic material, and wherein the individual's genetic material is found in substances selected from the group consisting of the individual's bulk diploid tissue, one or more diploid cells taken from the individual, one or more haploid cells taken from the individual, one or more blastomeres taken from the individual, one or more embryos created from a gamete from the individual, one or more blastomeres taken from such an embryo, the individual's sperm, the individual's egg, the individual's polar body, extra-cellular genetic material found on the individual, extra-cellular genetic material from the individual found in maternal blood, extracellular genetic material from the individual found in maternal plasma, cells from the individual found in maternal blood, genetic material known to have originated from the individual, and combinations thereof.

28. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the chromosome of interest is selected from the group consisting of chromosome 13, chromosome 18, chromosome 21, the X chromosome, the Y chromosome, and combinations thereof.

29. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the chromosomal abnormality is selected from the group consisting of monosomy, uniparental disomy, trisomy, other aneuploidies, unbalanced translocations, insertions, deletions, and combinations thereof.

30. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the method comprises determining whether the individual has Down Syndrome, Klinefelters syndrome, or Turner syndrome.

31. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an

individual, where the method further comprises normalizing the genetic data for differences in amplification and/or measurement efficiency between the loci.

32. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the method further comprises amplifying the genetic material of the target individual, and normalizing the genetic data for differences in amplification and/or measurement efficiency between the loci.

33. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual, where the method further comprises amplifying the genetic material of the target individual; and normalizing the genetic data for differences in measurement efficiency between the loci, chromosome segments, or chromosomes.

34. Another advantage of the present invention is that it allows the determination of the number of copies of a chromosome or a chromosome segment of interest in the genome of an individual by creating a set of one or more hypotheses specifying the number of copies of the chromosome or chromosome segment of interest and determining the probability of each of the hypotheses, where the probability of the hypotheses is determined without use of a reference sample.

Background Regarding the Infringing Activities

35. On information and belief, Verinata began selling and offering to sell its commercial non-invasive prenatal test for detecting chromosomal aneuploidies, Verifi®, around March 2012.

36. Verifi® uses massively parallel sequencing to analyze genetic material from a maternal blood sample and determine if there are too many or too few copies of a chromosome in a fetus's genome.

37. On information and belief, Illumina began offering to sell its commercial non-invasive prenatal test for detecting chromosomal aneuploidies, Verifi® Plus, in 2017.

38. Verifi® Plus uses massively parallel sequencing to analyze genetic material from a maternal blood sample and determine if there are too many or too few copies of a chromosome in the

fetal genome. Verifi® Plus also expands the capabilities of Verifi® to detect five specific microdeletion regions.

39. On information and belief, Illumina began offering to sell its commercial pre-plantation genetic screening test for detecting chromosomal aneuploidies, VeriSeq™ PGS on April 29, 2014.

40. Veriseq™ PGS uses massively parallel sequencing to analyze genetic material from a single cell or a few cells from an embryonic biopsy and determine if there are too many or too few copies of a chromosome in the embryo's genome.

41. On information and belief, Illumina began offering to sell its commercial non-invasive prenatal test for detecting chromosomal aneuploidies, VeriSeq™ NIPT, on April 10, 2017.

42. VeriSeq™ NIPT uses massively parallel sequencing to analyze genetic material from a maternal blood sample and determine if there are too many or too few copies of a chromosome in the fetal genome.

43. Illumina signed an Agreement to acquire Verinata on January 7, 2013, and completed its acquisition of Verinata on February 21, 2013.

44. Illumina licenses the right to perform the Verifi® test to other non-Illumina entities.

45. Illumina licenses the right to perform the VeriSeq™ PGS test to other non-Illumina entities.

46. Illumina licenses the right to perform the VeriSeq™ NIPT test to other non-Illumina entities.

FIRST COUNTERCLAIM

(NON-INFRINGEMENT OF THE '831 PATENT)

47. The foregoing paragraphs are realleged and incorporated by reference as if fully stated herein.

48. As demonstrated by Illumina's allegations in Count I of the Complaint, there is an actual, substantial, continuing and justiciable controversy between the parties regarding whether Natera has, either directly or indirectly, infringed any valid and enforceable claim of the '831 patent. Absent a declaration of non-infringement, Illumina will continue to wrongfully assert the '831 patent against

Natera, and thereby cause Natera irreparable injury and damage. Natera therefore has standing to seek declaratory judgment of non-infringement.

49. Natera has not infringed, and is not infringing directly, indirectly, contributorily, by inducement, or in any other manner any valid, enforceable claim of the '831 patent, either literally or under the doctrine of equivalents. Accordingly, Natera is entitled to a declaratory judgment that it has not infringed, contributed to the infringement of, nor induced infringement of any valid, enforceable claim of the '831 patent.

50. For example, Natera does not infringe the asserted claims of the '831 patent because the documents on which Illumina relies in its Complaint and Infringement Contentions (served on July 6, 2018) neither represent individually nor collectively the sample preparation aspects of Natera's accused Panorama™ Prenatal Screen. They are instead a mixing and matching of unrelated documents, and Illumina fails to explain how the documents fit together or relate to one another. In addition, at least some of the documents do not mention the accused Panorama™ Natera Prenatal Screen and/or are dated well before the '831 patent issued on November 15, 2016, or have no date at all.

51. Natera also does not infringe the asserted claims of the '831 patent because they are not patent-eligible under 35 U.S.C. § 101. Natera also does not infringe the asserted claims of the '831 patent because they are invalid based on prior art that anticipates and/or renders obvious the Asserted Claims. Natera also does not infringe the asserted claims because they are invalid for inadequate written description and enablement, and because they are invalid as indefinite. Further, Natera does not infringe the asserted claims because the '831 patent is unenforceable for failing to comply with the conditions required by the terminal disclaimer made during prosecution.

SECOND COUNTERCLAIM

(INVALIDITY OF THE '831 PATENT)

52. The foregoing paragraphs are realleged and incorporated by reference as if fully stated herein.

53. The '831 patent is invalid for failing to satisfy one or more of the requirements of the Patent Act, 35 U.S.C. § 1, *et seq.*, including but not limited to, the conditions of patentability set forth

in 35 U.S.C. §§ 101, 102, 103, and 112.

54. As demonstrated by Illumina's allegations in Count I of the Complaint, there is an actual, substantial, continuing and justiciable controversy between the parties regarding whether Natera has, either directly or indirectly, infringed any valid and enforceable claim of the '831 patent. Absent a declaration of invalidity, Illumina will continue to wrongfully assert the '831 patent against Natera, and thereby cause Natera irreparable injury and damage. Natera therefore has standing to seek declaratory judgment of invalidity.

55. For example, one or more claims of the '831 patent is ineligible under 35 U.S.C. § 101, including for the reasons set forth in Natera's Motion to Dismiss Under Federal Rule of Civil Procedure 12(b)(6) (Dkt. 24). As the Court has found, "the '831 patent is directed towards patent-ineligible subject matter." Dkt. 41 at 6. The '831 patent also does not contain an inventive concept because the selective enrichment of DNA sequences and successive rounds of amplification using primers are routine and conventional.

56. In addition, one or more claims of the '831 patent are invalid in view of the prior art, including references cited on the face of the '831 patent, as well as the prior art and grounds set forth in Natera's Petition for Inter Partes Review of the '831 patent (IPR2018-01317), and articles, products and processes that were publicly available or disclosed before the priority date of the '831 patent. For example, the asserted claims of the '831 patent are anticipated or rendered obvious over U.S. Patent Application Publication No. 2010/0120038 in view of the knowledge of a person of ordinary skill in the art.

57. Further, one or more claims of the '831 patent are invalid because the full scope of those claims is not enabled, nor described, by the written description of the '831 patent and those claims are indefinite.

58. Accordingly, Natera is entitled to a declaratory judgment that the '831 patent is invalid.

THIRD COUNTERCLAIM

(DIRECT INFRINGEMENT OF U.S. PATENT NO. 8,682,592)

59. The foregoing paragraphs are realleged and incorporated by reference as if fully stated

herein.

60. Illumina has infringed and continues to infringe: (a) at least claims 1, 5, 7–9, 15, 17, and 19–26 of the '592 patent under 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the Verifi® and Verifi® Plus tests; (b) at least claims 1–4, 7–9, 15, and 19–27 of the '592 patent under 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the VeriSeq™ PGS test; and (c) at least claims 1, 5, 7–9, 15, 17, and 21–24 of the '592 patent under 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the VeriSeq™ NIPT test.

61. By way of example and not limitation, each of the Verifi®, Verifi® Plus, VeriSeq™ PGS, and/or VeriSeq™ NIPT tests practices each limitation of claim 1 of the '592 patent. Specifically, Claim 1 of the '592 patent recites:

> 1. An ex vivo method for determining a number of copies of a chromosome or chromosome segment of interest in the genome of an individual, the method comprising:
>
> using a single nucleotide polymorphism (SNP) genotyping array or high throughput DNA sequencing to measure genetic material and produce genetic data for some or all possible alleles at a plurality of at least 100 loci on the chromosome or chromosome segment of interest in the individual, wherein the genetic data is noisy due to a small amount of genetic material from the individual; and wherein the small amount of genetic material from the individual is from fifty or fewer of the individual's cells, 0.3 ng or less of the individual's DNA, extracellular DNA from the individual found in maternal blood, or combinations thereof;
>
> creating a set of one or more hypotheses specifying the number of copies of the chromosome or chromosome segment of interest in the genome of the individual;
>
> determining, on a computer, the probability of each of the hypotheses given the produced genetic data; and
>
> using the probabilities associated with each hypothesis to determine the most likely

number of copies of the chromosome or chromosome segment of interest in the genome of the individual.

62. Preliminary claim charts demonstrating infringement by Illumina and third parties who license from Illumina and practice one or more of the Verifi® and Verifi® Plus, VeriSeq™ PGS, and/or VeriSeq™ NIPT tests are attached as Appendices A, B, and C respectively, and are incorporated herein by reference in their entirety. Each element in each of Appendices A, B, and C that is mapped to Verifi®, Verifi® Plus, VeriSeq™ PGS, and/or VeriSeq™ NIPT tests, respectively, is an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each claim element is required. The Exhibits and allegations in Appendices A, B, and C are exemplary only.

63. As set forth in **Appendix A**, each of the Verifi® and Verifi® Plus tests includes an ex vivo method for determining chromosome copy number in the genome of an individual (a fetus). Each of the Verifi® and Verifi® Plus tests use high throughput DNA sequencing (*i.e.*, massively parallel sequencing) to measure genetic material and produce genetic data for some or all possible alleles at a plurality of at least 100 loci on the chromosome or chromosome segment of interest (*i.e.*, the whole-genome data) in the individual, wherein the genetic data is noisy due to a small amount of genetic material from the individual; and wherein the small amount of genetic material from the individual is from extracellular DNA from the individual (*i.e.*, cell-free fetal DNA) found in maternal blood. Each of the Verifi® and Verifi® Plus tests creates a single hypothesis that the number of copies of a chromosome of interest in the genome of the individual is normally two and calculates a Normalized Chromosome Value (NCV), which is equivalent to a statististical z score for the single hypothesis. Each of the Verifi® and Verifi® Plus tests determines on a computer, the NCV of the chromosome of interest of each individual sample, which represents the probability of the single hypothesis given the produced genetic data, and uses the probability associated with the single hypothesis and thresholding to determine the most likely number of copies of the chromosome in the genome of the individual.

64. As set forth in **Appendix B**, the VeriSeq™ NIPT test includes an ex vivo method for determining chromosome copy number in the genome of an individual (a fetus). VeriSeq™ NIPT uses high throughput DNA sequencing (*i.e.*, massively parallel sequencing) to measure genetic material and

produce genetic data for some or all possible alleles at a plurality of at least 100 loci on the chromosome or chromosome segment of interest (*i.e.*, the whole-genome data) in the individual, wherein the genetic data is noisy due to a small amount of genetic material from the individual; and wherein the small amount of genetic material from the individual is from extracellular DNA from the individual (*i.e.*, cell-free fetal DNA) found in maternal blood. VeriSeq™ NIPT creates a single hypothesis that the number of copies of a chromosome of interest in the genome of the individual is normally two and calculates a Log Likelihood Ratio (LLR), which reflects the probability of a sample being affected, given the observed counting statistics and fetal fraction information, versus the probability of a sample being unaffected, given the same counting data. VeriSeq™ NIPT determines on a computer, the LLR score of the chromosome of interest of each individual sample, which represents the probability of the single hypothesis given the produced genetic data, and uses the probability associated with the single hypothesis and thresholding to determine the most likely number of copies of the chromosome in the genome of the individual.

65. As set forth in **Appendix C**, the VeriSeq™ PGS test includes an ex vivo method for determining chromosome copy number in the genome of an individual (an embryo). It uses high throughput DNA sequencing (*i.e.*, massively parallel sequencing) to measure genetic material and produce genetic data for some or all possible alleles at a plurality of at least 100 loci on the chromosome or chromosome segment of interest (*i.e.*, the whole-genome data) in the individual, wherein the genetic data is noisy due to a small amount of genetic material from the individual; and wherein the small amount of genetic material from the individual is from fifty or fewer of the individual's cells (*i.e.*, a single cell or a few cells from the embryo). VeriSeq™ PGS creates a set of one or more hypotheses specifying the number of copies of the chromosome or chromosome segment of interest in the genome of the individual (*i.e.*, among other things, an assumption that the normal copy number state for autosomes is two and most chromosomes have a normal copy number state). VeriSeq™ PGS determines on a computer, the probability of each of the hypotheses given the produced genetic data and uses the probabilities associated with each hypothesis to determine the most likely number of copies of the chromosome or chromosome segment of interest in the genome of the individual (for

example, determining the probabilities to the possible copy number states (0-4) for a chromosome of interest and using the highest probability to a particular copy number state to determine the chromosome copy number.)

66. Illumina has had notice of the ’592 patent since at least September 26, 2017, and since at least that time Illumina’s infringement has been willful and deliberate.

FOURTH COUNTERCLAIM

(INDIRECT INFRINGEMENT OF U.S. PATENT NO. 8,682,592)

67. The foregoing paragraphs are realleged and incorporated by reference as if fully stated herein.

68. Illumina actively induces infringement by others of at least claims 1–5, 7–9, 15, 17, and 19–27 of the ’592 patent under 35 U.S.C. § 271(b). For example, upon information and belief, Illumina’s licensees directly infringe, at least claims 1–5, 7–9, 15, 17, and 19–27 of the ’592 patent, literally or under the doctrine of equivalents, by performing within the United States the Verifi®, Verifi® Plus, VeriSeq™ PGS, and/or VeriSeq™ NIPT non-invasive prenatal tests. Illumina knowingly induces such infringement and possesses specific intent to encourage such infringement, for example by licensing the right to perform the these non-invasive prenatal tests to other non-Illumina entities. Illumina has had actual notice of the ’592 patent since at least September 26, 2017.

69. Illumina actively contributes to infringement by others of at least claims 1–5, 7–9, 15, 17, and 19–27 of the ’592 patent under 35 U.S.C. § 271(c). For example, upon information and belief, Illumina’s licensees directly infringe, at least claims 1–5, 7–9, 15, 17, and 19–27 of the ’592 patent, literally or under the doctrine of equivalents, by performing within the United States the Verifi®, Verifi® Plus, VeriSeq™ PGS, and/or VeriSeq™ NIPT non-invasive prenatal tests. As set forth above with respect to inducement, Illumina knows of the ’592 patent and knows that the performance of these tests is infringing. Finally, the Verifi®, Verifi® Plus, VeriSeq™ PGS, and/or VeriSeq™ NIPT tests that Illumina licenses to non-Illumina entities have no substantial non-infringing use.

PRAYER FOR RELIEF

FOR THESE REASONS**,** Natera respectfully requests that this Court enter judgment in its favor and grant the following relief:

a. An order declaring that Illumina, its respective officers, directors, agents, servants, employees, and attorneys, and those persons in active concert with it, take nothing on the claims asserted in the Complaint against Natera;

b. A judgment dismissing Illumina's Complaint against Natera with prejudice;

c. A judgment in favor of Natera against Illumina declaring that Natera has not and does not infringe, induce infringement, or contribute to any infringement of any valid and enforceable claim of the '831 patent;

d. A judgment in favor of Natera against Illumina declaring that the claims of the '831 patent are invalid and/or unenforceable;

e. An order declaring that Illumina's conduct in commencing and pursuing its claims of patent infringement renders this an exceptional case and awarding Natera its costs, expenses, and reasonable attorneys' fees under 35 U.S.C. § 285 and all other applicable statutes, rules, and common law;

f. An order denying Illumina's recovery of any costs;

g. A judgment that Illumina directly infringes, induces infringement, or contributorily infringes one or more claims of the '592 patent and that the '592 patent is valid;

h. A declaration that Illumina's infringement has been willful and deliberate since at least September 26, 2017, and an increase to the award of damages of three times the amount found or assessed by the Court, in accordance with 35 U.S.C. § 284;

i. An order enjoining Illumina and its officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting in active concert therewith from further infringement of the '592 patent;

j. A determination in favor of Natera against Illumina that Natera's Third and Fourth Counterclaims constitute an exceptional case under 35 U.S.C. § 285 and an award of

attorneys' fees and costs to Natera in this action;

k. Damages or other monetary relief, including, but not limited to, costs and pre- and post-judgment interest, to Natera; and

l. An order awarding Natera any such other relief as the Court may deem just and proper under the circumstances.

JURY DEMAND

Natera hereby demands a jury trial on all issues so triable.

Respectfully Submitted,

Dated: August 16, 2018

/s/ Tracey B. Davies

Tracey B. Davies (*pro hac vice*)
tdavies@gibsondunn.com
Mark Reiter (*pro hac vice*)
mreiter@gibsondunn.com
GIBSON, DUNN & CRUTCHER LLP
555 Mission Street, Suite 3000
San Francisco, CA 94105-0921
Telephone: 415.393.8200
Facsimile: 415.393.8306

Karen I. Boyd, SBN 189808
boyd@turnerboyd.com
TURNER BOYD LLP
702 Marshall Street, Suite 640
Redwood City, CA 94063
Telephone: 650.521.5930
Facsimile: 650.521.5931

Attorneys for Defendant
NATERA, INC.

CERTIFICATE OF SERVICE

I hereby certify that on August 16, 2018, I caused to be electronically filed the foregoing Answer and Affirmative Defenses with the Clerk of the Court via CM/ECF. Notice of this filing will be sent by email to all parties by operation of the Court's electronic filing systems.

Dated: August 16, 2018

By: /s/ *Tracey B. Davies*