IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CAREDX, INC.,		§	
		§	
	Plaintiff,	§	**Civil Action No. 19-662-CFC-CJB**
		§	
vs.		§	
		§	
NATERA, INC.,		§	**JURY DEMANDED**
		§	
	Defendant.	§	
		§	
		§	

FIRST AMENDED COMPLAINT

I. SUMMARY AND NATURE OF THE ACTION

1. CareDx, Inc. ("**CareDx**") has invested talent, time and treasure to develop AlloSure® ("**AlloSure**"), its patented kidney transplant surveillance diagnostic test. CareDx's innovations promise to revolutionize the treatment of kidney transplant patients by giving healthcare professionals an unprecedented ability to follow patients and detect rejection of a donated organ earlier and more accurately than the current standard of care. Competitor Natera, Inc. ("**Natera**") has begun a false advertising campaign designed to deceive doctors, healthcare professionals, insurance companies, and patients – as well as investors – into believing that Natera's "me too" test is superior to AlloSure when that has simply not been shown. Natera's dissemination of false and misleading claims about AlloSure is an attempt to poison the marketplace and must be stopped.

2. CareDx is dedicated to improving the care and management of organ transplant patients by inventing, developing, manufacturing, and distributing noninvasive cell-free DNA transplant surveillance products. Combining the latest advances in genomics and bioinformatics technology, along with its commitment to generating high quality clinical evidence through trials

and registries, CareDx markets and sells AlloSure. AlloSure is a clinically and analytically validated, Medicare-covered, non-invasive blood test that accurately detects active kidney rejection. It is a game-changer in the treatment of kidney transplant patients because it can ensure that healthcare professionals get the critical and reliable information necessary to treat patients – information that was previously available only (if at all) through invasive and expensive exploratory biopsies.

3. CareDx is informed and believes that Natera has taken improper advantage of CareDx's pioneering work to develop a competing kidney transplant rejection test. Upon information and belief, Natera is in the midst of launching its competing test, Prospera™ ("**Prospera**"). Natera is making various false and misleading claims that Prospera is superior to CareDx's AlloSure based upon a kidney transplant study (the "**Natera Study**," *see* Exhibit 1), which purports to validate the performance of Natera's kidney transplant rejection test. Natera's claims are false.

4. Any comparative claims regarding products such as kidney transplant surveillance tests should be supported by head-to-head clinical trials comparing the two products – ideally, randomized, well-controlled trials. Cross-test comparisons, especially cross-test comparisons where the methodology of the underlying studies differs significantly, often lead to misleading, unreliable or false conclusions. Here, Natera is using the results of its flawed, single-center, retrospective Natera Study to compare Prospera's performance to AlloSure's performance, which was validated by a robust, multi-center, prospective, peer-reviewed clinical trial. Even putting aside the substantial material flaws that render the Natera Study unreliable, the methodology of the two studies differs so significantly that it is entirely improper to draw meaningful or reliable comparisons between the performances of the two products.

5. Natera compounds the deception because the Natera Study's methodology is so deeply flawed as to be unreliable. Natera's subsequent claims about the supposedly superior performance of Prospera are still false and misleading because they are based upon numerous unscientific, unreliable, and inappropriate conclusions and comparisons of the Natera Study performance data with CareDx's data. Natera's deceptive claims also disparage AlloSure.

6. Natera's false and misleading claims are contained in promotional, product marketing and investor materials and presentations that are being disseminated in connection with Prospera. These unlawful claims are designed to persuade, among others, medical personnel who purchase, recommend, or use cell-free DNA tests in kidney transplant patients, insurance companies who cover medical treatments, kidney transplant patients who are seeking medical treatment, and investors who invest in biotech companies that offer diagnostic testing into believing that Prospera is superior to CareDx's AlloSure when it has not been shown. Natera's false statements are harming CareDx's reputation, as well as causing lost sales and business opportunities.

7. Natera's misrepresentations violate the federal Lanham Act, 15 U.S.C. § 1125(a), the Delaware Unfair or Deceptive Trade Practices Act, and the common law of unfair competition. CareDx seeks to enjoin Natera's false and misleading statements concerning Prospera and AlloSure, as well as its disparaging statements concerning AlloSure. Natera also seeks monetary and other relief for damages incurred.

II. PARTIES

8. CareDx is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 3260 Bayshore Blvd., Brisbane, CA 94005.

9. CareDx was formed in 1998 by pioneers in molecular diagnostics. Since its inception, CareDx has focused its expertise on the discovery, development and commercialization

of clinically differentiated, high-value solutions for organ transplant recipients. It was the first company to develop and commercialize non-invasive transplant surveillance testing to follow transplant recipients' immune status with the aim to improve long-term patient outcomes.

10. Today, CareDx markets and sells AlloSure. AlloSure uses advanced DNA sequencing methods to quantify donor-derived cell-free DNA (dd-cfDNA) in transplant recipients without having to conduct separate genotyping. Measuring dd-cfDNA in a transplant recipient's blood enables early detection of kidney transplant rejection and may facilitate personalized immunosuppressive treatment. AlloSure has helped numerous nephrologists manage their patients' post-transplant care, while avoiding the high costs and added risks of renal biopsies.

11. On information and belief, Natera is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 201 Industrial Road, Suite 410, San Carlos, CA 94070. Upon information and belief, Natera is actively advertising and seeking Medicare coverage for Prospera, a kidney transplant rejection test, which it performs at its CLIA-certified laboratory in San Carlos, CA.

III. JURISDICTION AND VENUE

12. This action arises under the Lanham Act, 15 U.S.C. § 1125(a) *et seq.*, and this Court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. § 1331 and 1338. This Court has supplemental jurisdiction over CareDx's state-law claim pursuant to 28 U.S.C. § 1367(a) because it is related to CareDx's Lanham Act claim and it forms part of the same case or controversy.

13. Venue is proper in this Court pursuant to 28 U.S.C. § 1391(b)(2) because Natera is a Delaware corporation.

14. The Court has personal jurisdiction over Natera because Natera is a Delaware corporation.

IV. FACTUAL ALLEGATIONS

A. Organ Transplant Rejection

15. Human kidneys, two bean-shaped organs located on either side of the spine just below the rib cage, are vital organs in the human body. The kidneys continuously filter the bloodstream, provide balance of the body's fluid and acid-base equilibrium, and eliminate from the body certain waste or toxins in the urine. Various diseases can cause kidneys to lose their filtering ability, which results in the accumulation of harmful levels of fluid and toxins in the body, and may progress to kidney failure, also known as end-stage renal disease or end-stage kidney disease. To stay alive, individuals with end-stage kidney disease must either have fluid and toxins removed from their bloodstream through hemodialysis (which involves significant patient inconvenience and relatively high cost), or have a kidney transplant (which has superior long-term outcomes and cost effectiveness, but are not always available).

16. Kidney transplant recipients have an increased risk for complications such as infections and cancers, and generally require long-term immune system suppression medications to prevent organ rejection. Early detection of rejection is critical—the earlier the patient and his/her medical professional team learns of the transplant rejection, the sooner preventive measures and treatment can occur.

17. The generally-accepted method for diagnosis of active rejection ("**AR**") of a transplanted kidney is assessment, by light microscopy examination, of kidney tissue obtained from a needle biopsy. However, biopsies are invasive, can be painful, can cause complications in patients and are expensive; accordingly, they are generally not used for regular surveillance for rejection in transplant patients.

18. Prior to the development of AlloSure, there were no existing non-invasive biomarkers that had established adequately-validated performance to detect active rejection of a

kidney transplant. The current standard of care is a screening blood test to measure creatinine (an indicator of kidney function) in a transplant recipient's blood. A high serum creatinine level may indicate that the kidney is in rejection, but unfortunately, creatinine is not specific for kidney rejection. Moreover, an increased creatinine may not be observed until after irreversible damage to the kidney has already occurred.

B. Cell-free DNA

19. Practical use of cell-free DNA (cfDNA) technology for care of kidney transplant recipients has been led by CareDx. Cell-free DNA are fragments of DNA found in the bloodstream of the transplant recipient. When a transplant recipient's immune system is rejecting a donor kidney, cell-free DNA originating from the donor kidney (donor-derived cell-free DNA or dd cfDNA) is released from the organ cells undergoing cell injury and death into the patient's bloodstream. High levels of the donor-derived cell-free DNA in a recipient's blood may indicate the transplanted organ is being rejected.

20. CareDx markets and sells AlloSure, which measures the proportion (percentage) of donor-derived cell-free DNA found in a transplant patient's bloodstream. The AlloSure test value indicates the health or injury of the transplanted organ. This testing method provides a new and different dimension and versatility for surveillance of the well-being of the patient and the transplanted organ than serum creatinine testing or kidney biopsies.

C. CareDx's Clinical Studies to Validate the Results of Cell-free DNA Testing

21. At substantial time and expense, CareDx conducted a multi-center, prospective observational clinical trial to validate the clinical performance of AlloSure. This clinical trial is named the Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Acute Rejection in Kidney Transplant Recipients ("DART") study. It involved collecting blood specimens at scheduled intervals and at the time of clinically-indicated biopsies from 14 clinical sites

representative of the United States renal transplant registry population and comparing the levels of donor-derived cell-free DNA with the biopsy results. The report of study results was peer-reviewed and published in the July 2017 issue of the *Journal of the American Society of Nephrology*, authored by RD Bloom (the "**CareDx Study**," *see* Exhibit 2).

22. Cell-free DNA nephrology (kidney) diagnostic test performance can be measured by metrics including **Specificity, Sensitivity,** and **AUC** (area under the curve).

23. **Sensitivity** is the measure of the percentage of true positive test results—i.e., it quantifies the percentage of test results that correctly identify kidney rejection. Also referred to as the "rule-out" scenario, if a positive test result is highly sensitive (meaning it is good at identifying nearly all true positives), and a patient receives a negative test result, the healthcare provider is fairly certain that the patient does *not* have the disease under consideration.

24. **Specificity** is the measure of the percentage of true negative results—i.e., it quantifies the percentage of test results that correctly identify where a transplant patient is not in active rejection. Also referred to as the "rule-in" scenario, if a test result is highly specific (meaning it is good at identifying true negatives), and a patient receives positive test results, the healthcare provider is fairly certain that the patient *does* have the disease under consideration.

25. Whereas the sensitivity and specificity values are dependent upon the chosen cut-off value of the test (*e.g.*, 1% dd-cfDNA), the **AUC**, on the other hand, is a performance metric that uses the sensitivity and specificity at all possible test cut-off values to calculate a measure for the overall accuracy of the test. The **AUC** is determined by drawing a graph for the range of potential test result cut-off values, with the test's true positive rate (sensitivity) plotted on the y-axis and the false positive rate (specificity, plotted as 1-specificity) on the x-axis, and measuring the area under this curve. The chart plots all possible values for the test's sensitivity and

specificity. If a test has only a random ability to identify true positives and negatives (and thus is not predictive or useful to make a diagnosis), the AUC will be 0.5—a straight diagonal, in which the true positive rate proportionally increases with the false positive rate at different cut-off points. As a test nears perfect diagnostic performance, the AUC will approach 1.0.

26. The DART study showed that CareDx's AlloSure markedly outperformed serum creatinine testing in sensitivity, specificity, and AUC for detecting active rejection, and that AlloSure, unlike serum creatinine, is highly accurate in being able to distinguish rejection from no rejection.

D. The Natera Study is Too Flawed and Unreliable to Support Claims About Prospera's Performance, Let Alone Comparative Claims

27. Wanting to capitalize on CareDx's innovative success, Natera developed its own cell-free DNA test—Prospera—and sponsored a clinical study purportedly to validate its effectiveness. Natera then falsely represented, in numerous investor, press, and advertising materials that the results of the Natera Study show that Prospera is superior to CareDx's AlloSure. But unlike the DART study, the Natera Study is so flawed as to both its methodology and its execution that not only are its results unreliable, they cannot be used to support any fair comparisons between the performance of Prospera and the performance of AlloSure of the kind that Natera has attempted.

28. Unlike the CareDx study, which utilized an observational protocol that involved gathering and analyzing samples from 14 clinical centers at pre-defined timepoints, the investigators for the Natera Study chose instead to retrospectively select samples that had been collected for unrelated purposes by a single clinical center and archived. The results of the retrospective study purporting to validate the test that would come to be known as Prospera were published in the December 23, 2018 issue of the *Journal of Clinical Medicine*, authored by Tara

K. Sigdel (the **"Natera Study Publication**"). Unlike the rigorous and prestigious Journal of American Society of Nephrology that published the CareDx AlloSure Study, the *Journal of Clinical Medicine* has yet to establish a level of quality of content and is *not* a kidney or transplant specific publication, and therefore has limited experience and depth of peer review for reviewing kidney transplant rejection tests.

a. The Sample Set From the Natera Study is Not Representative of the Transplant Population

29. To begin with, the samples analyzed in the Natera Study are not representative of the real-world kidney transplant population, as they were taken retrospectively from a pre-existing sample archive collected from a single study center with biopsies purportedly re-interpreted by a single pathologist. Accordingly, the Natera Study had to rely on existing samples and had no control over when these samples were collected or analyzed. Consequently, the results obtained from Natera's narrow sample set cannot be used to extrapolate results that are representative of the results that can be expected of the test in the broad range and diversity of the kidney transplant population and sample handling procedures encountered in the real world. In contrast, the CareDx Study was prospectively planned and collected samples from a representative patient population across the United States. The CareDx Study was a multi-center study, which means that samples analyzed in the CareDx Study were collected from fourteen (14) study centers with biopsies primarily interpreted by the real-world pathologists at each center. Whereas the biopsies in the CareDx Study reflect real-world pathologists' readings of tissue specimens, the Natera Study represents only a *single* center's pathologist readings. In other words, to the extent that any systemic biases were inherent in the way that samples were collected, labeled, read, stored, handled or shipped from a single location, these biases would have been reflected in the final results of the study as they were not balanced by methods from other centers. Accordingly, the data obtained

from Natera's pre-existing sample set cannot reliably be used to extrapolate results for the entire kidney transplant population.

30. Further, 20% of the patients from whom samples were analyzed in the Natera Study were under the age of 18, and *all* of the under-18 patients are classified as "**NR**" (no rejection). Such uniform results are surprising and suspicious because children are *more likely* to suffer active rejection of an organ transplant ("**AR**"), yet there is no indication that any attempt was made either to understand these anomalous results or to exclude the samples. Furthermore, the inclusion of samples from children under 18 generally demonstrates a lack of concern for the potential biasing effect, given the different likelihood of rejection between children and adults. In contrast, the CareDx Study methodology included only samples from adult patients.

b. Claims Based on the Natera Study Include Excluded Samples

31. The investigators in the Natera Study "collected" from the sample bank archive 300 samples from 193 unique renal transplant recipients. In its initial representations about the Natera Study – for example, in an 8K filed with the FTC and a June 2018 investor call – Natera made claims about Prospera's performance based on its analysis of 292 samples from 187 patients. *See* Exhibit 3. Yet, in the Natera Study Publication, the results are based an analysis of only 217 samples. Of the 300 collected samples, 60 samples were eliminated because they were not biopsy matched (meaning no biopsy corresponded with the plasma sample); 15 samples were excluded because they were collected within three (3) days from transplant and an additional 8 samples were excluded as they were unable to be sequenced (a sample set that excludes only these last 8 samples is the basis for Natera's oft-cited, misleading "292-set" sample size). Nevertheless, Natera continued to represent that its study was based on 292 samples. This misleading statement unfairly magnified the significance of the study.

c. The Natera Study Improperly Mixes Population Sets

32. "For cause" kidney biopsies are conducted on patients for whom a warning sign about possible AR has been triggered (for example, a high serum creatinine level). A "protocol" (or "surveillance") biopsy is conducted even though the patient has no prior indication of AR. "Protocol" biopsies are not a standard practice at most U.S. centers; instead, most centers do not perform "protocol" biopsies due to the low frequency of finding rejection compared to the risks and costs of the procedure. The Natera Study further biases its sample selection by mixing "for cause" and "protocol" biopsy samples in a manner that inappropriately skews the performance metrics of the Natera Study in Prospera's favor.

33. Because "for cause" biopsies are prompted by a warning sign for AR, one would expect that a higher proportion of "for cause" biopsies would show AR than "protocol" biopsies, which are not prompted by a warning sign. Similarly, one would expect that a higher proportion of "protocol" biopsies would show NR than "for cause" biopsies. However, rather than analyze the "for cause" and "protocol" biopsies separately, as would be appropriate, Natera chose to pool the biopsy data. Because Natera analyzed by NR and AR groups, this pooling meant that "protocol" biopsies were (predictably) underrepresented in the AR group and (predictably) overrepresented in the NR group, improving the apparent performance of the Natera Study. Including "protocol" biopsies because they are not likely to show rejection tends to artificially inflate Prospera's ability to identify true negatives (i.e., specificity). The "protocol" biopsy samples are more likely to be "easy" calls in that there is no AR, inflating the appearance of Prospera's accuracy. In contrast, CareDx *only* analyzed "for cause" biopsies, the population most vulnerable to AR.

d. The Natera Study Does Not Adhere to the Banff Rules

34. The Banff Classification of Allograft Pathology (the "**Banff Rules**") is an international consensus classification for the reporting of biopsies from solid organ transplants. The Banff Rules provide criteria for the diagnosis of types of kidney rejections. The Banff Rules are reviewed and updated every two (2) years in light of the rapidly expanding information about kidney transplants. Only kidney transplant rejection studies conducted in accordance with the Banff Rules are accepted in the transplant research and scientific community.

35. Although the Natera Study Publication claims to adhere to the 2017 Banff Rules ("All pathology samples were read at UCSF by a single renal pathologist and rated according to the recently updated Banff criteria"), the detailed criteria found in the Natera Study Publication do not consistently comport with the 2017 Banff Rules, especially in classifications of T cell-mediated rejection ("**TCMR**") and antibody-mediated rejection ("**ABMR**"), forms of AR. For instance, the Natera Study methods define TCMR by excluding the most common type of TCMR (grade IA). Further, the Natera Study introduced new ABMR terms not found or recognized in the Banff classification system. Natera likely excluded such samples in order to obtain more favorable, but scientifically invalid, test performance results. In contrast, the CareDx Study strictly adhered to all Banff 2013 criteria (the relevant standard at the time) in its analysis, including TCMR IA, without sample selection or rule interpretation bias.

36. By misclassifying the types of AR, Natera is either excluding certain patients/samples by leaving out certain patients/samples entirely, or improperly classifying them as NR by placing them in the NR group, distorting the performance metrics of Natera's product, and preventing any lawful comparison to AlloSure.

E. The Natera Study Cannot Support Any Comparative Claims Between Prospera and AlloSure

37. Natera bases its false and misleading claims for Prospera on a purported comparison between the results of the Natera Study and the results of the CareDx Study, but any comparison is entirely invalid. Any comparative claims regarding products such as kidney transplant surveillance tests must be supported by head-to-head clinical trials comparing the two products. Cross-test comparisons, especially cross-test comparisons where the methodology of the underlying studies differ significantly, are not reliable and often lead to misleading or false conclusions. Here, Natera is using the results of its flawed, single-center, retrospective Natera Study to compare Prospera's performance to AlloSure's performance based on the results of a robust, multi-center, prospective peer-reviewed clinical trial that validated the performance of AlloSure. Even putting aside the substantial material flaws that render the Natera Study unreliable, the methodology of the two studies differs so significantly that no meaningful or reliable comparisons can be drawn between the performance of the two products. The Natera Study is not "equal" to the clinically and analytically validated CareDx Study, nor are they head-to-head studies. Accordingly, all claims that these tests demonstrate anything about Prospera's performance compared to AlloSure's performance are literally false and entirely misleading.

38. Natera's manipulation of its test results, combined with its pattern of blatant falsehoods concerning the accuracy and veracity of Prospera as compared to AlloSure, reflects Natera's intent to unlawfully deceive and mislead consumers. CareDx respectfully seeks an immediate halt to Natera's continued false and misleading advertising claims, along with monetary damages and other requested relief.

F. Natera Makes False and Misleading Representations About the Natera Study's Results

39. Natera has, and, unless prevented, will continue to make false, misleading, and harmful representations about the Natera Study's results, including, but not limited to, the following examples.

40. **June 2018 Press Release:** Natera's June 21, 2018 press release refers to data pulled from the Natera Study and makes false claims such as, "This performance data suggests the potential of Natera's assay for use in both rule-in and rule-out applications" and "This sensitivity compares favorably against competition [citation to the CareDx Study], which reported only 59% sensitivity in a 2017 study." *See* Exhibit 4. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that its comparison claims are precluded. Moreover, Natera does not report its value for specificity—required for "rule-in" applications—which is actually significantly lower than its sensitivity value and the non-comparable value from the CareDx Study. In addition, in the press release, Natera asserts that the performance data for Prospera was derived from "300 plasma samples from 193 unique kidney transplant patients." Such a statement is false because the conclusions of the Natera Study were made from a study of 217 samples from 178 unique patients.

41. **8K:** Natera's June 27, 2018 8K included a slide entitled "Natera Assay Outperforms Competition," comparing the performance metrics from Prospera to AlloSure. *See* Exhibit 3. The data used in the 8K slide is from the Natera Study, and from a data set of 292 samples, which wrongfully includes both 15 samples excluded from the Natera Study Publication for failure to meet inclusion criteria, *and* an additional 60 samples eliminated from the Natera Study in the Natera Study Publication because they were not biopsy matched (meaning no biopsy

corresponded with the plasma sample). Moreover, although the methodology differs and the studies cannot support comparative claims, it is clear from the data that Natera presents that even with all the advantages of the biases in the Natera Study, the specificity for Prospera as measured in the Natera Study and presented on the slide (73%) is lower than the non-comparable specificity value for AlloSure in the CareDx Study presented on the slide (85%). The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

42. **July 2018 Prospectus Supplement:** Natera's July 12, 2018 Prospectus Supplement claims that Natera evaluated "292 plasma samples from 187 unique kidney transplant patients" and that "Natera's dd-cfDNA assay demonstrated 92% sensitivity in detecting acute rejection….[t]his sensitivity compares favorably against competition, which reported only 59% sensitivity in a 2017 study." *See* Exhibit 5. These statements are false. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

43. **January 2019 Press Release:** Natera's January 7, 2019 press release purports to compare the performances of Prospera with AlloSure and falsely states that Prospera "include[s] higher sensitivity and nearly 18% area under the curve (AUC) than the competitive assay [AlloSure]," and "the [Natera] study results also showed higher sensitivity (89% vs. 59%) and higher AUC (0.87 vs. 0.74) than the competitive assay [AlloSure]." *See* Exhibit 6. These statements are false. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's

methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

44. **January 2019 JP Morgan Presentation:** The January 9, 2019 Natera Company Presentation at the J.P. Morgan Healthcare Conference contains literally false statements about Prospera, including "driven by superior clinical data." The presentation also wrongfully compares Prospera with AlloSure, with statements such as, "Highest area under the curve; First test to consistently detect subclinical acute rejection." *See* Exhibit 7. These statements are false. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

45. **Steve Chapman's Misleading Public Statements:** At the J.P. Morgan Healthcare Conference, Steve Chapman, President and CEO of Natera, gave an oral presentation in which he wrongfully claimed that Prospera is superior to AlloSure, "So second, the performance [uh] was eighteen percent better than the competitor's clinical valuation as measured by area under the curve, which is a metric that combines sensitivity and specificity. Third, [uh] we were the first company to perform well in T-cell mediated rejection, which is about one third of rejection cases, where we have one hundred percent sensitivity compared to our competitor's twenty seven percent sensitivity." These statements are false. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

46. **February 1, 2019 Press Release:** Natera's February 1, 2019 press release falsely states that its Assay is superior to AlloSure, including through statements such as, "Natera's assay

detected acute rejection (AR) with 89% sensitivity and 0.87 area under the curve (AUC) . . . compar[ing] favorably against competition, which in a 2017 study [the CareDx Study] reported 59% sensitivity and 0.74 AUC . . . No other dd-cfDNA assay has been shown to detect TCMR or validated to detect subclinical AR . . ." *See* Exhibit 8. These statements are false. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

47. **February 22, 2019 Press Release:** Natera's February 22, 2019 press release also falsely states that its Assay is superior to AlloSure, including through statements such as, "The excellent analytical performance of Natera's dd-cfDNA assay underpins its superior clinical performance in detecting active allograft rejection (AR)," and "In its recently published clinical validation study, Natera reported higher sensitivity (89% vs. 59%) and higher area under the curve (0.87 vs. 0.74) than the competing dd-cfDNA assay." *See* Exhibit 9. These statements are false. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

48. **False Advertisement at CEOT Conference:** In a false advertisement included within the conference bag of each attendee at the February 21-23, 2019 American Society of Transplantation CEOT Conference, Natera, citing both the Natera and CareDx Studies, falsely wrote: "Natera's assay detected acute rejection (AR) with 89% sensitivity and 0.87 area under the curve (AUC). This test performance . . . compares favorably against competition, which in a 2017 study reported 59% sensitivity and 0.74 AUC." *See* Exhibit 10. These statements are false. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially

flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

49. **March 2019 Press Release:** Natera's March 28, 2019 press release falsely states that its Assay is superior to Allosure, including through statements such as, "Natera reported higher sensitivity (89% vs. 59%) and higher area under the curve (0.87 vs. 0.74) than the competing dd-cfDNA assay." *See* Exhibit 11. These statements are false. The comparisons to AlloSure are false both because the Natera Study is so materially and substantially flawed that it is unreliable, and because the Natera Study's methodology differs so significantly from the CareDx Study's methodology that comparison claims are precluded.

50. Natera's campaign of deception and false advertising is ongoing; the foregoing examples merely represent some of Natera's false and misleading communications.

G. Natera's False and Misleading Statements Have Harmed and Will Continue to Harm CareDx

51. Natera and CareDx are competitors. Both companies have introduced genomic-based testing services and products. Natera's false and misleading statements about AlloSure have harmed and will continue to harm CareDx though loss of goodwill, reputation, profits, and prospective business contracts.

52. Upon information and belief, Natera has begun significant marketing efforts for Prospera, including by making Prospera available for use in clinical trials and marketing Prospera to major clinical centers for such use.

53. Upon information and belief, Natera's false and misleading statements have harmed CareDx's reputation and have caused it to lose sales.

CAUSES OF ACTION

COUNT ONE – LANHAM ACT VIOLATION
False Advertising in Violation of 15 U.S.C. § 1125(a)

54. CareDx incorporates by reference all the allegations set forth above as if fully set forth herein.

55. Natera and its representatives and agents made false and misleading statements, including but not limited to direct communications and written promotional materials to healthcare professionals, insurance companies, patients, and the general public about the nature, characteristics, and quality of AlloSure. These false and misleading statements include representations that the Natera Study showed that Prospera is superior to AlloSure, including because (i) Prospera detects AR with greater sensitivity; (ii) Prospera detects AR with higher AUC; (iii) the Natera Study is reliable; and (iv) the results of the Natera Study can be used to support claims comparing the performances of Prospera and AlloSure. These statements are literally false and/or misleading commercial speech in violation of the Lanham Act, 15 U.S.C. § 1125(a).

56. Natera's false and misleading statements were made in interstate commerce, and in the context of commercial advertising or promotion, as they were made for the purpose of influencing healthcare providers, insurance companies, patients, and the general public to use Prospera, or recommend or cover Natera instead of AlloSure or CareDx, as well as to harm CareDx's reputation and business prospects in the marketplace.

57. Natera made its false and misleading statements knowingly and willfully, or recklessly to healthcare providers, insurance companies, patients, and the general public.

58. Natera's false and misleading statements likely have (and, unless stopped, will continue to) deceive healthcare providers, insurance companies, patients, and the general public about the capabilities and accuracy of AlloSure.

59. Natera's false and misleading statements are material and will affect the purchasing and investment decisions of healthcare providers, patients, and insurance companies.

60. Natera's false and misleading statements have and are likely to cause substantial harm to CareDx in the marketplace, including lost business and loss of goodwill and reputation. Natera's conduct constitutes false and misleading descriptions or representations about its own and a competitor's goods and services under the Lanham Act, 15 U.S.C. § 1125(a). CareDx is entitled to all relief available for such false and misleading statements, including but not limited to injunctive relief, disgorgement of Natera's ill-gotten profits, recovery of CareDx's damages, attorneys' fees, the costs of this action, and treble damages. *See id.* § 1117(a).

COUNT TWO
COMMON LAW UNFAIR COMPETITION

61. CareDx incorporates by reference all the allegations set forth above as if fully set forth herein.

62. Natera and its representatives and agents willfully made false and misleading statements, including but not limited to direct communications and written promotional materials to healthcare professionals, insurance companies, patients, and the general public about the nature, characteristics, and quality of AlloSure. These false and misleading statements include representations that the Natera Study showed that Prospera is superior to AlloSure, including because (i) Prospera detects AR with greater sensitivity; (ii) Prospera detects AR with higher AUC; (iii) the Natera Study is reliable; and (iv) the results of the Natera Study can be used to support claims comparing the performances of Prospera and AlloSure.

63. Natera's false and misleading statements were made in interstate commerce, and in the context of commercial advertising or promotion, as they were made for the purpose of influencing patients and healthcare providers to use Natera's products instead of AlloSure when

testing for kidney transplant rejection, as well as to harm CareDx's reputation and business prospects in the marketplace.

64. Natera made its false and misleading statements knowingly or recklessly to healthcare providers, insurance companies, patients, and the general public.

65. Natera's false and misleading statements likely have (and, unless stopped, will continue to) deceive healthcare providers, patients, insurance companies, and the general public about the capabilities and accuracy of AlloSure.

66. Natera's false and misleading statements have and are likely to cause substantial harm to CareDx in the marketplace, including lost business and loss of goodwill and reputation. CareDx is entitled to damages from Natera, as well as other remedies provided under the law.

COUNT THREE
DELAWARE UNFAIR OR DECEPTIVE TRADE PRACTICES
6 Del. C. §§2532(a)(5), (8), (12)

67. CareDx incorporates by reference all the allegations set forth above as if fully set forth herein.

68. Natera's false and misleading advertising, investor, and promotional materials falsely compare the Natera Study with the CareDx Study, even though the two Studies are incapable of head-to-head comparison because their methodologies greatly differ, and because the Natera Study's data sets are too unreliable to allow for such comparison. Natera's false and misleading statements relating to Prospera and AlloSure have violated subsections 5, 8, and 12 of the Delaware Unfair and Deceptive Trade Practices Act (the "**UDTPA**").

69. In violation of Section 5 of the UDTPA Natera's false and misleading statements represent that Prospera has uses or benefits that it does not have. For example, Natera falsely claims that Prospera: (i) has a superior clinical performance in detecting AR; (ii) is the first test to

consistently detect subclinical acute rejection; and (iii) is more sensitive than competing assays. These advertising and promotional materials claims are based on the severely flawed Natera Study and misrepresent Prospera's efficacy.

70. In violation of Section 8 of the UDTPA Natera's false and misleading statements disparage AlloSure and CareDx by representing that AlloSure is of a lower standard, quality, or grade than it actually is. Natera is making statements touting Prospera's superiority to AlloSure, including: (i) Prospera's "sensitivity compares favorably against competition;" (ii) Prospera's "performance [uh] was eighteen percent better than the competitor's clinical valuation;" and (iii) "[n]o other dd-cfDNA assay has been shown to detect TCMR or validated to detect subclinical AR." These statements falsely represent that AlloSure is inferior to Prospera, when that has not been shown by any study, including the Natera Study.

71. Natera's false and misleading statements cause likelihood of confusion or of misunderstanding as to the affiliation, connection, or association with Prospera and AlloSure in violation of section 12 of the UDTPA. These false and misleading statements include representations that the Natera Study showed that Prospera is superior to AlloSure, including because: (i) Prospera detects AR with greater sensitivity; (ii) Prospera detects AR with higher AUC; (iii) the Natera Study is reliable; and (iv) the results of the Natera Study can be used to support claims comparing the performances of Prospera and AlloSure.

72. Natera made its false and misleading statements knowingly or recklessly.

73. These false and misleading statements violate the Delaware Deceptive Trade Practices Act, 6 Del. C. §§2532(a)(5), (8), (12).

JURY DEMAND

74. CareDx requests a trial by jury.

PRAYER

WHEREFORE, CareDx respectfully requests that the Court enter an order awarding the following relief:

a. Judgment in favor of CareDx and against Natera;

b. An Order preliminarily and permanently enjoining Natera from disseminating or causing the dissemination of the false and misleading statements as alleged herein;

c. An Order requiring Natera to take all necessary corrective measures to correct the false and misleading impressions created among healthcare professionals by the false and misleading statements alleged herein;

d. CareDx's actual monetary damages, including but not limited to CareDx's lost business and profits, harm to CareDx's goodwill and reputation, and Natera's ill-gotten and unjustly derived revenues

e. Punitive and exemplary damages;

f. Pre- and post-judgment interest on all monetary damages, as permitted by law;

g. Costs of this litigation, including expert witness fees, as permitted by law;

h. Attorneys' fees, as permitted by law;

i. Statutory damages, including multipliers and equitable enhancements, as permitted by law; and

j. Such other and further relief, at law or in equity, to which CareDx is justly entitled.

Dated: February 7, 2020

Respectfully submitted,

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EXHIBIT 1

Journal of
Clinical Medicine

MDPI

Article

Optimizing Detection of Kidney Transplant Injury by Assessment of Donor-Derived Cell-Free DNA via Massively Multiplex PCR

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Abstract: Standard noninvasive methods for detecting renal allograft rejection and injury have poor sensitivity and specificity. Plasma donor-derived cell-free DNA (dd-cfDNA) has been reported to accurately detect allograft rejection and injury in transplant recipients and shown to discriminate rejection from stable organ function in kidney transplant recipients. This study used a novel single nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) methodology to measure dd-cfDNA in various types of renal transplant recipients for the detection of allograft rejection/injury without prior knowledge of donor genotypes. A total of 300 plasma samples (217 biopsy-matched: 38 with active rejection (AR), 72 borderline rejection (BL), 82 with stable allografts (STA), and 25 with other injury (OI)) were collected from 193 unique renal transplant patients; dd- cfDNA was processed by mmPCR targeting 13,392 SNPs. Median dd-cfDNA was significantly higher in samples with biopsy-proven AR (2.3%) versus BL (0.6%), OI (0.7%), and STA (0.4%) ($p < 0.0001$ all comparisons). The SNP-based dd-cfDNA assay discriminated active from non-rejection status with an area under the curve (AUC) of 0.87, 88.7% sensitivity (95% CI, 77.7–99.8%) and 72.6% specificity (95% CI, 65.4–79.8%) at a prespecified cutoff (>1% dd-cfDNA). Of 13 patients with AR findings at a routine protocol biopsy six-months post transplantation, 12 (92%) were detected positive by dd-cfDNA. This SNP-based dd-cfDNA assay detected allograft rejection with superior performance compared with the current standard of care. These data support the feasibility of using this assay to detect disease prior to renal failure and optimize patient management in the case of allograft injury.

Keywords: cfDNA; kidney transplantation; rejection

1. Introduction

Precision medicine and personalized tailoring of immunosuppressive drug regimens can improve the current state of organ transplant management [1]. Transplantation injuries may be delayed in detection, and therefore treated ineffectively, because diagnosis can be difficult and biopsy, an invasive and potentially morbid procedure, may be inconclusive. Though advances in immunosuppressive drugs, organ procurement methods, and human leukocyte antigen-typing have lowered the number of clinical- and biopsy-confirmed rejection episodes, sub-clinical rejection of kidney grafts remains a significant risk [2,3]. Kidney transplant management is particularly challenging owing to the lack of sensitivity and specificity of the serum creatinine assay, which, in addition to the late detection of transplant injuries, makes immunosuppression dosage and adjustment far from personalized [4,5]. Therefore, rapid and non-invasive detection and prediction of allograft injury/rejection holds promise for improving the post-transplantation management of patients who have received kidney allografts.

Diagnosis of renal transplant rejection is generally dependent on an increase in serum creatinine levels or its algorithmic derivative, estimated glomerular filtration rate (eGFR), which indicates altered renal filtration functioning. Methods of estimating kidney rejection in allograft recipients based on serum creatinine or eGFR, however, lack sufficient accuracy. Since there are many causes of the baseline drift in altered renal filtering in these patients, biopsy is required for definitive diagnosis. However, biopsies are invasive and costly procedures, which limit their use in clinical practice. Furthermore, biopsy results are often plagued by expert reader variance and can lead to delayed diagnosis of active rejection, after which irreversible organ damage may have occurred [6,7]. There is a current unmet need for a rapid, accurate, and noninvasive approach to detecting allograft rejection and/or injury—one which may require integration of the current "gold" standard morphological assessments with modern molecular diagnostic tools [8].

Donor-derived cell-free DNA (dd-cfDNA) detected in the blood of transplant recipients has been reported as a noninvasive marker to diagnose allograft injury/rejection [9–12], and holds promise for producing faster and more quantitative results compared with current diagnostic options. Recently, it was demonstrated that plasma dd-cfDNA fraction, typically between 0.3% and 1.2% in stable patients [13], can discriminate active rejection status from stable organ function in kidney transplant recipients [14]. Previously we validated the clinical application of a targeted, single nucleotide polymorphism (SNP)-based cell-free assay targeting greater than 10,000 loci as a successful screening tool for the detection of fetal chromosomal abnormalities [15–17] and show here that a similar approach targeting 13,392 SNPs can be used to evaluate differences in donor cfDNA burden in different transplant rejection injuries over time. This study uses a novel SNP-based mmPCR-next generation sequencing (NGS) methodology to measure dd-cfDNA in renal transplant recipients for the detection of allograft rejection/injury without prior knowledge of donor genotypes.

2. Materials and Methods

2.1. Study Design

This was a retrospective analysis of blood samples from kidney transplant recipients who had transplant surgeries at the University of California at San Francisco (USCF) Medical Center. The study was approved by the institutional review board at the UCSF Medical Center. All patients provided written informed consent to participate in the research, in full adherence to the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

2.2. Study Population and Samples

Male and female adult or young-adult patients received a kidney from related or unrelated living donors, or unrelated deceased donors. Plasma samples were obtained from an existing biorepository; time points of patient blood draw following transplantation surgery were either at the time of an

allograft biopsy or at various pre-specified time intervals based on lab protocols. Typically, samples were biopsy-matched and had blood drawn at the time of clinical dysfunction and biopsy or at the time of protocol biopsy (at which time most patients did not have clinical dysfunction). In addition, some patients had serial post transplantation blood drawn as part of routine Internal Review Board approved bio-sampling studies. The selection of study samples was based on (a) adequate plasma being available, and (b) if the sample was associated with biopsy information. Among the full 300 sample cohort, 72.3% were drawn on the day of biopsy. Patients without biopsy-matched samples were excluded from the primary analyses.

2.3. Biopsy Samples

All kidney biopsies were analyzed in a blinded manner by a UCSF pathologist and were graded by the 2017 Banff classification [18] for active rejection (AR); intragraft C4d stains were performed [19] to assess for acute humoral rejection [20]. Biopsies were not done in cases of active urinary tract infection (UTI) or other infections. Transplant "injury" was defined as a >20% increase in serum creatinine from its previous steady-state baseline value and an associated biopsy that was classified as either active rejection (AR), borderline rejection (BL), or other injury (OI) (e.g., drug toxicity, viral infection). Active rejection was defined, at minimum, by the following criteria: (1) T-cell-mediated rejection (TCMR) consisting of either a tubulitis (t) score >2 accompanied by an interstitial inflammation (i) score >2 or vascular changes (v) score >0; (2) C4d positive antibody-mediated rejection (ABMR) consisting of positive donor specific antibodies (DSA) with a glomerulitis (g) score >0/or peritubular capillaritis score (ptc) >0 or v > 0 with unexplained acute tubular necrosis/thrombotic micro angiopathy (ATN/TMA) with C4d = 2; or (3) C4d negative ABMR consisting of positive DSA with unexplained ATN/TMA with g + ptc $\geq$2 and C4d is either 0 or 1. Borderline change (BL) was defined by t1 + i0, or t1 + i1, or t2 + i0 without explained cause (e.g., polyomavirus-associated nephropathy (PVAN)/infectious cause/ATN). Other criteria used for BL changes were g > 0 and/or ptc > 0, or v > 0 without DSA, or C4d or positive DSA, or positive C4d without nonzero g or ptc scores. Normal (STA) allografts were defined by an absence of significant injury pathology as defined by Banff schema.

2.4. dd-cfDNA Measurement in Blood Samples

Cell-free DNA was extracted from plasma samples using the QIAamp Circulating Nucleic Acid Kit (Qiagen) and quantified on the LabChip NGS 5k kit (Perkin Elmer, Waltham, MA, USA) following manufacturer's instructions. Cell-free DNA was input into library preparation using the Natera Library Prep kit as previously described [21], with a modification of 18 cycles of library amplification to plateau the libraries. Purified libraries were quantified using LabChip NGS 5k as previously described [21]. Target enrichment was accomplished using massively multiplexed-PCR (mmPCR) using a modified version of a previously described method [22], with 13,392 single nucleotide polymorphisms (SNPs) targeted. Amplicons were then sequenced on an Illumina HiSeq 2500 Rapid Run, 50 cycles single end, with 10–11 million reads per sample.

2.5. Statistical Analyses of dd-cfDNA and eGFR

In each sample, dd-cfDNA was measured and correlated with rejection status, and results were compared with eGFR. Where applicable, all statistical tests were two sided. Significance was set at $p < 0.05$. Because the distribution of dd-cfDNA in patients was severely skewed among the groups, data were analyzed using a Kruskal–Wallis rank sum test followed by Dunn multiple comparison tests with Holm correction [23,24]. eGFR (serum creatinine in mg/dL) was calculated as described previously for adult [25] and pediatric patients [26]. Briefly, eGFR = 186 $\times$ Serum Creatinine$^{-1.154}$ $\times$ Age$^{-0.203}$ $\times$ (1.210 if Black) $\times$ (0.742 if Female).

To evaluate the performance of dd-cfDNA and eGFR (mL/min/1.73m^2) as rejection markers, samples were separated into an AR group and a non-rejection group (BL + STA + OI). Using this

categorization, the following predetermined cut-offs were used to classify a sample as AR: >1% for dd-cfDNA [14] and <60.0 for eGFR [27].

To calculate the performance parameters of each marker (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC)), a bootstrap method was used to account for repeated measurements within a patient [28]. Briefly, at each bootstrap step, a single sample was selected from each patient; by assuming independence among patients, the performance parameters and their standard errors were calculated. This was repeated 10,000 times; final confidence intervals were calculated using the bootstrap mean for the parameter with the average of the bootstrap standard errors with standard normal quantiles. Standard errors for sensitivity and specificity were calculated assuming a binomial distribution; for PPV and NPV a normal approximation was used; and for AUC the DeLong method was used. Performance was calculated for all samples with a matched biopsy, including the sub-cohort consisting of samples drawn at the same time as a protocol biopsy.

Differences in dd-cfDNA levels by donor type (living related, living non-related, and deceased non-related) were also evaluated. Significance was determined using the Kruskal–Wallis rank sum test as described above. Inter- and intra-variability in dd-cfDNA over time was evaluated using a mixed effects model with a logarithmic transformation on dd-cfDNA [29]; 95% confidence intervals (CI) for the intra- and inter-patient standard deviations were calculated using a likelihood profile method.

Post hoc analyses evaluated (a) different dd-cfDNA thresholds to maximize NPV (Table S1) and (b) combined dd-cfDNA and eGFR to define an empirical rejection zone that may improve the PPV for AR diagnosis (Figure S1).

All analyses were done using R 3.3.2 using the FSA (for Dunn tests), lme4 (for mixed effect modeling) and pROC (for AUC calculations) packages.

3. Results

3.1. Patients and Blood Samples

A total of 300 plasma samples were collected from 193 unique renal transplant recipients. Of these, 23 samples from 15 patients did not meet inclusion criteria and were excluded from analyses; this included samples collected within three days from transplant (15), and samples unable to be sequenced (8). Of the remaining 277 samples, 217 were biopsy-matched, including 38 collected from patients with biopsy-proven active rejection (AR), 72 with biopsy-proven borderline rejection (BL), 82 normal, stable allografts (STA), and 25 with a biopsy that indicated other injury (OI) (Figure 1). Of the 178 unique patients included in the study, 20% (35) were under 18 years of age; 30% (54) were between 18 and 40 years, and 50% (89) were older than 40 years of age at the time of first blood sample.

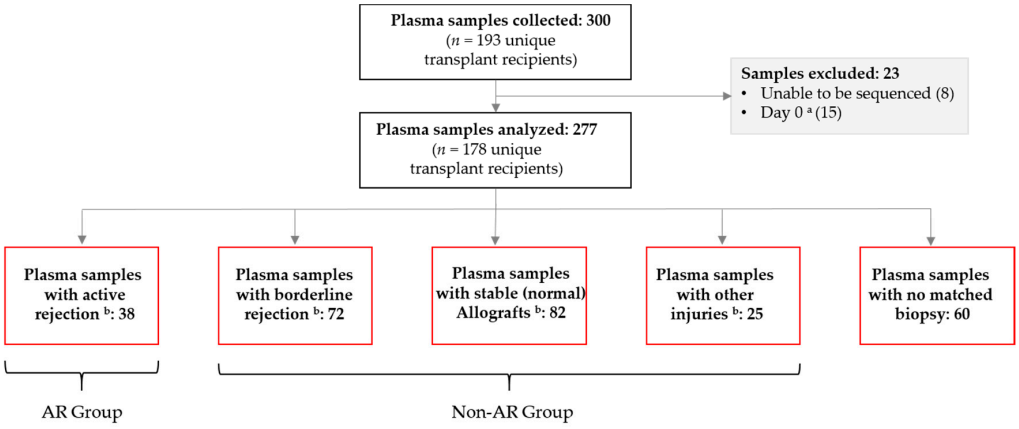


Figure 1. Plasma sample breakdown. AR, active rejection. [a] Collected within three days post transplantation; [b] samples drawn on the day of biopsy (i.e., were biopsy-matched).

Published data have shown that dd-cfDNA fractions in patients with AR are significantly higher than patients with non-rejection; however, these data have shown an inability of dd-cfDNA to detect all types of AR, specifically failing to detect TCMR [14]. In this data set, the performance of the assay to detect rejection was evaluated for all types of rejection combined (ABMR, TCMR), based on the assumption that elevated dd-cfDNA levels are indicative of ongoing damage to the transplanted organ, irrespective of the underlying biology of rejection. Therefore, the ability of the assay to detect AR versus non-rejection was calculated, where non-rejection was defined as all specimens that were classified as STA, BL, or OI. Additionally, the performance of the assay to discriminate AR from complete absence of injury (STA) was also evaluated. A summary of demographic information and sample characteristics are provided in Table 1. All pathology samples were read at UCSF by a single renal pathologist and rated according to the recently updated Banff criteria [18].

Table 1. Demographics and characteristics [a].

Phenotype Characteristic	Active Rejection (38 Samples)	Non-Rejection			
		Stable (82 Samples)	Borderline AR (72 Samples)	Other Injury (25 Samples) [b]	Combined (179 Samples)
Recipient age, year * (p-value < 0.0001)					
(0, 18)	0 (0)	44 (53.7)	1 (1.4)	4 (16.0)	49 (27.4)
(18, 40)	10 (26.3)	32 (39.0)	18 (18.0)	8 (32.0)	58 (32.4)
(40, 80)	28 (73.7)	6 (7.3)	53 (73.6)	13 (52.0)	72 (40.2)
Mean ± SD	47.91 ± 14.31	20.04 ± 11.97	47.88 ± 13.24	44.75 ± 23.73	34.65 ± 19.87
Median	49.13	19.96	47.46	40.97	31.33
Range	23–76	3–70	5–74	3–80	3–80
Male/female, no. (%) (p-value = 0.5988)					
Male	17 (44.7)	48 (58.5)	40 (55.6)	15 (60)	103 (57.5)
Female	21 (55.3)	34 (41.5)	32 (44.4)	10 (40)	76 (42.5)
Ethnicity, no. (%) (p-value = 1)					
Hispanic or Latino	13 (34.2)	28 (34.1)	24 (33.3)	10 (40)	62 (34.6)
Not Hispanic or Latino	25 (65.8)	54 (65.9)	48 (66.7)	15 (60)	117 (65.4)
Race groups, no. (%) (p-value = 0.4695)					
White or Caucasian	10 (26.6)	42 (51.2)	16 (22.2)	6 (24)	64 (35.8)
Black or African American	6 (15.8)	7 (8.5)	14 (19.4)	4 (16)	25 (14.0)
Asian or Pacific Islander	8 (21.1)	4 (4.9)	15 (20.8)	4 (16)	23 (12.8)
Other/Not reported	14 (36.8)	29 (35.4)	27 (37.8)	11 (44.0)	67 (37.4)
Recipient weight, kg (p-value = 0.6039)					
Mean ± SD	76.22 ± 19.7	70.9 ± 8.8	79.18 ± 18.7	78.33 ± 17.1	78.1 ± 17.6
Median	72.5	73.0	78.0	76.0	76.0
Range	45–119	52–81	46–134	47–109	46–134
Unknown	6	72	7	7	86
DSA positive, no. (%) (p-value = 0.1928)					
Yes	15 (39.5)	0 (0)	18 (25)	2 (8)	20 (11.2)
No	21 (55.3)	0 (0)	48 (66.7)	3 (12)	51 (28.5)
Not recorded	2 (5.3)	82 (100)	6 (8.3)	20 (80)	108 (60.3)
Indication for renal transplantation, no. (%) (p-value = 0.4869)					
Glomerulonephritis	5 (13.2)	6 (7.3)	4 (5.6)	1 (4)	11 (6.1)
Focal segmental glomerulosclerosis	5 (13.2)	5 (6.1)	6 (8.3)	2 (8)	13 (7.3)
Diabetes mellitus	5 (13.2)	3 (3.7)	15 (20.8)	5 (20)	23 (12.8)
Thin basement membrane nephropathy	0 (0)	0 (0)	2 (2.8)	0 (0)	2 (1.1)
Polycystic kidney disease	3 (7.9)	2 (2.4)	7 (9.7)	1 (4)	10 (5.6)
Solitary kidney	0 (0)	0 (0)	3 (4.2)	0 (0)	3 (1.7)
Hypertension	4 (10.5)	2 (2.4)	13 (18.1)	3 (12)	18 (10.1)
IgA nephropathy	3 (7.9)	0 (0)	7 (9.7)	1 (4)	8 (4.5)
Lupus nephritis	2 (5.3)	0 (0)	0 (0)	0 (0)	0 (0.0)
ANCA—vasculitis	1 (2.6)	0 (0)	2 (2.8)	0 (0)	2 (1.1)
Other/Unknown	10 (26.3)	64 (78.1)	13 (18.1)	12 (48)	89 (49.7)

Table 1. *Cont.*

Phenotype Characteristic	Active Rejection (38 Samples)	Non-Rejection			
		Stable (82 Samples)	Borderline AR (72 Samples)	Other Injury (25 Samples) [b]	Combined (179 Samples)
Donor source *, no. (%) (p-value < 0.0001)					
Living related	1 (2.8)	2 (2.4)	9 (12.5)	3 (12)	14 (7.8)
Living unrelated	2 (5.3)	50 (61)	18 (25)	7 (28)	75 (41.9)
Deceased unrelated	35 (92.1)	30 (36.6)	45 (62.5)	15 (60)	90 (50.3)

* Indicates the association with AR status (AR/non rejection) was statistically significant ($p < 0.001$). Categorical variables were tested using Fisher's exact test for count data, and numerical variables were tested using a likelihood ratio test based on a logistic regression. [a] Characteristics and demographic information are based on all samples drawn on the day of biopsy; data reflects multiple samples for some patients. [b] Other injuries included: chronic allograft nephropathy (10 samples), drug toxicity (11 samples), BK nephritis (1 sample), acute tubular necrosis (1 sample), transplant glomerulopathy (1 sample), and post borderline-TCMR (1 sample). DSA, donor specific antibodies; AR, active rejection.

3.2. dd-cfDNA and eGFR in Kidney Transplant Recipients

The amount of dd-cfDNA was significantly higher in the circulating plasma of the AR group (median = 2.32%) compared with the non-rejection group (median = 0.47%, $p < 0.0001$) (Table 2, Figure S2). Additionally, the median level of dd-cfDNA was significantly higher in the AR group compared with all three individual non-rejection subgroups: BL group (0.58%), STA group (0.40%), and OI (0.67%, all comparisons, adj. $p < 0.0001$) (Figure 2A, Table S2). That the dd-cfDNA burden was higher in the AR group as compared to the BL group indicates that dd-cfDNA fraction may be used to track the evolution of early injury to more established rejection, as well as any subsequent recovery. The differences between the levels of dd-cfDNA between any of the non-rejection subgroups (STA, BL, and OI) were not significant (Figure 2A; Table S2).

In contrast to dd-cfDNA, eGFR scores did not have as much discriminatory ability for differentiating AR and individual non-rejection groups (Table 2, Figure S2). Overall, the median eGFR score in the AR group (45.67) was significantly lower than that observed in the non-rejection group (76.6, $p < 0.0001$) (Table 2 and Table S2, Figure S2) and even lower compared to the STA group alone (104.5, adj. $p < 0.0001$) (Table 2 and Table S2, Figure 2B). However, unlike the dd-cfDNA results, there was no difference in median eGFR scores between the AR and BL groups (45.67 vs. 55.99, adj. $p = 0.461$) (Table 2 and Table S2; Figure 2B). Additionally, compared with the STA group, eGFR levels were significantly higher in the BL (55.99, adj. $p < 0.0001$) and OI (57.4, adj. $p < 0.0001$) groups (Table 2 and Table S2, Figure 2B).

Table 2. Summary statistics for donor-derived cell-free DNA (dd-cfDNA) and estimated glomerular filtration rate (eGFR) variables across AR and non-rejection groups.

Parameter	Active Rejection	Non-Rejection			
		Stable	Borderline AR	Other Injury	Combined
dd-cfDNA					
Number of samples (%)	38 (17.5)	82 (37.8)	72 (33.2)	25 (11.5)	179 (82.5)
Mean (SD)	4.64 (5.45)	0.90 (1.36)	0.95 (1.31)	0.89 (0.91)	0.92 (1.28)
Median (range)	2.32 (0.1–23.9)	0.4 (0.03–6.8)	0.58 (0.02–6.7)	0.67 (0.08–3.69)	0.47 (0.04–6.78)
eGFR					
Number of samples (%)	38 (17.5)	82 (37.8)	72 (33.2)	25 (11.5)	179 (82.5)
Score mean (SD)	49.0 (22.4)	99.5 (16.1)	55.9 (21.4)	63.8 (29.0)	77.0 (8.45)
Score median (range)	45.67 (8.0–100.4)	104.5 (47.4–131.1)	55.99 (6.4–109.4)	57.4 (25.0–116.9)	76.06 (6.4–131.1)

AR, active rejection.

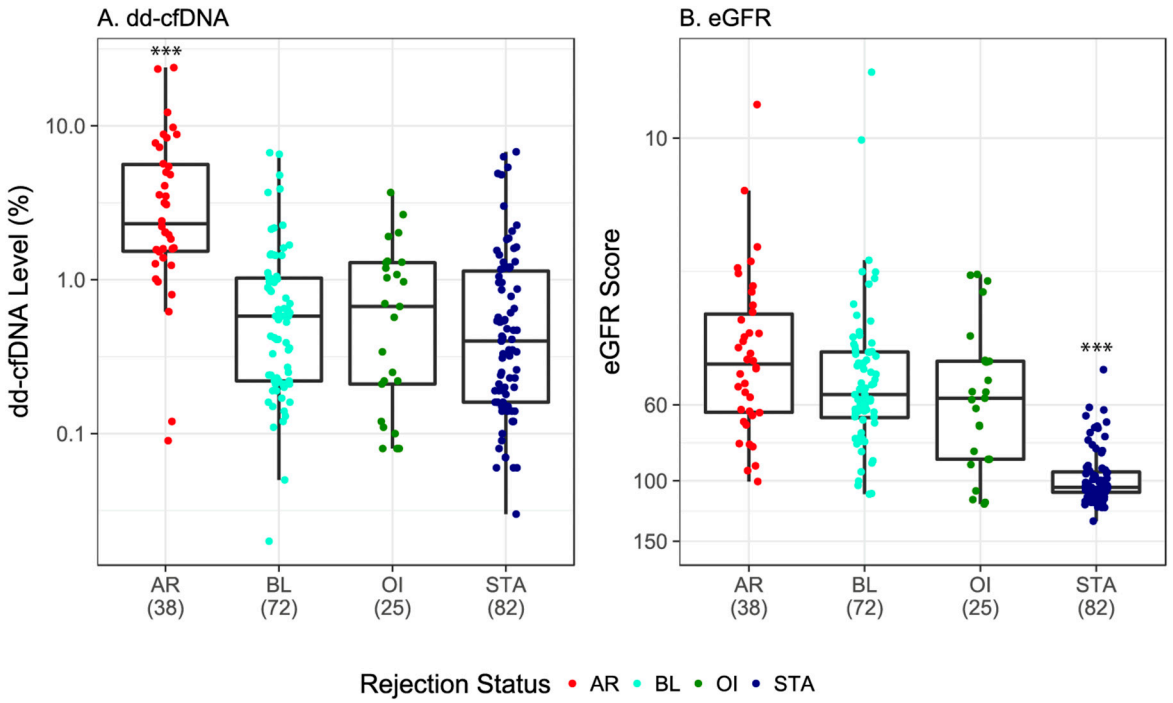


Figure 2. Discrimination of active rejection by dd-cfDNA versus eGFR. (**A**) and (**B**): Boxes indicate interquartile range (25th to 75th percentile); horizontal lines in boxes represent medians; each dot depicts one sample. *p*-values for dd-cfDNA and eGFR adjusted using Kruskal–Wallis rank sum test followed by Dunn multiple comparison tests with Holm correction. *** indicates adj. $p < 0.0001$ from all other group comparisons (see Table S2). AR, active rejection; BL, borderline; OI, other injury; STA, stable; dd-cfDNA, donor-derived cell-free DNA; eGFR, estimate glomerular filtration rate.

3.3. Performance Estimates for Discriminatory Ability of Tests

With a dd-cfDNA cutoff of >1%, the mmPCR-NGS method had an 88.7% sensitivity (95% CI, 77.7–99.8%) and 72.6% specificity (95% CI, 65.4–79.8%) for detection of AR. Sensitivity and specificity values are shown over the range of dd-cfDNA cutoffs in Figure 3A. The AUC was 0.87 (95% CI, 0.80–0.95). Based on a 25% prevalence of rejection in an at-risk population, the positive predictive value (PPV) was projected to be 52.0% (95% CI, 44.7–59.2%) and the negative predictive value (NPV) was projected to be 95.1% (95% CI, 90.5–99.7%).

Sensitivity and specificity were lower using eGFR (Figure 3B). Using an eGFR cutoff score <60 for AR, sensitivity and specificity values were 67.8% (95% CI, 51.3–84.2%) and 65.3% (57.6–73.0%), respectively, with an AUC of 0.74 (0.66–0.83). The projected PPV and NPV values of eGFR were 39.4% (31.6–47.3%) and 85.9% (75.9–92.2%), respectively.

As a post hoc analysis, we also evaluated a combination of eGFR with dd-cfDNA. Although we do not have a large number of samples to train a combined model, we can still see potential empirical rejection zones. Samples with a very high eGFR score, for example, tend to correspond to non-rejection samples (Figure S1). Defining the active rejection zone to be dd-cfDNA level >1% and eGFR <100, and non-rejection to be dd-cfDNA level <1% or eGFR >100, the combined dd-cfDNA and eGFR markers correctly classified 32/38 (84.2%) AR samples, and 145/179 (81.0%) non-rejection samples. Meanwhile at an equivalent specificity of 81.0%, (using a cut off of 1.3% dd-cfDNA) the sensitivity of the dd-cfDNA marker alone was 82.3%. Therefore the combined biomarker approach appeared to add little or no value over cfDNA alone.

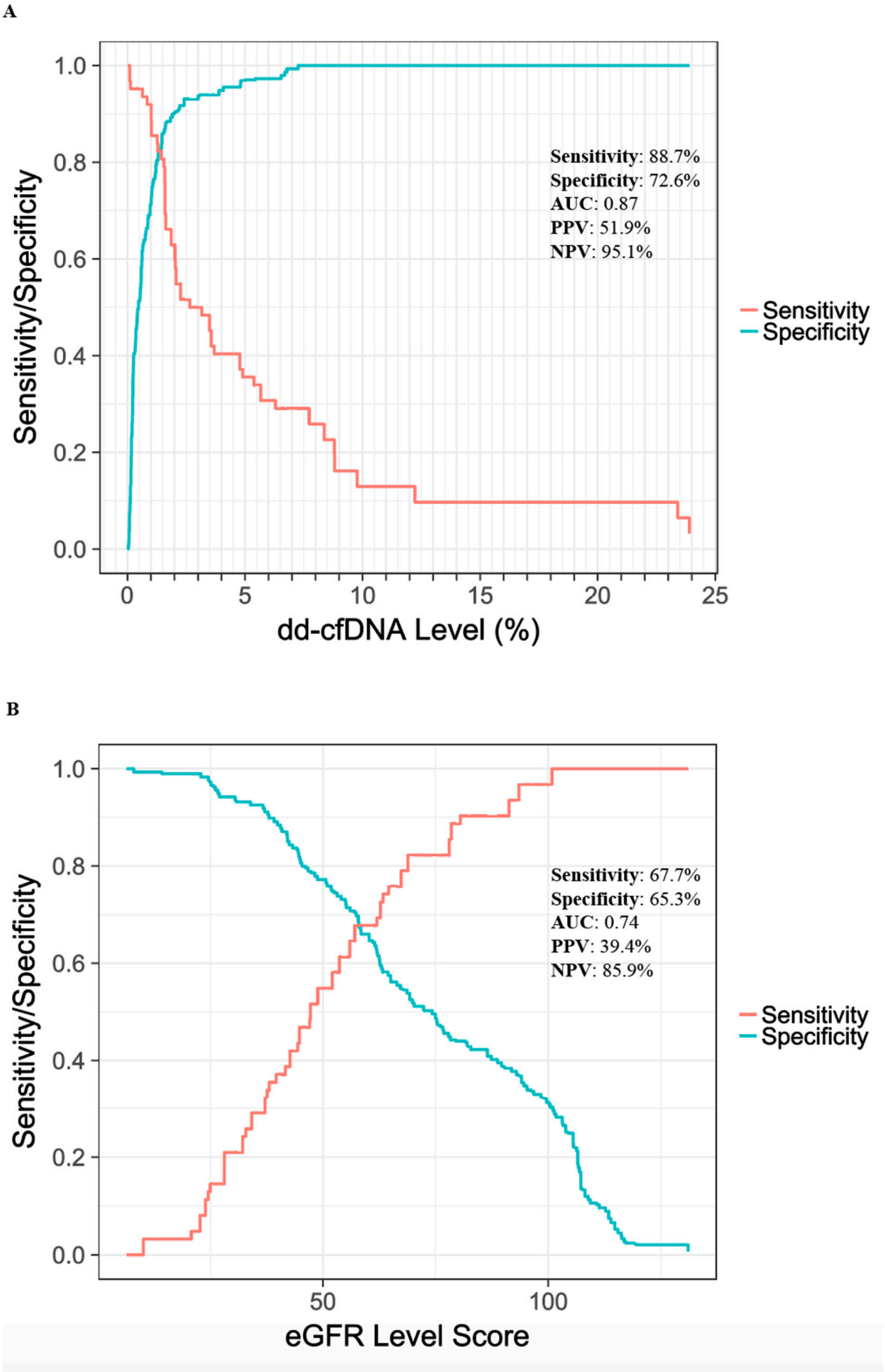


Figure 3. Predictive statistics for active rejection versus non-rejection. Sensitivity (red line) and specificity (blue line) are depicted over the observed range of dd-cfDNA levels (**A**) and eGFR scores (**B**). Reported sensitivity and specificity correspond to cutoffs of 1% for dd-cfDNA and a score of 60 for eGFR. PPV and NPV are based on a 25% AR prevalence. AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

3.4. dd-cfDNA Performance in Unique Biopsy-Confirmed Subgroups

Among the biopsy-matched samples, 103 (47.5%) were biopsied for clinical reasons, whereas 114 (52.5%) were biopsied according to protocol (Table 3 and Table S3). Figure 4 depicts sample dd-cfDNA levels among all subgroups; 85 (39.2%) had dd-cfDNA levels >1%. Of those, 22 (25.9%) were STA; the remainder were AR (33 (38.8%)), OI (10 (11.8%)), or BL (20 (23.5%)). Of the individual groups, 33 (86.8%) of the total AR samples and 22 (26.8%) of the total STA samples had dd-cfDNA levels above 1%. In comparison, 20 (27.8%) of the total BL samples and 10 (40.0%) of the total OI samples had dd-cfDNA levels above 1%.

Table 3. Cohort breakdown into for-cause and protocol biopsy.

Rejection Status	Biopsy Reason	Total	Median	Low	High	Mean	SD
AR	For-cause	25	2.04	0.09	23.9	3.85	4.81
	Protocol	13	3.56	0.12	23.4	6.16	6.44
BL	For-cause	39	0.64	0.02	6.54	1.07	1.32
	Protocol	33	0.33	0.05	6.69	0.82	1.30
OI	For-cause	12	0.865	0.08	3.69	1.03	1.02
	Protocol	13	0.25	0.08	2.65	0.76	0.82
STA	For-cause	27	0.54	0.12	5.38	1.12	1.36
	Protocol	55	0.26	0.03	6.78	0.80	1.37

AR, active rejection; BL, borderline; OI, other injury; STA, stable.

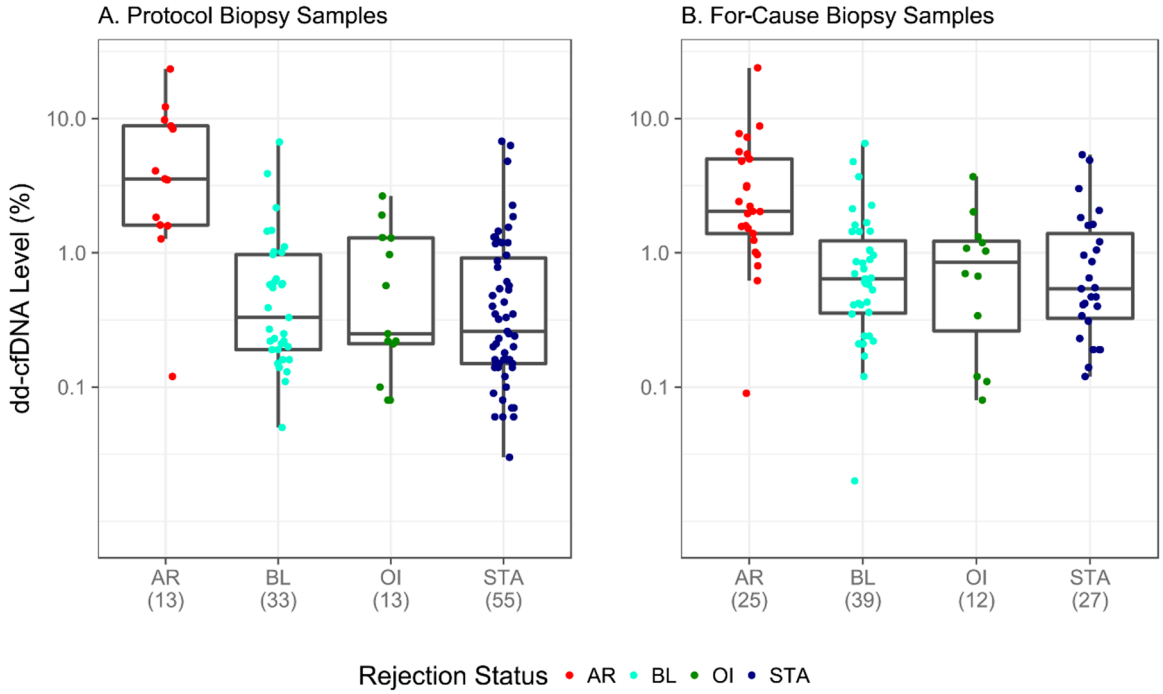


Figure 4. Discrimination of active rejection by dd-cfDNA in biopsy-matched samples stratified by biopsy type. The number of samples per group and the distribution of their dd-cfDNA levels are depicted for protocol biopsy (**A**) and for-cause biopsy (**B**) samples. Boxes indicate inter-quartile range, horizontal lines represent medians. AR, active rejection; BL, borderline; OI, other injury; STA, stable.

Figure 4 shows assay performance for the subset of samples drawn at the time of a for-cause biopsy (4A) and protocol biopsy (4B); performance shown in protocol biopsies is expected to reflect performance when the assay is used in routine surveillance, that is, when there are no signs of renal injury. This cohort of 114 samples showed a 92.3% sensitivity (95% CI, 64.0–99.8%) and 75.2% specificity (95% CI, 65.7–83.3%) for detection of AR. The AUC was 0.89 (95% CI, 0.76–0.99). Based on a 25% prevalence of rejection in an at-risk population, the positive predictive value (PPV) was projected to be

55.4% (95% CI, 46.2–64.7%) and the negative predictive value (NPV) was projected to be 96.7% (95% CI, 90.6–99.9%).

Sensitivity, specificity, PPV and NPV were also calculated at different dd-cfDNA level rejection cutoffs. Table S1 shows the metrics at 0.6%, 0.8%, 1.0%, 1.2%, 1.4%, and 1.6%. Raising the cutoff has the effect of improving the specificity and the PPV; lowering the cutoff improves sensitivity and NPV.

3.5. Relationship Between dd-cfDNA and Rejection Type

Of the 38 samples with biopsy-proven AR, 16 were classified as either ABMR or ABMR and borderline T-cell-mediated rejection (bTCMR); 12 had a combination of both ABMR and TCMR; 10 were classified as either TCMR or TCMR and bABMR. In addition, 13 and 59 BL samples were classified as bAMBR and bTCMR, respectively. Figure 5 shows the relationship between dd-cfDNA level and type of rejection (for groups with known ABMR or known TCMR). Median dd-cfDNA did not differ significantly between AMBR (2.2%), ABMR/TCMR (2.6%), or TCMR (2.7%) groups ($p = 0.855$) (Table S4). The study contained a range of pathologies, and the data indicate that this assay, unlike other published studies measuring cfDNA by other assays [14], is robust to different rejection types (Table S5). The dd-cfDNA breakdown of bABMR and bTCMR samples are depicted in Figure S3.

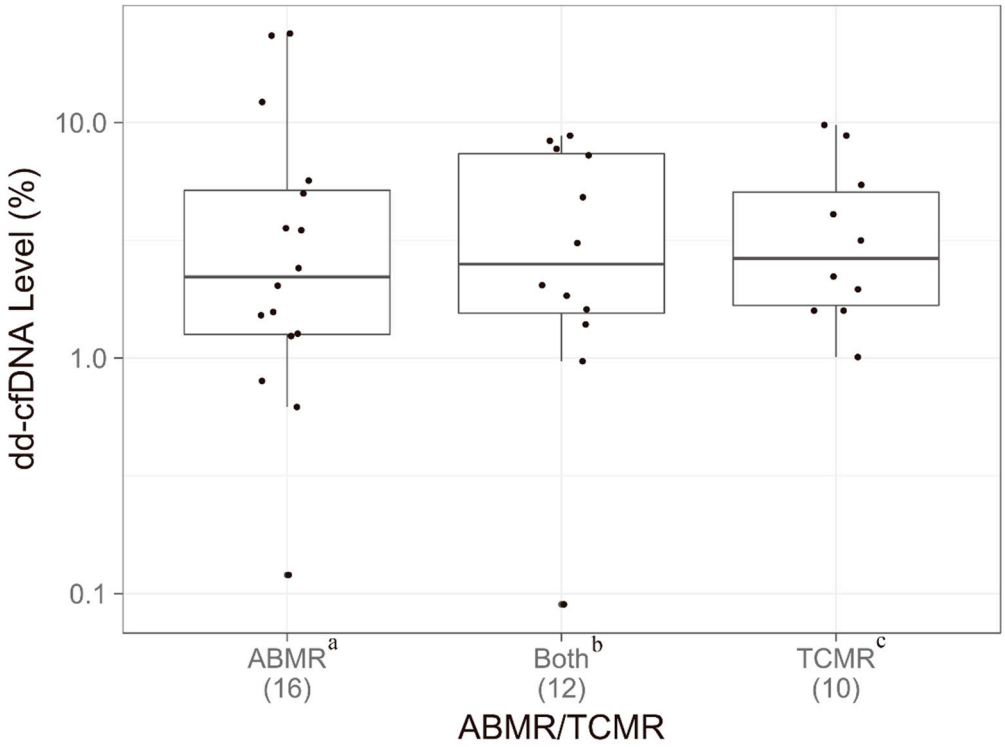
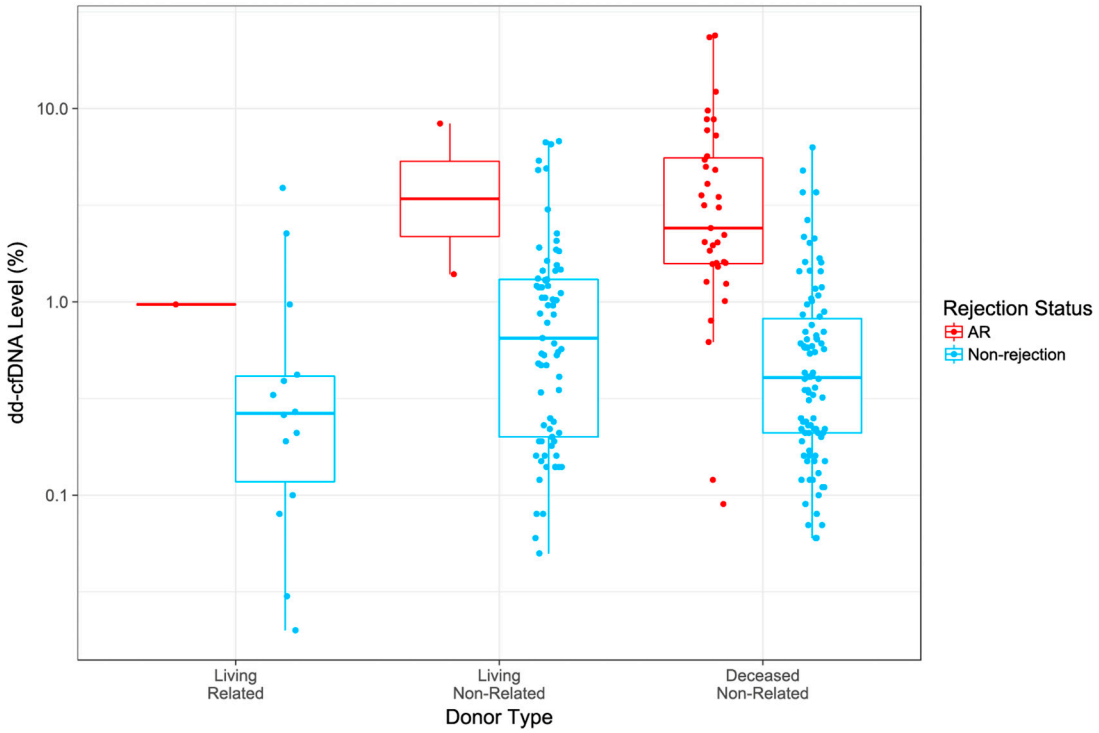


Figure 5. dd-cfDNA as a function of antibody-mediated—versus T-cell—mediated rejection. Boxes indicate interquartile range (25th to 75th percentile); horizontal lines in boxes represent medians; dots indicate all individual data points. *p*-values for dd-cfDNA adjusted using Kruskal–Wallis rank sum test. [a] Samples assigned ABMR or ABMR and bTCMR. [b] Samples assigned ABMR and TCMR. [c] Samples assigned TCMR or TCMR and bABMR. ABMR, antibody-mediated rejection; TCMR, T-cell-mediated rejection.

3.6. dd-cfDNA Levels by Donor Type

To assess the relationship between dd-cfDNA and donor type (living related, living non-related, and deceased non-related) a linear mixed-effects model was constructed using a log transformed dd-cfDNA as the response and donor type as the predictor for the non-rejection group. The log-transformation was applied to satisfy the model's assumptions. The test was limited to the non-rejection group due to the limited number of AR samples in two groups (living related and living non-related). An ANOVA

Wald-test with Kenward–Roger approximation for the degrees of freedom showed significance ($p = 0.045$). Tukey's post-hoc test was used to determine the difference among the three groups: none of the post-hoc tests demonstrated any association (Figure 6, Table S6). It is possible that the overall effect is driven by a sub-category of the non-rejection group (STA, BL, or OI) or the effect between the groups is smaller than detectable with the current sample size [30].

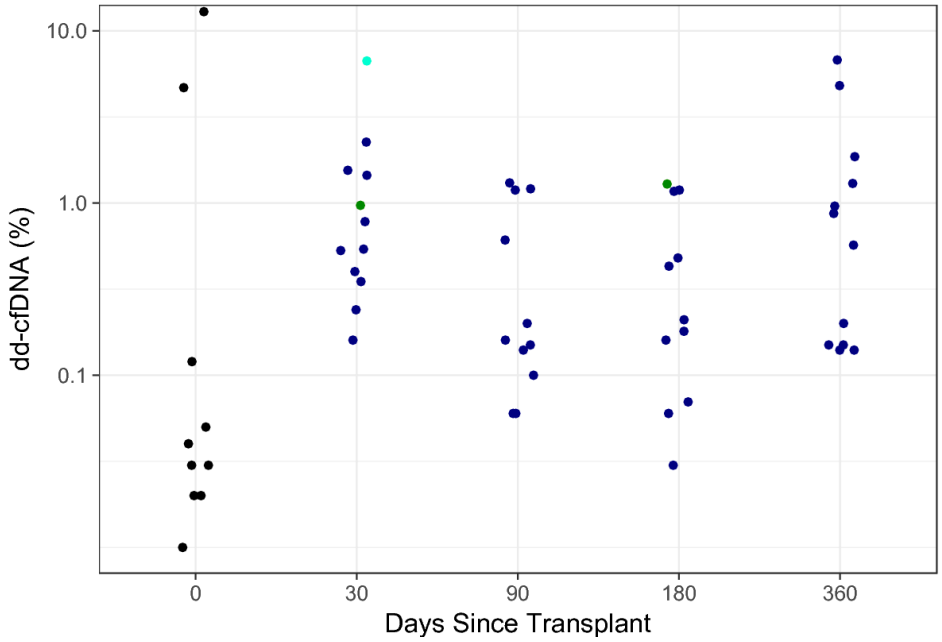


Comparison	P-value
Living related versus living non-related	0.0623
Living related versus deceased non-related	0.3728
Living non-related versus deceased non-related	0.1803

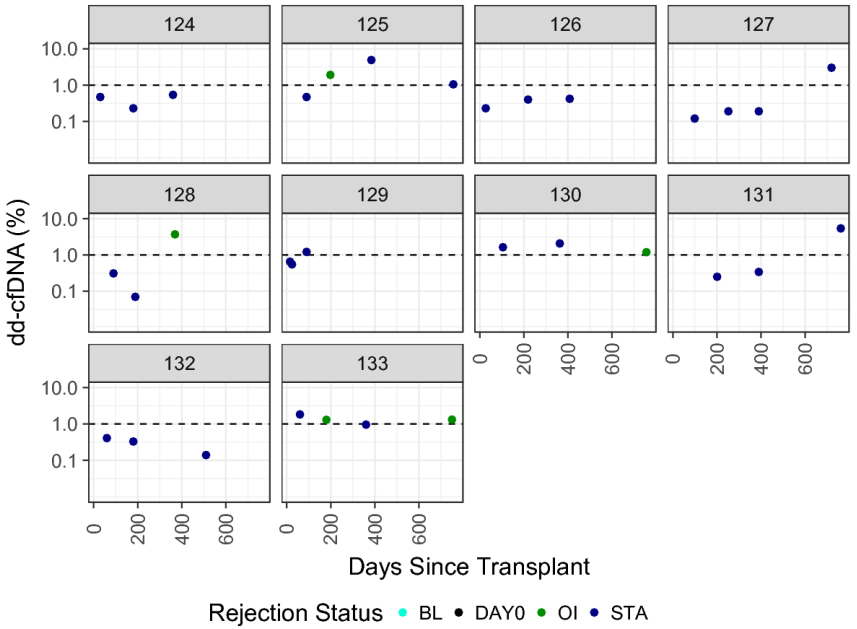
Figure 6. Relationship between dd-cfDNA and donor type. Boxes indicate inter-quartile range, horizontal lines represent medians. *p*-values for dd-cfDNA an ANOVA Wald-test with Kenward–Roger approximation for the degrees of freedom was followed by Tukey's post-hoc test. AR, active rejection.

3.7. dd-cfDNA Variability over Time

Two analyses were designed to evaluate the natural variability in dd-cfDNA over time in biopsy-matched, non-rejection patients. The first sub-analysis was a cross-sectional analysis of 60 plasma samples from 60 different patients, collected immediately following surgery (within three days ("Day 0")) or at 1, 3, 6, or 12 months post-surgery. Among these STA patients, dd-cfDNA levels were lower at month 0 than subsequent time points; however, for most of these STA samples dd-cfDNA levels were <1% across all time points (Figure 7A). No association was observed between Day 0 samples and the other time points, although the overall distribution of dd-cfDNA levels in the Day 0 group appears lower in comparison (Figure 7A).

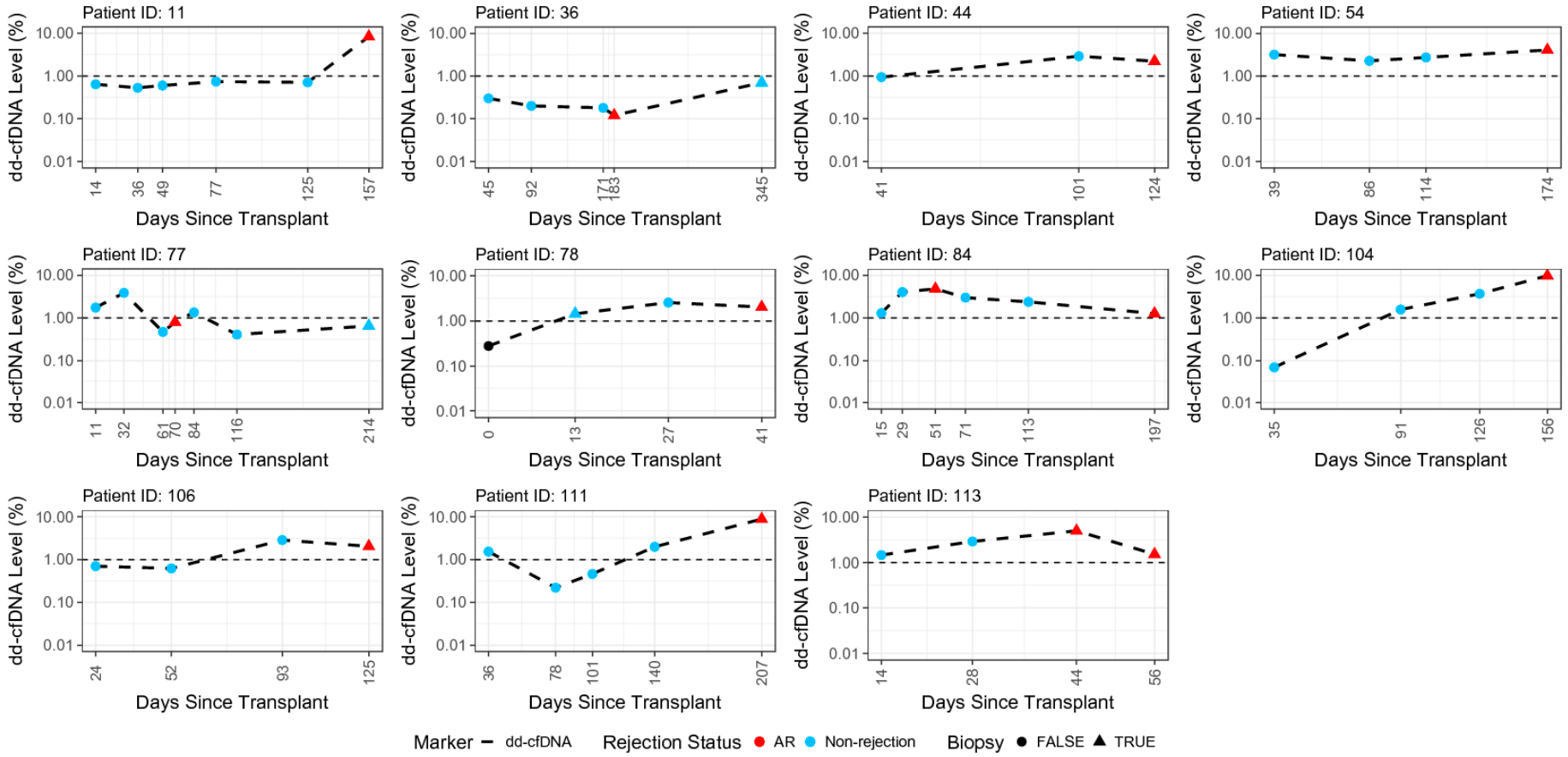


(**A**)



(**B**)

Figure 7. *Cont.*



(C)

Figure 7. Variability in dd-cfDNA in non-rejection patients over time. (**A**) Inter-patient variability (60 samples from 60 patients over time); (**B**) intra-patient variability (samples from the same 10 patients over time); (**C**) change in dd-cfDNA levels over time in patients with active rejection. AR, active rejection; BL, borderline; OI, other injury; STA, stable.

To evaluate the normal intra-patient variation in donor fraction, the second sub-analysis longitudinally assessed 10 individual patients across four time points (varying between about 1 month and 1 year post transplantation (minimum interval: 11 days, maximum interval: 345 days)). Overall, organ injury occurred at dd-cfDNA levels above 1% (Figure 7B). The inter-patient standard deviation within this cohort was 0.16 (95% CI, 0.0–0.37) and the intra-patient standard deviation was 0.42 (95% CI, 0.32–0.56). The intraclass-correlation coefficient was low (0.1193), which suggests that the variability in these data are mostly due to intra-patient variation. Figure 7C depicts all available longitudinal data among patients that experienced a rejection. In 9/11 patients, dd-cfDNA levels were above 1% prior to rejection.

4. Discussion

In this study, median dd-cfDNA was significantly higher in the AR group (2.32%) versus the non-rejection group (0.47%; $p < 0.0001$). Analysis of performance estimates demonstrated that the mmPCR-NGS method was able to discriminate active from non-rejection status with an AUC of 0.87 and high sensitivity (88.7%) and specificity (72.6%) at an AR cutoff of >1% dd-cfDNA. Based on a 25% prevalence of rejection, projected PPV and NPV were 52.0% and 95.1%, respectively. In contrast, eGFR scores were generally less discriminatory, with a 67.7% sensitivity and 65.3% specificity, and projected PPV and NPV of 39.4% and 85.9%, respectively. Therefore, if eGFR measurements were used as the sole clinical decision point, about 1 in 7 patients found to be at low risk of rejection would actually be experiencing rejection, and would not be referred for an indication biopsy—this is in comparison to the projected NPV for dd-cfDNA that suggests that only 1 in 20 patients would miss an indication biopsy where it might be clinically necessary. Taken together, the superior performance of this SNP-based dd-cfDNA assay over that of the current standard of care for the evaluation of allograft rejection holds promise for enabling patients a greater opportunity for timely therapy in the case of an allograft injury.

Levels of dd-cfDNA also provided discrimination of AR from the three non-rejection subgroups (STA, BL, and OI); median dd-cfDNA levels were significantly higher for samples with biopsy-proven AR (2.3%) versus BL (0.6%), OI (0.7%), and STA (0.4%). In a post hoc analysis, we examined the ability of dd-cfDNA combined with eGFR to predict rejection status (AR/non-rejection) in biopsy matched samples (Figure S1). This combined approach correctly classified 32/38 (84.2%) AR and 145/179 (81.0%) non-rejection samples, though in a head-to-head comparison it showed little to no improvement over dd-cfDNA alone. Combining dd-cfDNA with other markers may provide improved predictive value, but this was outside the scope of this study. Also of note, while both dd-cfDNA and eGFR can be used to differentiate AR and STA cases, the BL and OI samples stratify differently: they tend to aggregate with STA when using dd-cfDNA and with AR when using eGFR. This suggests that dd-cfDNA could be used together with eGFR to differentiate patients into three groups—STA patients, AR patients, and patients experiencing BL or OI.

In a recent study that amplified hundreds of target SNPs in dd-cfDNA to detect active rejection in kidney allografts, that method was able to discriminate AR from non-rejection with an AUC of 0.74, 59% sensitivity, and 85% specificity [14]. In comparison with that study, the novel dd-cfDNA test described in the current study showed a higher AUC value (0.87) as well as greater sensitivity (89%). On the other hand, specificity (73%) was slightly lower in the current study, partly driven by the fact that a majority of the "false positives" were cases with BL and OI indicating some form of organ injury. The predefined analysis in this study used 1% dd-cfDNA cutoff, based on prior experience [14]; however, as a different sensitivity/specificity tradeoff may be optimal in different use cases, performance was calculated, in a post hoc fashion, for additional cfDNA cutoffs: 0.6%, 0.8%, 1.2%, 1.4%, and 1.6 % (Table S1).

Another important finding of this study was that the fraction of dd-cfDNA did not differ between ABMR and TCMR groups, with dd-cfDNA levels of 2.2% and 2.7%, respectively. These results are novel considering that a previously conducted study by Bloom et al. (2017), which used a different assay, found significantly higher dd-cfDNA levels for ABMR (2.9%) than for TCMR ($\leq$1.2%) [14],

showing a lower ability to detect T-cell mediated rejections. Though the assay used in that study also measured dd-cfDNA, the methods used by the two assays differ greatly. It is unclear whether that test could not differentiate AR from non-rejection in cases of TCMR or if the result was due to the smaller sample size of that group in that study (n = 11). Regardless, it appears that dd-cfDNA measurements based on the mmPCR assay in this study can accurately discriminate AR from non-rejection across a range of pathologies, including both acute and chronic findings, in both the ABMR and TCMR groups. An additional finding in this study is that borderline, or early rejection injury, has a lower burden of dd-cfDNA than more established injury, making it possible to use this sensitive assay to track evolution of, or recovery from, AR.

One barrier to widespread clinical use of dd-cfDNA as a diagnostic tool for monitoring organ transplant has been the limitations in measuring dd-cfDNA in certain cases, such as when the donor genotype is unknown or when the donor is a close relative. Given the design of the assay used here, it is possible to quantify dd-cfDNA without prior recipient or donor genotyping. Further, there is no need for a computational adjustment based on whether the donor is related to the recipient. In this study, evaluation of dd-cfDNA levels by donor type revealed that regardless of donor type (living related, living non-related, deceased non-related), dd-cfDNA levels were similar across all donor types within in the AR and non-rejection categories.

A limitation of this study is that it was a retrospective analysis of archived samples from a single center. However, the central geographical area enabled all biopsies to be performed by a single pathologist, which may have helped minimize variability in biopsy classification; further, all experimenters were kept blinded during the process of data generation. The retrospective study design may have led to differences in patient characteristics across the rejection groups; for example, the STA group was enriched with younger patients who may be better suited immunologically to tolerate transplanted organs compared to older-aged patients. However, these age differences likely did not affect the validity of the study findings.

A strength of this study is the large number of samples drawn at the time of a protocol biopsy. Performance of the assay among samples drawn at the time of a protocol biopsy are more reflective of expected performance during routine use of the assay, where there are no overt signs of injury; this is in contrast to for-cause biopsies, which are performed in a high-risk cohort where there are peripheral signs of organ injury. In this study, more than half (53%, 114/217) of the biopsy-matched samples were performed on protocol. The assay showed better performance in this cohort, with a sensitivity of 92.3%, specificity of 75.2%, and AUC of 0.89%. This data suggests that application of the dd-cfDNA assay in a clinical setting could potentially reduce the need for protocol biopsies.

Another strength is the variety of patient samples in the non-rejection group, which comprised not only STA, but also BL and OI samples. This allowed for additional analyses in this study, which found that dd-cfDNA was significantly different in the AR group versus BL and OI groups. Additional sub-analyses by type of AR (ABMR and TCMR), as well as by donor type, demonstrated that dd-cfDNA levels were able to discriminate AR versus non-rejection in a variety of rejection and patient types. Further, the SNP-based mmPCR methodology underlying this assay has been extensively validated in the context of prenatal testing, and has been used to determine the DNA fraction of the minor constituent in a clinical setting in over a million maternal/fetal DNA samples. Finally, the inclusion of longitudinal data enabled a unique evaluation of the natural variability of dd-cfDNA in transplant patients over time. Inter-patient variability data demonstrated that between 0 and 12 months post-surgery, most patients with STA biopsies had dd-cfDNA levels below 1%, and most patients with a positive biopsy had a positive dd-cfDNA test at a time point prior to the positive biopsy. Taken together, this suggests that this mmPCR assay may be used for routine monitoring, to determine whether a renal transplant patient is experiencing organ injury that may require a change in management.

5. Conclusions

In conclusion, this study validates the use of dd-cfDNA in the blood as an accurate marker of kidney injury/rejection across a range of pathologies with acute and chronic findings. This rapid, accurate, and noninvasive technology allows for detection of significant renal injury in patients better than the current standard of care, with the potential for better patient management, more targeted biopsies, and improved renal allograft function and survival.

Supplementary Materials: The Tables S1–S6 and Figures S1–S3 are available online at http://www.mdpi.com/2077-0383/8/1/19/s1.

Author Contributions: Conceptualization, S.M. and M.M.S.; Data curation, F.A.A., M.M.S., T.K.S., R.D.S., C.C.-O., S.-C.H., T.C., J.L., I.D., P.T., S.A.P., and S.N.; Formal analysis, F.A.A. and M.M.S.; Funding acquisition, S.M. and M.M.S.; Investigation, T.K.S., S.M., and M.M.S.; Methodology (cfDNA), F.A.A., T.C., A.R., and B.Z.; Methodology (study design), M.M.S.; Project administration, S.A.P.; Resources, T.K.S., M.M.S., and P.R.B.; Software, F.A.A. and E.K.; Supervision, Z.P.D., A.R., S.S., B.Z., M.M.S., P.R.B., and S.M.; Validation, M.M.S., T.C., and E.K.; Visualization, A.R., M.M.S., and S.M.; Writing—original draft, S.A.P.; Writing—review & editing, F.A.A., T.K.S., T.C., S.A.P., J.L., P.T., S.N., Z.P.D., A.R., S.S., R.D.S., C.C.-O., S.-C.H., B.Z., P.R.B., and M.M.S.

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Conflicts of Interest: T.K.S., J.L., I.D., P.T., R.D.S., C.C.-O., S.-C.H, and M.M.S. declare no conflicts. F.A.A., T.C., S.A.P., S.N., E.K., Z.P.D., A.R., S.S., B.Z., P.R.B., and S.M. are or were employees of Natera, Inc. with stock/options to own stock in the company.

References

1. Jacquemont, L.; Soulillou, J.P.; Degauque, N. Blood biomarkers of kidney transplant rejection, an endless search? *Expert Rev. Mol. Diagn.* **2017**, *17*, 687–697. [CrossRef] [PubMed]
2. Humar, A.; Kerr, S.; Hassoun, A.; Granger, D.; Suhr, B.; Matas, A. The association between acute rejection and chronic rejection in kidney transplantation. *Transplant. Proc.* **1999**, *31*, 1302–1303. [CrossRef]
3. Nankivell, B.J.; Alexander, S.I. Rejection of the kidney allograft. *N. Engl. J. Med.* **2010**, *363*, 1451–1462. [CrossRef] [PubMed]
4. Sigdel, T.K.; Sarwal, M.M. The proteogenomic path towards biomarker discovery. *Pediatr. Transplant.* **2008**, *12*, 737–747. [CrossRef] [PubMed]
5. Lo, D.J.; Kaplan, B.; Kirk, A.D. Biomarkers for kidney transplant rejection. *Nat. Rev. Nephrol.* **2014**, *10*, 215–225. [CrossRef]
6. Nasr, M.; Sigdel, T.; Sarwal, M. Advances in diagnostics for transplant rejection. *Expert Rev. Mol. Diagn.* **2016**, *16*, 1121–1132. [CrossRef] [PubMed]
7. Yang, J.Y.; Sarwal, M.M. Transplant genetics and genomics. *Nat. Rev. Genet.* **2017**, *18*, 309–326. [CrossRef]
8. Loupy, A.; Haas, M.; Solez, K.; Racusen, L.; Glotz, D.; Seron, D.; Nankivell, B.J.; Colvin, R.B.; Afrouzian, M.; Akalin, E.; et al. The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology. *Am. J. Transplant.* **2017**, *17*, 28–41. [CrossRef]
9. Snyder, T.M.; Khush, K.K.; Valantine, H.A.; Quake, S.R. Universal noninvasive detection of solid organ transplant rejection. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6229–6234. [CrossRef]
10. Beck, J.; Bierau, S.; Balzer, S.; Andag, R.; Kanzow, P.; Schmitz, J.; Gaedcke, J.; Moerer, O.; Slotta, J.E.; Walson, P.; et al. Digital droplet PCR for rapid quantification of donor DNA in the circulation of transplant recipients as a potential universal biomarker of graft injury. *Clin. Chem.* **2013**, *59*, 1732–1741. [CrossRef]
11. De Vlaminck, I.; Valantine, H.A.; Snyder, T.M.; Strehl, C.; Cohen, G.; Luikart, H.; Neff, N.F.; Okamoto, J.; Bernstein, D.; Weisshaar, D.; et al. Circulating cell-free DNA enables noninvasive diagnosis of heart transplant rejection. *Sci. Transl. Med.* **2014**, *6*, 241ra77. [CrossRef] [PubMed]
12. Sigdel, T.K.; Vitalone, M.J.; Tran, T.Q.; Dai, H.; Hsieh, S.C.; Salvatierra, O.; Sarwal, M.M. A rapid noninvasive assay for the detection of renal transplant injury. *Transplantation* **2013**, *96*, 97–101. [CrossRef] [PubMed]
13. Knight, S.R.; Thorne, A.; Faro, M.L.L. Donor-specific Cell-Free DNA as a Biomarker in Solid Organ Transplantation. A Systematic Review. *Transplantation* **2018**. [CrossRef] [PubMed]

14. Bloom, R.D.; Bromberg, J.S.; Poggio, E.D.; Bunnapradist, S.; Langone, A.J.; Sood, P.; Matas, A.J.; Mehta, S.; Mannon, R.B.; Sharfuddin, A.; et al. Cell-Free DNA and Active Rejection in Kidney Allografts. *J. Am. Soc. Nephrol.* **2017**, *28*, 2221–2232. [CrossRef] [PubMed]
15. Dar, P.; Curnow, K.J.; Gross, S.J.; Hall, M.P.; Stosic, M.; Demko, Z.; Zimmermann, B.; Hill, M.; Sigurjonsson, S.; Ryan, A.; et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. *Am. J. Obstet. Gynecol.* **2014**, *211*, e1–e17. [CrossRef] [PubMed]
16. Ryan, A.; Hunkapiller, N.; Banjevic, M.; Vankayalapati, N.; Fong, N.; Jinnett, K.N.; Demko, Z.; Zimmermann, B.; Sigurjonsson, S.; Gross, S.J.; et al. Validation of an Enhanced Version of a Single-Nucleotide Polymorphism-Based Noninvasive Prenatal Test for Detection of Fetal Aneuploidies. *Fetal Diagn. Ther.* **2016**, *40*, 219–223. [CrossRef] [PubMed]
17. Pergament, E.; Cuckle, H.; Zimmermann, B.; Banjevic, M.; Sigurjonsson, S.; Ryan, A.; Hall, M.P.; Dodd, M.; Lacroute, P.; Stosic, M.; et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. *Obstet. Gynecol.* **2014**, *124 Pt 1*, 210–218. [CrossRef]
18. Haas, M.; Loupy, A.; Lefaucheur, C.; Roufosse, C.; Glotz, D.; Seron, D.; Nankivell, B.J.; Halloran, P.F.; Colvin, R.B.; Akalin, E.; et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am. J. Transplant.* **2018**, *18*, 293–307. [CrossRef]
19. Chen, J.; Xie, W.; Wang, H.; Jin, J.; Wu, J.; He, Q. C4d as a significant predictor for humoral rejection in renal allografts. *Clin. Transplant.* **2005**, *19*, 785–791.
20. Crespo, M.; Pascual, M.; Tolkoff-Rubin, N.; Mauiyyedi, S.; Collins, A.B.; Fitzpatrick, D.; Farrell, M.L.; Williams, W.W.; Delmonico, F.L.; Cosimi, A.B.; et al. Acute humoral rejection in renal allograft recipients: I. Incidence, serology and clinical characteristics. *Transplantation* **2001**, *71*, 652–658. [CrossRef]
21. Abbosh, C.; Birkbak, N.J.; Wilson, G.A.; Jamal-Hanjani, M.; Constantin, T.; Salari, R.; Le Quesne, J.; Moore, D.A.; Veeriah, S.; Rosenthal, R.; et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature* **2017**, *545*, 446–451. [CrossRef] [PubMed]
22. Zimmermann, B.; Hill, M.; Gemelos, G.; Demko, Z.; Banjevic, M.; Baner, J.; Ryan, A.; Sigurjonsson, S.; Chopra, N.; Dodd, M.; et al. Noninvasive prenatal aneuploidy testing of chromosomes 13, 18, 21, X, and Y, using targeted sequencing of polymorphic loci. *Prenat. Diagn.* **2012**, *32*, 1233–1241. [CrossRef] [PubMed]
23. Holm, S. A Simple Sequentially Rejective Multiple Test Procedure. *Scand. J. Stat.* **1979**, *6*, 65–70.
24. Dunn, O.J. Multiple Comparisons Using Rank Sums. *Technometrics* **1964**, *6*, 241–252. [CrossRef]
25. Levey, A.S.; Bosch, J.P.; Lewis, J.B.; Greene, T.; Rogers, N.; Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann. Intern. Med.* **1999**, *130*, 461–470. [CrossRef]
26. Schwartz, G.J.; Munoz, A.; Schneider, M.F.; Mak, R.H.; Kaskel, F.; Warady, B.A.; Furth, S.L. New equations to estimate GFR in children with CKD. *J. Am. Soc. Nephrol.* **2009**, *20*, 629–637. [CrossRef]
27. National Institute of Diabetes and Digestive and Kidney Diseases. Chronic Kidney Disease Tests & Diagnosis. Available online: https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/tests-diagnosis (accessed on 31 August 2018).
28. Efron, B.; Tibshirani, R. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. *Stat. Sci.* **1986**, *1*, 54–75. [CrossRef]
29. Laird, N.M.; Ware, J.H. Random-effects models for longitudinal data. *Biometrics* **1982**, *38*, 963–974. [CrossRef]
30. Kenward, M.G.; Roger, J.H. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* **1997**, *53*, 983–997. [CrossRef]

Table S1. Performance characteristics for different dd-cfDNA cut-offs.

	dd-cfDNA Cut-offs					
	0.6%	0.8%	1.0%	1.2%	1.4%	1.6%
Sensitivity (95% CI)	95.2% (87.8–100)	93.5% (85.0–100)	88.7% (77.7–99.8)	85.5% (73.2–97.8)	80.7% (66.9–94.5)	69.4% (53.2–85.6)
Specificity (95% CI)	59.6% (51.7–67.6)	66.3% (58.7–74.0)	72.6% (65.4–79.8)	79.5% (73.0–76.0)	82.8% (76.7–88.9)	86.9% (81.4–92.3)
PPV (95% CI)	44.0% (38.8–49.2)	48.1% (42.0–54.2)	51.9% (44.7–59.2)	58.2% (49.7–66.7)	61.0 (51.6–70.3)	63.8% (52.8–74.8)
NPV (95% CI)	97.4% (93.4–100)	96.9% (92.8–100)	95.1% (90.5–99.7)	94.3% (89.7–98.9)	92.8 (88.0–97.6)	89.5% (84.5–94.5)

Table S2. Multiple groups comparisons.

dd-cfDNA

Comparison	Z	P.adj
AR - BL	**5.711116**	**0**
AR - OI	**4.569421**	**2.00E-05**
BL - OI	0.13599	0.891829
AR - STA	**6.746807**	**0**
BL - STA	1.107485	0.804253
OI - STA	0.644728	1

eGFR

Comparison	Z	P.adj
AR - BL	-1.17381	0.460946
AR - OI	-1.95735	0.15092
BL - OI	-1.15746	0.247085
AR - STA	**-8.65195**	**0**
BL - STA	**-9.08226**	**0**
OI - STA	**-5.19251**	**1.00E-06**

Significant (adj. $p < 0.0001$) results are bolded. The test to compares dd-cfDNA and eGFR for AR vs. Non-AR was a Kruskal-Wallis test.

Table S3. Cohort breakdown into for-cause and protocol biopsy for AR versus Non-AR.

Status	Biopsy_Reason	Total	Median	Low	High	Mean	SD
AR	For cause	25	2.04	0.09	23.9	3.85	4.81
	Protocol	13	3.56	0.12	23.4	6.16	6.44
Non-AR	For cause	78	0.645	0.02	6.54	1.08	1.27
	Protocol	101	0.27	0.03	6.78	0.80	1.28

Table S4. Descriptive statistics dd-cfDNA as a function of ABMR/TCMR

	Count	Median	Low	High	Mean	SD
ABMR	16	2.22	0.12	23.9	5.55	7.64
Both	12	2.56	0.09	8.8	4.00	3.21
TCMR	10	2.69	1.01	9.77	3.96	3.11

Table S5. Histology report for all active rejection cases.

Histology Report	dd-cfDNA Assay Result	
	<1% dd-cfDNA	>1% dd-cfDNA
ABMR	0	1
ABMR + acute bTCMR	0	1
ABMR + acute TCMR IA	0	4
ABMR + acute TCMR IIB	0	2
ABMR + bTCMR	3	2
ABMR + chronic active bTCMR	0	5
ABMR + chronic active TCMR IA	0	1
ABMR + chronic active TCMR IB	1	0
ABMR + chronic active TCMR II	0	2
ABMR + chronic active TCMR IIA	0	1
acute ABMR	0	1
acute TCMR IA	0	2
bABMR + acute TCMR IA	0	2
bC4d-positive ABMR + TCMR-IA	1	0
chronic active ABMR + bTCMR	0	2
chronic active TCMR IA	0	1
chronic active TCMR IB	0	3
TCMR IA	0	2
TG + cABMR	0	1

Table S6. Descriptive statistics for dd-cfDNA as a function of donor type.

Group	Donor_type	Total	Median	Low	High	Mean	SD
AR	Living Related	1	0.97	0.97	0.97	0.97	N/A
	Living Non-related	2	4.88	1.39	8.37	4.88	4.94
	Deceased Non-related	35	2.41	0.09	23.9	4.74	5.59
Non-AR	Living Related	14	0.265	0.02	3.89	0.67	1.09
	Living Non-related	75	0.65	0.05	6.78	1.17	1.54
	Deceased Non-related	90	0.405	0.06	6.3	0.75	1.02

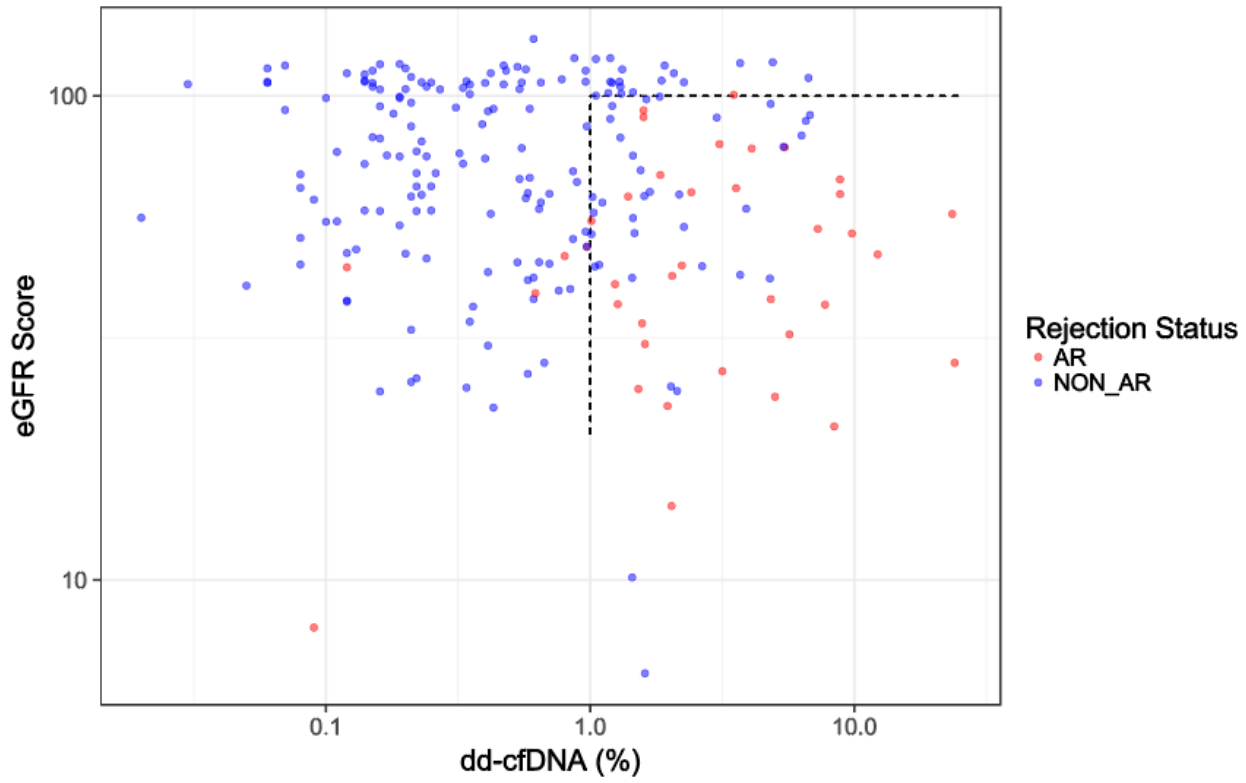

Figure S1. dd-cfDNA and eGFR in biopsy matched samples.

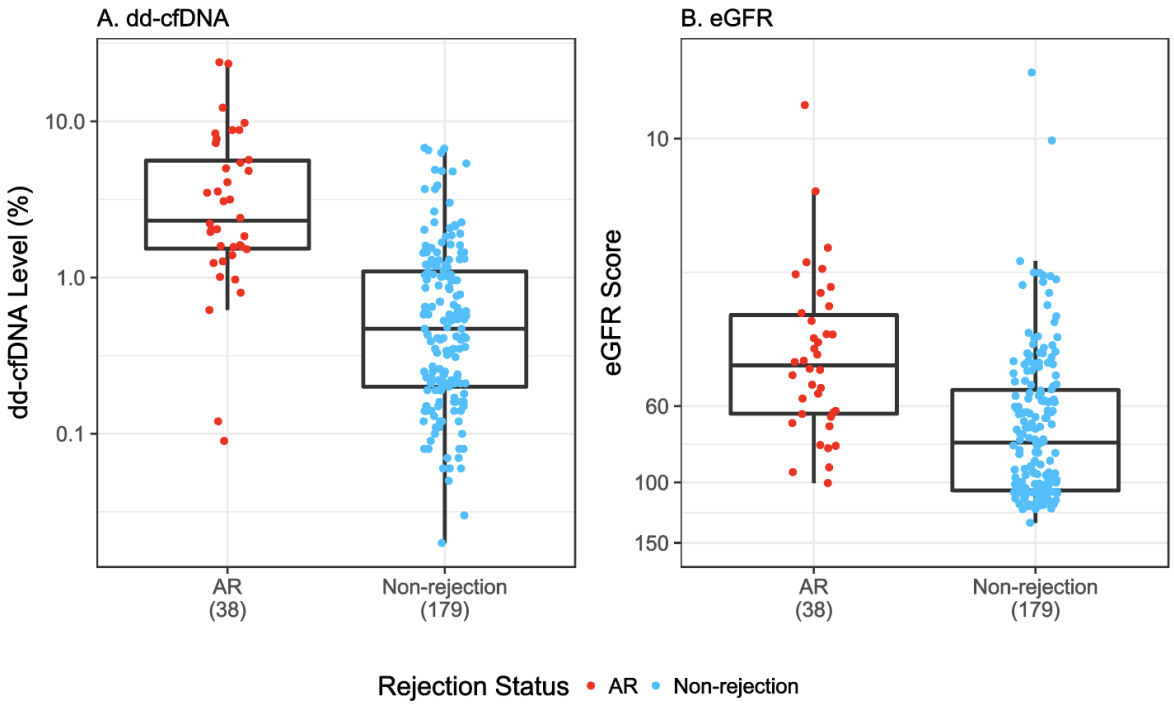

Figure S2. Discrimination of active rejection by dd-cfDNA versus eGFR in AR versus non-AR.

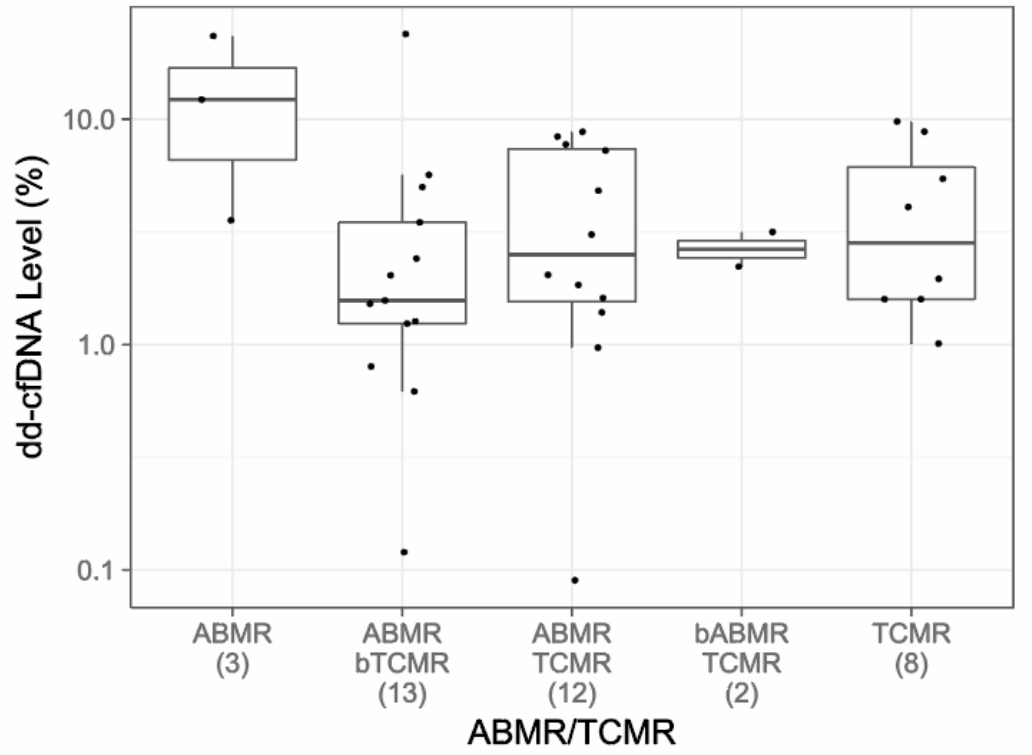

Figure S3. Percent dd-cfDNA by ABMR/TCMR status.

EXHIBIT 2

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Cell-Free DNA and Active Rejection in Kidney Allografts

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ABSTRACT

Histologic analysis of the allograft biopsy specimen is the standard method used to differentiate rejection from other injury in kidney transplants. Donor-derived cell-free DNA (dd-cfDNA) is a noninvasive test of allograft injury that may enable more frequent, quantitative, and safer assessment of allograft rejection and injury status. To investigate this possibility, we prospectively collected blood specimens at scheduled intervals and at the time of clinically indicated biopsies. In 102 kidney recipients, we measured plasma levels of dd-cfDNA and correlated the levels with allograft rejection status ascertained by histology in 107 biopsy specimens. The dd-cfDNA level discriminated between biopsy specimens showing any rejection (T cell–mediated rejection or antibody-mediated rejection [ABMR]) and controls (no rejection histologically), $P<0.001$ (receiver operating characteristic area under the curve [AUC], 0.74; 95% confidence interval [95% CI], 0.61 to 0.86). Positive and negative predictive values for active rejection at a cutoff of 1.0% dd-cfDNA were 61% and 84%, respectively. The AUC for discriminating ABMR from samples without ABMR was 0.87 (95% CI, 0.75 to 0.97). Positive and negative predictive values for ABMR at a cutoff of 1.0% dd-cfDNA were 44% and 96%, respectively. Median dd-cfDNA was 2.9% (ABMR), 1.2% (T cell–mediated types ≥IB), 0.2% (T cell–mediated type IA), and 0.3% in controls ($P=0.05$ for T cell–mediated rejection types ≥IB versus controls). Thus, dd-cfDNA may be used to assess allograft rejection and injury; dd-cfDNA levels <1% reflect the absence of active rejection (T cell–mediated type ≥IB or ABMR) and levels >1% indicate a probability of active rejection.

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Accurate and timely detection of allograft rejection and effective treatment are essential for long-term survival of renal transplants. Although histology obtained *via* needle biopsy remains the standard for diagnosis of rejection, this technique is infrequently used for surveillance because of the cost, logistics, potential complications, and patient discomfort and inconvenience. Donor-derived cell-free DNA (dd-cfDNA) detected in the blood of transplant recipients has been proposed as a noninvasive marker for diagnosis of graft rejection.[1–3] The premise for quantitative interpretation of this biomarker is that rejection entails injury, including increased cell death in the allograft, leading to increased dd-cfDNA released into the bloodstream.

Data from several single-center studies suggest that dd-cfDNA levels in blood, measured as a fraction of the total cell-free DNA (cfDNA), can discriminate rejection from nonrejection in heart, lung, liver, and kidney allografts. In stable heart transplant recipients, the fraction of cfDNA originating from the graft is nearly always <1%,[4–6] whereas during rejection the levels of dd-cfDNA are significantly higher.[5,7] In stable lung and liver transplant recipients, the level of dd-cfDNA is higher than in stable heart transplant recipients, and it further increases in moderate-to-severe rejection.[8,9] Up to now, dd-cfDNA has been least studied in renal transplants; levels in stable kidney recipients are similar to those in heart transplant recipients,[4,10] and analyses of individual patients and a small single-center study identified higher levels during biopsy-proven acute rejection.[11]

In kidney transplantation, there are no existing biomarkers that adequately measure the status of active injury to the allograft. Serum creatinine allows estimation of the GFR, but it is not specific or sensitive for allograft injury, and may not distinguish acute from chronic loss of function.[12,13]

This report from the Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Acute Rejection in Kidney Transplant Recipients (DART) study (ClinicalTrials.gov Identifier: NCT02424227) validates that plasma levels of dd-cfDNA can discriminate active rejection status. The DART study is the first multicenter study of renal allograft recipients using an analytically validated dd-cfDNA test[7] that employs targeted amplification and sequencing of single-nucleotide polymorphisms to quantify donor and recipient DNA contributions, without the need for prior genotyping of donor or recipient DNA (AlloSure).

RESULTS

Patients, Biopsies, and Blood Samples

From April of 2015 until May of 2016, 384 renal transplant patients were enrolled (245 within 1–3 months of their kidney transplantation and 139 at the time of a clinically indicated renal biopsy) from 14 clinical sites. Figures 1 and 2 show the pathologists' diagnostic findings for the 107 clinically indicated biopsies that had matched plasma dd-cfDNA results. This subset provides the core dataset used for the analyses of dd-cfDNA to discriminate rejection from no rejection status (using the biopsy-based pathologists' reports as the diagnostic standard).

The patient characteristics of the study cohort are shown in Table 1. The DART study population was representative of the United States renal transplant registry population (Supplemental Table 1). The active rejection subgroup contained a higher proportion of black and deceased donor organ recipients than the group without active rejection and the overall DART population. Patients with active rejection were also significantly younger than patients with no rejection.

At the time of data lock, 219 patients had at least one renal biopsy; 242 biopsies had sufficient specimens and associated pathologists' reported results (Figure 2). The majority of biopsies (204 of 242) were performed for clinical suspicion of rejection, 34 for surveillance, and four for follow-up of treated rejection. Only one of 34 (3%) surveillance biopsies revealed rejection (Supplemental Table 2). Therefore, we did not calculate the performance characteristics for dd-cfDNA to discriminate active rejection in the scenario of no clinical indication for biopsy.

Our primary analyses in this study combined three subclasses of rejection (T cell–mediated rejection [TCMR], "acute/active" antibody-mediated rejection [ABMR], and "chronic, active" ABMR) defined by the Banff working groups[14,15] because they share some common histologic criteria and the related cell injury manifestations have potential to involve active cell injury and death,[16] and therefore result in increased levels of dd-cfDNA (Supplemental Figure 1). We use the term active rejection to describe these rejection subclasses and distinguish them from all other biopsy-based diagnoses not phenotypically associated with active rejection (details in Concise Methods).

A diagnosis of active rejection was confirmed in review of 59 pathologists' biopsy reports: 58 cases of active rejection in 204 biopsies, performed for clinical suspicion, most commonly an elevation in serum creatinine, and one case of active rejection in 34 surveillance biopsies. The types of active rejection are summarized in Supplemental Table 2.

dd-cfDNA Levels in Blood Plasma

To define the area under the curve–receiver operating characteristic (AUC-ROC) performance of dd-cfDNA, we included all dd-cfDNA results that were collected at the same time that a clinically indicated biopsy was performed. There were 27 biopsy specimens from 27 patients with, and 80 biopsy specimens from 75 patients without, active rejection. A correlation matrix of Banff elementary lesions and clinical features for the 107 samples are rank-ordered and color-coded by dd-cfDNA level in Figure 1. Samples with >1% dd-cfDNA occurred significantly more often ($P<0.01$) in the following types of rejection and subelements: acute/active ABMR; chronic, active ABMR; any or moderate microvascular inflammation; linear C4d staining in peritubular capillaries; and presence

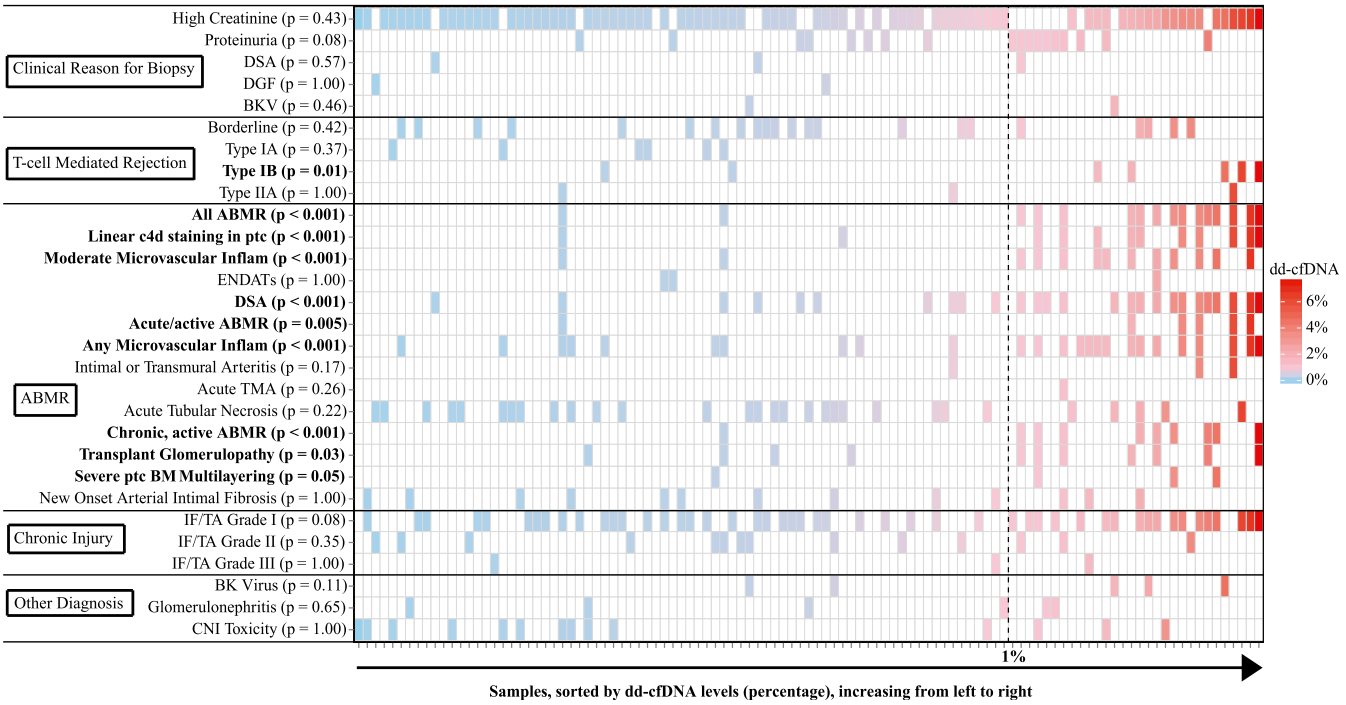

Figure 1. Banff elementary lesions and clinical features correlate with dd-cfDNA level. The 107 samples (27 patients with 27 samples with active rejection; 75 patients with 80 samples with no active rejection) are rank-ordered and color-coded by dd-cfDNA level. White indicates the element was not associated with that biopsy/visit. For each sample (*x* axis), associated elements (*y* axis) are shown as a colored box, by the level of dd-cfDNA associated with the sample; highest dd-cfDNA in red, lowest in blue, with a vertical dashed line at the 1% cutoff. The significance (*P* value) of association of dd-cfDNA >1% with each element is shown. BM, (glomerular) basement membrane; CNI, calcineurin inhibitor; DGF, delayed graft function; ENDATs, (gene expression profiles of) endothelial activation (and injury) transcripts; Inflam, inflammation; ptc, peritubular capillary.

of donor-specific antibody. The dd-cfDNA threshold of 1% also discriminated type IB TCMR (P=0.01) and transplant glomerulopathy (P=0.03). We computed the AUC-ROC performance of serum creatinine on this set. For estimating the positive predictive value (PPV) and negative predictive value (NPV) of dd-cfDNA to predict active rejection versus no active rejection, we used the prevalence of 58 active rejections in the 170 patients with 204 biopsy reports available from clinically indicated biopsies (Figure 2).

The fraction of dd-cfDNA in blood plasma differed significantly between the groups (Figure 3A). The median level of dd-cfDNA in patients with active rejection was significantly higher (1.6%) than in the comparator group (0.3%) of biopsy specimens without active rejection (P<0.001). Median dd-cfDNA levels varied by type of active rejection: 2.9% (ABMR), 1.2% (TCMR only, types IB and IIA), 0.2% (TCMR only type IA). Because of small numbers, comparison of TCMR types included the cases of mixed TCMR and ABMR. Figure 4B shows the data for TCMR ≥types IB (P=0.05 versus no active rejection) and TCMR type IA.

The fractions of true and false positive results for dd-cfDNA to discriminate active rejection are shown in Figure 3C. The area under the curve (AUC) was 0.74 (95% confidence interval [95% CI], 0.61 to 0.86). With a cutoff of 1.0%, dd-cfDNA had an 85% specificity (95% CI, 79% to 91%) and 59% sensitivity (95% CI, 44% to 74%) to discriminate active rejection from no rejection. This is graphed as the sensitivity and specificity over the range of dd-cfDNA (Figure 3E). The range of PPV and NPV for dd-cfDNA for discriminating active rejection is shown in Figure 3F; the PPV was 61% and NPV was 84%, with the 1.0% dd-cfDNA cutoff.

Serum creatinine at time of biopsy did not discriminate active rejection from no active rejection (Figure 3B). The ROC curve for creatinine to discriminate active rejection had an AUC of 0.54 (95% CI, 0.43 to 0.66); *i.e.*, at any cutoff level for creatinine, there were as many false as true positive results (Figure 3D).

When the cohort of ABMR (including mixed ABMR and TCMR) was compared with the cohort of all non-ABMR (including TCMR-only), the fraction of dd-cfDNA differed significantly (P<0.001, Figure 5A), whereas there was no discrimination by serum creatinine (Figure 5B). The fraction of true positive results and the fraction of false positive results for dd-cfDNA to discriminate ABMR status are shown in Figure 5C. The AUC was 0.87 (95% CI, 0.75 to 0.97). With a cutoff of 1.0%, dd-cfDNA has an 83% specificity (95% CI, 78% to 89%) and 81% sensitivity (95% CI, 67% to 100%) to discriminate ABMR from no ABMR. The sensitivity and specificity to

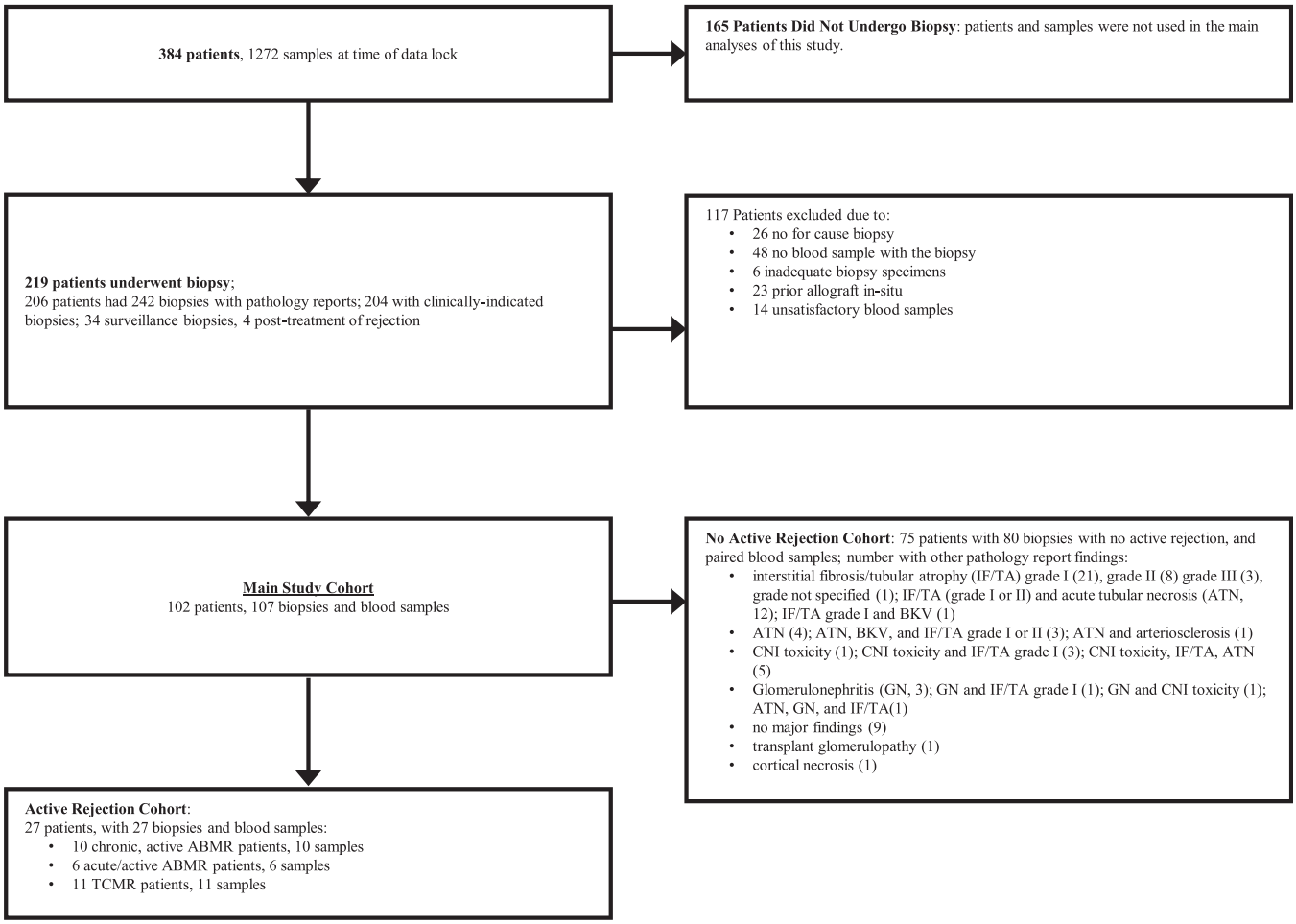

Figure 2. Patients, blood samples, and biopsies used in this study.

discriminate ABMR over the range of potential cutoffs is shown in Figure 5E. The range of PPV and NPV for discriminating ABMR is shown in Figure 5F; the PPV was 44% and NPV was 96% with the 1.0% dd-cfDNA cutoff. The ROC curve for creatinine to discriminate ABMR had an AUC of 0.57 (95% CI, 0.42 to 0.71) (Figure 5D).

Among the 58 active rejections found in the clinically indicated biopsies, the available 27 paired dd-cfDNA results are shown in Figure 4A, broken out by rejection subclass: ten were chronic, active ABMR; six acute/active ABMR; and 11 TCMR only (types IA [5], IB [5], and IIA [1]). As shown, the lowest types of TCMR (type IA) had lower dd-cfDNA than type IB or type IIA (Figure 4B), although the number of cases was very limited. The similarity in the pattern of dd-cfDNA values in the nominal two classes of ABMR was not surprising, because the histologic criteria overlap for these forms of ABMR. Figure 6 shows the dd-cfDNA results in the same 27 cases of active rejection, categorized by other findings in addition to histologic evidence of active rejection. For comparison, Figure 7 shows the results in the 80 biopsy specimens with no rejection, categorized by other histologic findings. In both the active rejection and no active rejection groups, interstitial fibrosis/tubular atrophy (IF/TA) and acute tubular necrosis were relatively common coincidental findings, and no obvious trend in the dd-cfDNA was associated with these. Because of the small number of cases of these other diagnoses, including calcineurin inhibitor (CNI) toxicity and BK virus (BKV), statistical analyses of these patterns were not performed.

Of 80 clinically indicated biopsies with no active rejection findings, only nine biopsy specimens were reported to show essentially normal histology (*i.e.*, no other coincidental findings, such as IF/TA, acute tubular necrosis, BKV, GN, CNI toxicity). We performed a comparison of dd-cfDNA in the group of the normal biopsy specimens to the biopsy specimens showing no active rejection but one or more coincidental findings: in the normal group (n=9) the median dd-cfDNA was 0.53% (interquartile range, 0.22%–0.67%); in the coincidental finding group (n=71), the median dd-cfDNA was 0.30% (interquartile range, 0.14%–0.77%) (Wilcoxon rank sum test P=0.9).

Among the 107 biopsy specimens in either the active rejection or no active rejection groups, there were two reports in

Table 1. Patient characteristics

Clinical Characteristic	Active Rejection Group	No Active Rejection Group	*P* Value[a]
Number of patients	27	75	
Number of samples	27	80	
Race, *n* (%)			0.23
Black	13 (48)	23 (31)	
White	13 (48)	41 (55)	
Native Hawaiian or Other Pacific Islander	1 (4)	0 (0)	
Hispanic/Latino	0 (0)	4 (5)	
Asian	0 (0)	1 (1)	
Other	0 (0)	6 (8)	
Men, *n* (%)	16 (59)	45 (60)	>0.99
Age at enrollment, y	46±16	53±13	0.04
Post-transplant, d	968±1107	1189±1482	0.42
CMV serologic status, *n* (%)			0.15
D−/R+	4 (15)	13 (17)	
D+/R+	5 (19)	24 (32)	
D−/R−	3 (11)	16 (21)	
D+/R−	4 (15)	9 (12)	
Unknown	11 (41)	13 (17)	
Donor type, *n* (%)			0.03
Deceased donor	20 (74)	42 (56)	
Living unrelated	2 (7)	24 (32)	
Living related	5 (19)	9 (12)	
Child	2 (7)	3 (4)	
Sibling	2 (7)	4 (5)	
Parent	0 (0)	1 (1)	
Half-sibling	0 (0)	0 (0)	
Other biologic blood relation	1 (4)	1 (1)	
Creatinine	2.5±1.0	2.4±1.4	0.69
eGFR	32±12	36±21	0.21
HLA class 1 no. of mismatches (A, B)	2.7±1.4	2.6±1.4	0.59
HLA class 2 no. of mismatches (DR)	1.2±0.6	1.1±0.8	0.67
Weight, kg	85±19	84±21	0.73
Height, cm	170±10	171±8	0.58

Data ranges are presented as mean±standard deviation. CMV, cytomegalovirus.
[a]The *P* values are the level of statistical significance in the differences of values found in the DART active rejection group and the no active rejection group. For continuous covariates, Wilcoxon rank sum test was used to generate the *P* values. For categoric covariates, Fisher exact test was used to generate the *P* values.

which the pathologists noted findings of papilloma BKvirus. In case one, there was a viral load of >2 million copies of BKV/ml blood, and inflammation equivalent to Banff 1B intensity (i2–3, t3). In case two, there was moderate IF/TA and 9.99 million copies of BKV/ml blood. The dd-cfDNA level was 4.6% and 2.3%, respectively, in these cases.

DISCUSSION

In this study, most (204 of 242) kidney transplant biopsies were triggered by an elevation in serum creatinine over baseline with concerns for alloimmune injury, yet only 27% of these clinically indicated biopsies revealed active rejection. The results in the 107 biopsy specimens paired with plasma cfDNA showed that dd-cfDNA levels discriminated an active rejection status with an ROC-AUC of 0.74 and provided an estimated NPV 84% and PPV 61% at a cutoff of 1.0% dd-cfDNA. These results validated and extended prior reports of the performance characteristics of this assay.[7] There was stronger performance of dd-cfDNA in discriminating ABMR from no ABMR allograft status (ROC-AUC 0.87, NPV 96%, PPV 44%, cutoff of 1.0% dd-cfDNA). dd-cfDNA in 16 cases of ABMR was significantly higher (2.9%) than in 11 cases of TCMR rejection (0.2% in type IA [five patients], 1.2% in combined type IB [five patients] and type IIA [one patient]), and 0.3% in the no active rejection cohort (n=80). Because there is a clear trend that dd-cfDNA was higher in type IB TCMR than in type IA, we speculate that dd-cfDNA is likely to be higher in the more severe types of TCMR, but this cohort did not have enough cases to test this hypothesis.

The elevation of dd-cfDNA (>1%) was significantly associated with acute/active and chronic, active ABMR (Figure 1). The dd-cfDNA levels across the threshold of 1% also

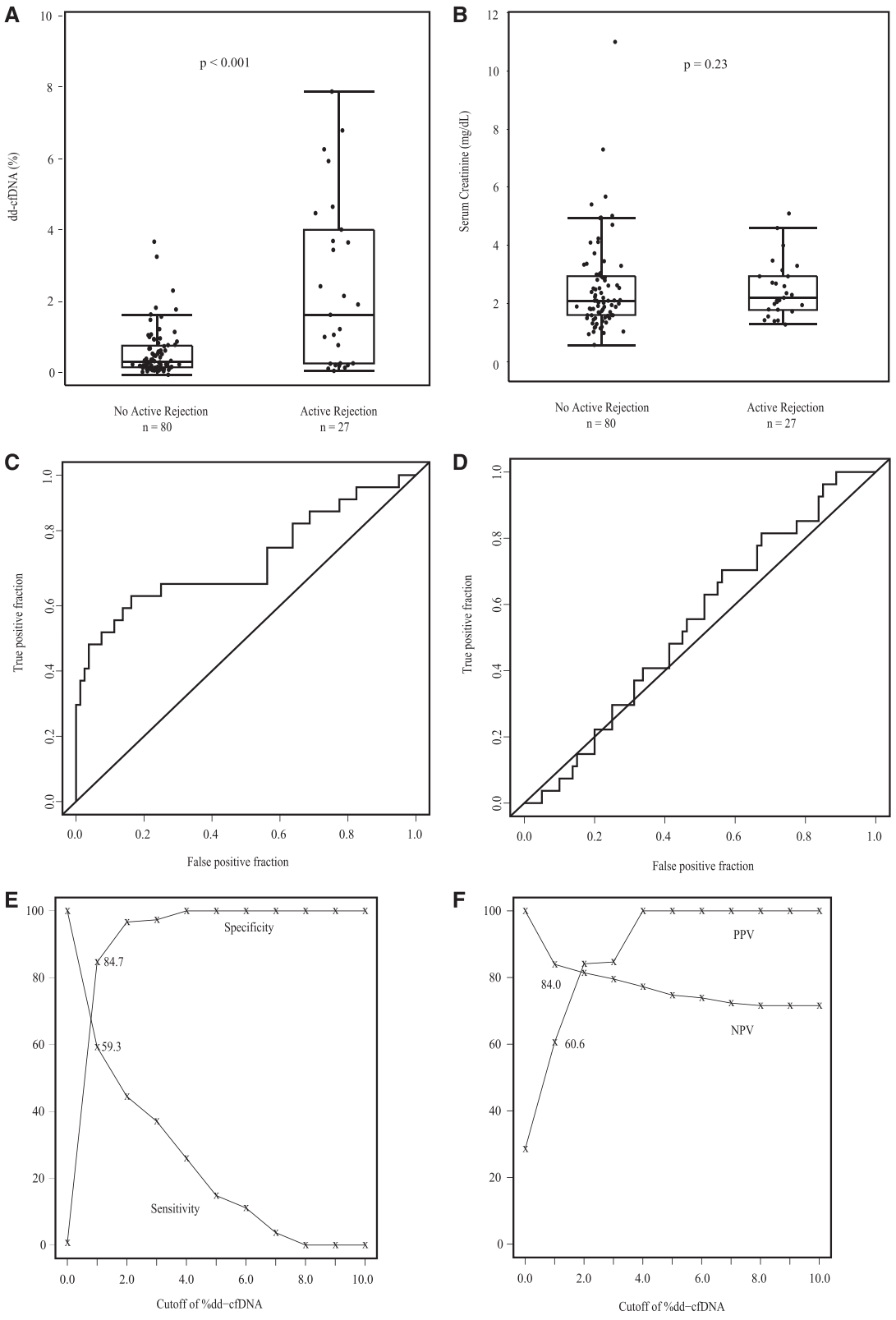

Figure 3. dd-cfDNA discriminates active rejection. (A) Fraction of dd-cfDNA in active rejection (*n*=27) versus no active rejection (*n*=80). Box and whisker plots; horizontal line represents the median; bottom and top of each box represents 25th and 75th percentiles. Dots are individual results. Median dd-cfDNA in active rejection 1.6% versus 0.3% for no rejection ($P<0.001$). (B) Serum creatinine (milligrams per deciliter) in active rejection (*n*=27) versus no active rejection (*n*=80). Box and whisker plots; horizontal line represents the

associated with type IB TCMR and transplant glomerulopathy. With the limited number of rejection events and intrinsic coupling to Banff histopathology subelements, we are unable to discern any obvious subelement (*e.g.*, microvascular inflammation) that may be more strongly associated with elevation of dd-cfDNA. This dd-cfDNA assay, which does not involve a biopsy and can be easily measured in a sequential manner, has potential to provide additional information along with *de novo* DSA in the diagnosis, management, and treatment of ABMR.

In contrast to dd-cfDNA, the serum creatinine level did not provide any discrimination of active rejection or ABMR from absence of active rejection or ABMR in the context of clinical indication for biopsy, because the creatinine ROC-AUC was near 0.50 (and the lower boundary of the 95th percentile confidence interval was well under 0.50 [Figure 3D and Figure 5D]).

Two cases of BKV were examples that demonstrate dd-cfDNA, by itself, may not be able to distinguish injury associated with the interstitial inflammation and tubulitis caused by BKV from similar degrees of inflammation and tubulitis caused by TCMR, but support the tenet that an elevation in dd-cfDNA may be used to reveal the degree of active allograft injury. A secondary method, most likely including a renal biopsy, will be needed to confirm the type of rejection or other injury. The observation that BKV is associated with the development of *de novo* DSA[17] raises the possibility that an elevation in dd-cfDNA in the setting of this infection could represent alloantibody-mediated microcirculation injury. Future studies will be required to illuminate the relationship among DSA, BKV, and dd-cfDNA elevation.

Scheduled surveillance needle biopsy evaluation for renal allograft rejection or other causes of injury is limited because its risks and costs versus benefits remain controversial.[18] In our study, only three of the 14 DART centers had surveillance biopsy protocols, accounting for 34 of 260 biopsies, and only one low-type TCMR was observed. This confirms other multicenter findings that protocol biopsies may not be useful because not enough reversible pathology is found.[18] Because we observed that, at the time of diagnosis of active rejection, median dd-cfDNA was 2.9% and 1.2% for ABMR and TCMR type ≥IB, respectively, it is reasonable to infer that serial measurements showing increases in dd-cfDNA may be useful to detect onset of a new rejection or other injury. Because the dd-cfDNA assay may be practical to repeat monthly (or more often), the stability of the biomarker below threshold levels could also be useful to guide the short- and long-term tapering or maintenance of immunosuppression medications. The half-life of cfDNA in the blood is <1 hour,[19] so changes in dd-cfDNA are expected to be a dynamic indicator of graft damage. The dd-cfDNA biomarker, in contrast to creatinine, may be a measure of cell injury in the allograft. The magnitude of increase in dd-cfDNA may be proportional to the acuity and severity of injury, akin to cardiac enzyme creatine phosphokinase or cardiac myocyte–specific protein troponin, which have been established as biomarkers of acute heart injury.[20]

Strengths of this dd-cfDNA study, which establishes the performance characteristics, include (*1*) an analytically validated assay in a College of American Pathologists-accredited, Clinical Laboratories Improvements Act (CLIA)–certified reference laboratory[7]; (*2*) the largest prospective, multicenter observational study of this test in renal transplant recipients; (*3*) a study population representative of United States renal transplant recipients; and (*4*) histopathology reports used as the reference to categorize rejection status.

There are several limitations to the study. First, we were not able to estimate the performance of dd-cfDNA to discriminate active rejection or ABMR in patients who may have had subclinical rejection because there were only 34 surveillance biopsies and only one finding of active rejection. However, this low rejection frequency is consistent with reports by others in an era of tacrolimus–mycophenolic acid–prednisone–based maintenance immunosuppression that question the utility of protocol biopsy for this purpose.[18] Second, the number of active rejections (27) and subclasses of rejection observed among these biopsy specimens was limited. However, these met the target total number of rejections prospectively stated in the statistical analysis, and indeed, the results proved this number to be sufficient to demonstrate statistically significant performance characteristics. Third, biopsy-matched blood samples were not collected for all biopsy specimens, and some of the matched blood samples were excluded due to issues such as inadequate amount of total DNA or timing of the blood draw relative to the biopsy. Of all collected blood samples, 4.5% did not render results due to some aspect of sample collection or testing. Most patients completed surveillance visits in compliance (77%) with the center schedule.

By design, dd-cfDNA in the assay is measured as a fraction of total cfDNA. It is possible that perturbations unrelated to active rejection or other direct injuries to the renal allograft, such as the turnover/death rate of cells originating from the recipient's tissues, could confound the results and interpretation of dd-cfDNA. Nevertheless, the approach used here (ratio) has been used by all published studies: increases in fraction of dd-cfDNA have been associated with rejection in independent studies of heart,[5–7] liver,[4,9,10] and lung[8] allografts.[1]

median; bottom and top of each box represents 25th and 75th percentiles. Dots are individual results. Serum creatinine was not significantly different in median values between two groups (P=0.23). (C) ROC curve for dd-cfDNA to discriminate active rejection. AUC=0.74 (95% CI, 0.61 to 0.86). (D) ROC curve for serum creatinine to discriminate active rejection. AUC=0.54 (95% CI, 0.43 to 0.66). (E) The sensitivity (%) and specificity (%) for dd-cfDNA to discriminate active rejection versus no active rejection status. (F) The PPV and NPV for dd-cfDNA for discriminating active rejection from no active rejection.

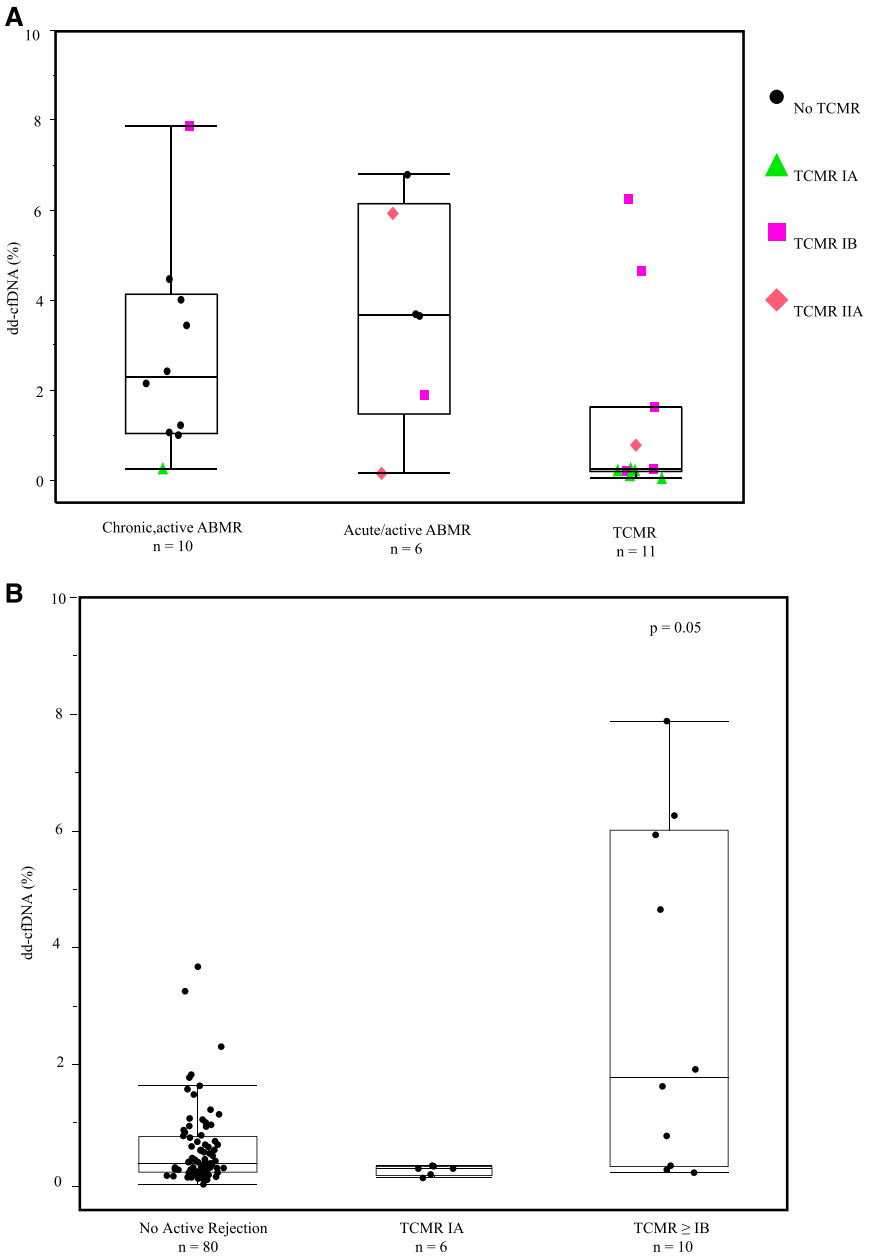

Figure 4. dd-cfDNA levels are higher in ABMR than TCMR. (A) dd-cfDNA in 27 biopsy-based rejections: 10 chronic, active ABMR; six acute/active ABMR; 16 TCMR, types IA (6, ▲), IB (7, ■), and IIA (3, ◆). Biopsy specimens diagnosed with AMBR and TCMR (mixed) are shown in the ABMR plots, with points colored to indicate the TCMR diagnosis also made on the same biopsy specimen. ABMR without TCMR is shown as a circle (●). Median dd-cfDNA 2.9% (ABMR). Median for TCMR-only, 1.2% (types ≥IB), 0.2% (TCMR type IA). (B) All data for samples classified as TCMR, including TCMR mixed with ABMR.

The optimal time interval for serial monitoring of dd-cfDNA for surveillance remains to be defined, but monthly would be feasible, because established clinical laboratory tests such as creatinine are measured on a monthly or more frequent schedule. Additionally, this test may be ordered if there is a clinical suspicion of rejection or injury, before deciding on the need for a renal biopsy. This would be especially useful in patients who are on anticoagulation therapy or have other reasons to avoid biopsy. As with all laboratory tests, clinical assessment of the patient's context is important when interpreting results. Although the dd-cfDNA test may not eliminate the need for biopsy, results with high PPV could increase the prebiopsy probability of detecting treatable injury, so that biopsy could be made an even more effective diagnostic tool. In association with a high NPV, dd-cfDNA results may reduce the need for biopsy in some cases of elevated creatinine.

In summary, this report sets the initial foundation for the performance characteristics of dd-cfDNA to detect active rejection and

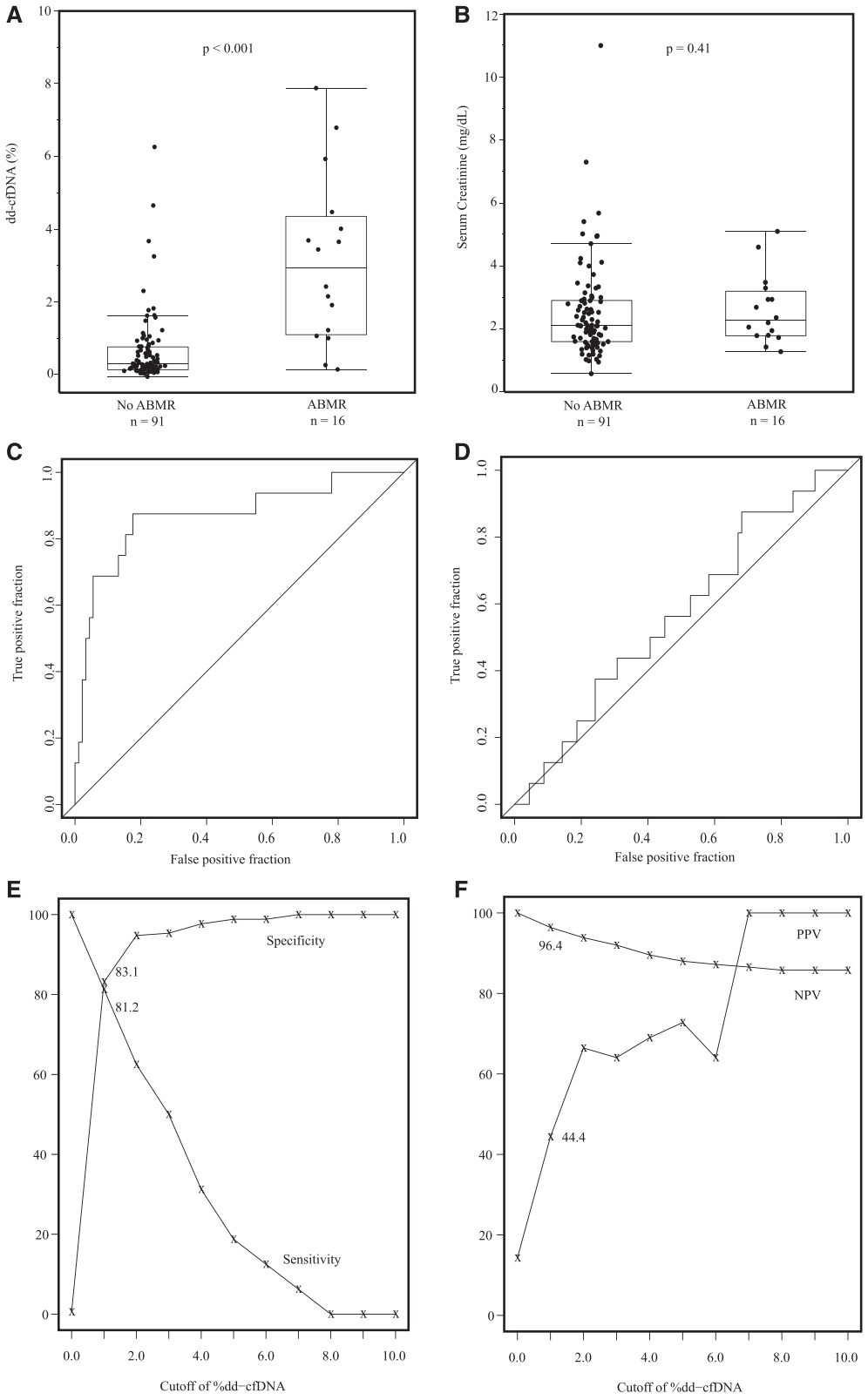

Figure 5. dd-cfDNA discriminates ABMR. (A) Fraction of dd-cfDNA in ABMR (*n*=16) versus no ABMR (*n*=91). Box and whisker plots; horizontal line represents the median; bottom and top of each box represents 25th and 75th percentiles. Dots are individual results. Median dd-cfDNA in ABMR 2.9% versus 0.29% for no ABMR ($P<0.001$). (B) Serum creatinine (milligrams per deciliter) in ABMR (*n*=16) versus no ABMR (*n*=91). Serum creatinine was not significantly different in median values between two groups ($P=0.41$). (C) ROC curve

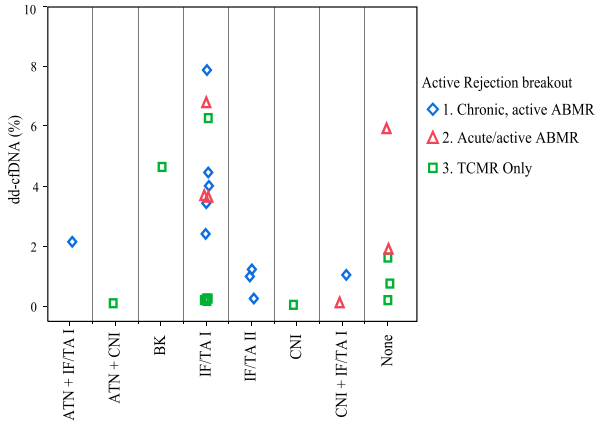

Figure 6. dd-cfDNA levels in plasma from patients with active rejection are not correlated with other histopathological findings. ◇, chronic, active ABMR; △, acute/active ABMR; □, TCMR only.

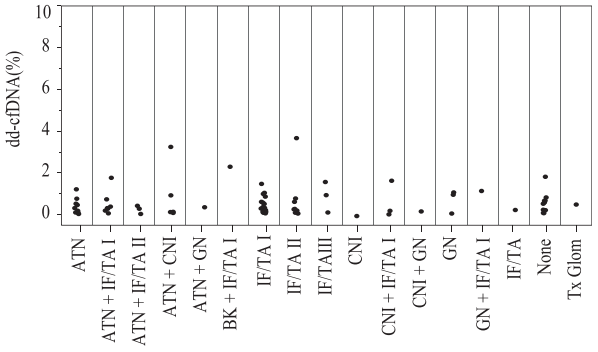

Figure 7. dd-cfDNA levels in plasma from patients without active rejection are not correlated with other histopathological findings. Each circle represents a biopsy specimen. BK, BK virus; Tx Glom, transplant glomerulopathy.

injury of the renal allograft beyond serum creatinine and without the need for a biopsy. The next steps of development include studies to validate these findings and to demonstrate the clinical utility of this new type of immune monitoring of the graft.

CONCISE METHODS

Study Design

The DART study was a prospective observational study. Renal transplant patients were enrolled within 1–3 months of their kidney transplantation and/or at the time of a clinically indicated renal biopsy from 14 clinical sites (Supplemental Table 3, Participating Sites).

The institutional review board at each site approved the study, and all of the patients provided written informed consent. The statistical analysis, data management, and clinical operations coordination were provided by staff employed by the study sponsor.

Blood Samples and dd-cfDNA Measurement

After transplantation, blood was collected at the time of scheduled surveillance visits at months 1, 2, 3, 4, 6, 9, and 12; or at the time of each kidney allograft biopsy and up to two follow-up samples within 8 weeks of the kidney allograft biopsy. Duplicate samples of venous blood were collected at the same venipuncture in Streck Cell-Free DNA BCT tubes, stored at room temperature, and shipped to the CLIA-certified laboratory at CareDx, Inc. (Brisbane, CA). Upon arrival, and within 7 days postdraw,[21] plasma was separated by centrifugation at 1600 × *g* for 20 minutes followed by a second centrifugation at 16,000 × *g* for 10 minutes and was either stored at −80°C or cfDNA was extracted immediately using the Circulating Nucleic Acid kit (Qiagen, Redwood City, CA).

We measured dd-cfDNA using a targeted next-generation sequencing assay that employs 266 single-nucleotide polymorphisms to accurately quantify dd-cfDNA in transplant recipients without need for separate genotyping of the recipient or the donor.[7] The assay quantifies the fraction of dd-cfDNA in both unrelated and related donor-recipient pairs. The dd-cfDNA assay is precise across the linear quantifiable range (0.2%–16% dd-cfDNA) with a mean across-run coefficient of variation of 6.8%.[7] Assay results of the clinical samples in this study were evaluated against established quality control criteria described previously,[7] and only passing results used for analysis. Samples that failed quality control were repeated at the step where they failed or were repeated using plasma from the duplicate Streck Cell-Free DNA BCT tube collected at the same venipuncture as the first sample. All measurements were performed by staff unaware of the identity of the samples. The final results (percentage dd-cfDNA) were reported to the database manager, who combined them with the clinical information and transferred the combined data set to the statistical team for analysis.

Renal Allograft Biopsies

We collected information on the number of, and clinical indication for, renal transplant biopsies for each patient. The on-site pathologist's official renal transplant biopsy diagnostic report was used by the site investigator to guide completion of the study case report form sections which captured the diagnosis of rejection in accordance with criteria designated by the Banff Working Groups.[14,15] The study clinical monitor independently reviewed the pathologists' reports to confirm that the findings met the criteria defined in the Banff Working Group classification system to support the recorded diagnostic classification, and final reconciled results were communicated with each study center and used in the final analysis dataset supplied to the study data manager.

for dd-cfDNA to discriminate active ABMR. AUC=0.87 (95% CI, 0.75 to 0.97). (D) ROC curve for serum creatinine to discriminate ABMR. AUC=0.57 (95% CI, 0.42 to 0.71). (E) The sensitivity (%) and specificity (%) for dd-cfDNA to discriminate active ABMR versus no active ABMR. (F) The PPV and NPV for dd-cfDNA to discriminate active ABMR from no active ABMR.

Classification of Rejection

Renal Allograft Rejection Histologic Diagnostic Nomenclature and Rationale for Active Rejection Definition Used in the Study Analyses of dd-cfDNA

The international classification schema includes two acute rejection phenotypes: TCMR[14] and acute/active ABMR.[15] In the Banff 2013 report,[15] there was recognition that intimal arteritis, which had been solely a criteria for TCMR (types IIA, IIB, and III) in the Banff 2007 classification,[14] can also be observed and is clinically impactful in ABMR. This led these TCMR microvascular injury phenotypes to be added to the histologic evidence criteria for acute/active ABMR: "acute tissue injury, including one or more of the following: microvascular inflammation, intimal or transmural arteritis, acute thrombotic microangiopathy, or acute tubular injury."[22]

In addition to "acute/active" ABMR, the international classification system designates "chronic, active" ABMR. These two ABMR subclasses have overlapping phenotypic criteria[22]: (*1*) evidence of current/recent antibody interaction with vascular endothelium (linear C4d staining in the peritubular capillaries, at least moderate microvascular inflammation, increased expression of endothelial activation, and injury transcripts or other gene expression markers of endothelial injury), and (*2*) serologic evidence of DSA. In practice, histologic findings observed in a single renal biopsy specimen may qualify for diagnosis of both acute/active and chronic, active ABMR and/or TCMR.[16]

Our primary analyses in this study combined these three subclasses of rejection defined by the Banff working groups[14,15] because they share common histologic criteria and the related cell injury manifestations have potential to involve active cell injury and death[16] and therefore increased levels of dd-cfDNA (Supplemental Figure 1). We use the term active rejection to describe these pooled classes of rejection. We combined these active rejection subclasses and distinguish them from all other biopsy-based diagnoses not phenotypically associated with active rejection (*e.g.*, IF/TA).

BANFF Working Group–Based Diagnostic Subcategories Derived from Pathologists' Reports of Renal Biopsy Findings

TCMR: Includes those biopsy reports which meet the Banff 2007 criteria[14] for TCMR types IA, IIA, IB, IIB, or III.

Acute/active ABMR: Includes those biopsy reports which meet all three requisite Banff 2013 acute/active ABMR criteria[15] (*i.e.*, histologic evidence of acute tissue injury, evidence of current/recent antibody interaction with vascular endothelium, and serologic evidence of DSA).

Chronic, active ABMR: Includes those biopsy reports which meet all three requisite Banff 2013 criteria for chronic, active ABMR (*i.e.*, histologic morphologic evidence of chronic tissue injury, evidence of current/recent antibody interaction with vascular endothelium, and "at least moderate microvasculature inflammation [(glomerulitis [g]+peritubular capillary inflammation [ptc] scores)≥2], and serologic evidence of DSA").

The biopsy reports which diagnosed mixed ABMR and TCMR were grouped together with the ABMR subgroup for purposes of the analyses.

All other biopsy specimens not qualifying for any of the "active rejection" subclasses listed above were defined as the "no active rejection" comparator group. These "no active rejection" biopsy specimens had one or more of the following findings: no major findings, nonspecific acute tubular necrosis (or "injury"), polyoma virus, CNI toxicity, GN, IF/TA (grades I, II, or III); and TCMR "suspicious" or "borderline."

The patients who did not undergo a renal biopsy due to clinical suspicion have been analyzed in a separate report that characterized the range of values of dd-cfDNA in the subset of DART renal allograft patients who had stable graft function.

Statistical Analyses

The objective of the primary statistical analysis was to determine whether the dd-cfDNA in a patient's plasma can discriminate active rejection from no active rejection allograft status in patients clinically indicated for biopsy, as determined by pathologists' renal biopsy readings, as described above. The execution of these analyses was triggered according to a prospective written plan which stated that the analysis should begin when a nominal quota of 30 biopsy-proven active rejection events had been accumulated in the database.

Secondary analyses included comparisons of dd-cfDNA performance in discriminating biopsy-based diagnosis of ABMR from all other samples that did not have biopsy evidence of ABMR.

We used the AUC, sensitivity, and specificity to evaluate the performance of dd-cfDNA in discriminating the active rejection from the comparator (no active rejection) status, using the biopsy-based, Banff Working Group classification as the standard for true allograft rejection status. The Emir method[23] was used to account for multiple samples from the same patient. We estimate PPV and NPV of dd-cfDNA in predicting biopsy-based allograft active rejection in the patient. For comparative purposes, we performed similar analyses to assess the performance of serum creatinine in discriminating active rejection.

All analyses were performed with the use of R software, version 3.2.0, 64-bit, copyright 2015.

ACKNOWLEDGMENTS

We thank Paula Lea, Alan Gee, Sarah Wang, Alesha Luxon, Susan Scott, John Collins, and Migdad Machrus at CareDx, Inc., and the study coordinators at the participating centers for supporting the study conduct and sample collection, laboratory testing, and data analyses.

DISCLOSURES

This study was supported by CareDx, Inc., Brisbane, CA.

REFERENCES

1. Gielis EM, Ledeganck KJ, De Winter BY, Del Favero J, Bosmans JL, Claas FH, Abramowicz D, Eikmans M: Cell-free DNA: An upcoming biomarker in transplantation. *Am J Transplant* 15: 2541–2551, 2015
2. Lo YM, Tein MS, Pang CC, Yeung CK, Tong KL, Hjelm NM: Presence of donor-specific DNA in plasma of kidney and liver-transplant recipients. *Lancet* 351: 1329–1330, 1998
3. Snyder TM, Khush KK, Valantine HA, Quake SR: Universal noninvasive detection of solid organ transplant rejection. *Proc Natl Acad Sci USA* 108: 6229–6234, 2011

4. Beck J, Bierau S, Balzer S, Andag R, Kanzow P, Schmitz J, Gaedcke J, Moerer O, Slotta JE, Walson P, Kollmar O, Oellerich M, Schütz E: Digital droplet PCR for rapid quantification of donor DNA in the circulation of transplant recipients as a potential universal biomarker of graft injury. *Clin Chem* 59: 1732–1741, 2013
5. De Vlaminck I, Valantine HA, Snyder TM, Strehl C, Cohen G, Luikart H, Neff NF, Okamoto J, Bernstein D, Weisshaar D, Quake SR, Khush KK: Circulating cell-free DNA enables noninvasive diagnosis of heart transplant rejection. *Sci Transl Med* 6: 241ra77, 2014
6. Hidestrand M, Tomita-Mitchell A, Hidestrand PM, Oliphant A, Goetsch M, Stamm K, Liang HL, Castleberry C, Benson DW, Stendahl G, Simpson PM, Berger S, Tweddell JS, Zangwill S, Mitchell ME: Highly sensitive noninvasive cardiac transplant rejection monitoring using targeted quantification of donor-specific cell-free deoxyribonucleic acid. *J Am Coll Cardiol* 63: 1224–1226, 2014
7. Grskovic M, Hiller DJ, Eubank LA, Sninsky JJ, Christopherson C, Collins JP, Thompson K, Song M, Wang YS, Ross D, Nelles MJ, Yee JP, Wilber JC, Crespo-Leiro MG, Scott SL, Woodward RN: Validation of a clinical-grade assay to measure donor-derived cell-free DNA in solid organ transplant recipients. *J Mol Diagn* 18:890–902, 2016
8. De Vlaminck I, Martin L, Kertesz M, Patel K, Kowarsky M, Strehl C, Cohen G, Luikart H, Neff NF, Okamoto J, Nicolls MR, Cornfield D, Weill D, Valantine H, Khush KK, Quake SR: Noninvasive monitoring of infection and rejection after lung transplantation. *Proc Natl Acad Sci USA* 112: 13336–13341, 2015
9. Schutz E, Blum A, Beck J, Harden M, Koch M, Wuensch T, Stockmann M, Nashan B, Kollmar O, Matthaei J, Kanzow P, Walson PD, Brockmöller J, Oellerich M: Graft-derived cell-free DNA - a promising rejection marker in liver transplantation - results from a prospective multicenter trial [Abstract]. *Clin Chem* 62: S41, 2016
10. Beck J, Oellerich M, Schulz U, Schauerte V, Reinhard L, Fuchs U, Knabbe C, Zittermann A, Olbricht C, Gummert JF, Shipkova M, Birschmann I, Wieland E, Schütz E: Donor-derived cell-Free DNA is a novel universal biomarker for allograft rejection in solid organ transplantation. *Transplant Proc* 47: 2400–2403, 2015
11. Grskovic M, Christie B, Hiller D, Woodward R, Yee J, Vincenti F: Donor-derived cell-free DNA in plasma increases with rejection and decreases after treatment in kidney transplant recipients [Abstract]. *J Am Soc Nephrol* 26: 1143, 2015
12. Josephson MA: Monitoring and managing graft health in the kidney transplant recipient. *Clin J Am Soc Nephrol* 6: 1774–1780, 2011
13. Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey AS, Gansevoort RT; CKD Prognosis Consortium: Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 369: 932–943, 2013
14. Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel M, Halloran PF, Baldwin W, Banfi G, Collins AB, Cosio F, David DS, Drachenberg C, Einecke G, Fogo AB, Gibson IW, Glotz D, Iskandar SS, Kraus E, Lerut E, Mannon RB, Mihatsch M, Nankivell BJ, Nickeleit V, Papadimitriou JC, Randhawa P, Regele H, Renaudin K, Roberts I, Seron D, Smith RN, Valente M: Banff 07 classification of renal allograft pathology: Updates and future directions. *Am J Transplant* 8: 753–760, 2008
15. Haas M: The revised (2013) Banff classification for antibody-mediated rejection of renal allografts: Update, difficulties, and future considerations. *Am J Transplant* 16: 1352–1357, 2016
16. Lefaucheur C, Loupy A, Vernerey D, Duong-Van-Huyen JP, Suberbielle C, Anglicheau D, Vérine J, Beuscart T, Nochy D, Bruneval P, Charron D, Delahousse M, Empana JP, Hill GS, Glotz D, Legendre C, Jouven X: Antibody-mediated vascular rejection of kidney allografts: A population-based study. *Lancet* 381: 313–319, 2013
17. Sawinski D, Forde KA, Trofe-Clark J, Patel P, Olivera B, Goral S, Bloom RD: Persistent BK viremia does not increase intermediate-term graft loss but is associated with de novo donor-specific antibodies. *J Am Soc Nephrol* 26: 966–975, 2015
18. Rush D, Arlen D, Boucher A, Busque S, Cockfield SM, Girardin C, Knoll G, Lachance JG, Landsberg D, Shapiro J, Shoker A, Yilmaz S: Lack of benefit of early protocol biopsies in renal transplant patients receiving TAC and MMF: A randomized study. *Am J Transplant* 7: 2538–2545, 2007
19. Yu SC, Lee SW, Jiang P, Leung TY, Chan KC, Chiu RW, Lo YM: High-resolution profiling of fetal DNA clearance from maternal plasma by massively parallel sequencing. *Clin Chem* 59: 1228–1237, 2013
20. Wu AH, Lu QA, Todd J, Moecks J, Wians F: Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: Implications for clinical practice. *Clin Chem* 55: 52–58, 2009
21. Norton SE, Luna KK, Lechner JM, Qin J, Fernando MR: A new blood collection device minimizes cellular DNA release during sample storage and shipping when compared to a standard device. *J Clin Lab Anal* 27: 305–311, 2013
22. Djamali A, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M: Diagnosis and management of antibody-mediated rejection: Current status and novel approaches. *Am J Transplant* 14: 255–271, 2014
23. Emir B, Wieand S, Su JQ, Cha S: Analysis of repeated markers used to predict progression of cancer. *Stat Med* 17: 2563–2578, 1998

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EXHIBIT 3

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of
the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **June 27, 2018**

Natera, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**001-37478**	**01-0894487**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

201 Industrial Road, Suite 410
San Carlos, California 94070
(Address of principal executive offices, including zip code)

(650) 249-9090
(Registrant's telephone number, including area code)

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01. Regulation FD Disclosure.

On June 27, 2018, Natera, Inc. ("Natera") will hold an investor call to discuss study data and its strategic roadmap for its emerging businesses in organ transplantation and oncology, and will provide a related investor presentation. A copy of the investor presentation is furnished herewith as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The information in this Current Report on Form 8-K and the accompanying Exhibit 99.1 shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, regardless of any general incorporation language in such filing, unless expressly incorporated by reference in such filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Investor Presentation.

EXHIBIT INDEX

Exhibit No.	Description
99.1	Investor Presentation.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Natera, Inc.

By: /s/ Michael Brophy
Michael Brophy
Chief Financial Officer (Principal Financial and Accounting Officer)

Dated: June 27, 2018

Exhibit 99.1

June 27, 2018

natera®
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Safe Harbor

This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, including statements regarding the market opportunity, products, commercial partners, user experience, clinical trials, financial performance, strategies, anticipated future performance and general business conditions of Natera, Inc. ("Natera", the "Company", "we" or "us"), are forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual results to differ materially, including: we may be unable to develop and successfully commercialize new products; our estimates of market opportunity and forecasts of market growth may prove to be inaccurate, and even if the market in which we compete achieves the forecasted growth, our business could fail to grow at similar rates; we may be unable to compete successfully with either existing or future prenatal testing or oncology diagnostic products or other test methods; our products may not perform as expected; the results of our clinical studies may not support the use of our tests, particularly in the average-risk pregnancy population or for microdeletions screening, or may not be able to be replicated in later studies required for regulatory approvals or clearances; if our sole CLIA-certified laboratory facility becomes inoperable, we will be unable to perform our tests and our business will be harmed; we rely on a limited number of suppliers or, in some cases, single suppliers, for some of our laboratory instruments and materials and may not be able to find replacements or immediately transition to alternative suppliers; if we are unable to successfully scale our operations, our business could suffer; the marketing, sale, and use of our products could result in substantial damages arising from product liability or professional liability claims that exceed our resources; we may be unable to expand third-party payer coverage and reimbursement for our tests, and we may be required to refund reimbursements already received; third-party payers may withdraw coverage or provide lower levels of reimbursement due to changing policies, billing complexities or other factors, such as the increased focus by third-party payers on requiring that prior authorization be obtained prior to conducting a test; if the FDA were to begin actively regulating our tests, we could incur substantial costs and delays associated with trying to obtain premarket clearance or approval and incur costs associated with complying with post-market controls; we could be subject to third party claims of intellectual property infringement, which could result in litigation or other proceedings and could limit our ability to commercialize our products or services; and any failure to obtain, maintain, and enforce our intellectual property rights could impair our ability to protect our proprietary technology and our brand. We discuss these and other risks and uncertainties in greater detail in the sections entitled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in the filings we make with the SEC from time to time. Given these uncertainties, you should not place undue reliance on the forward-looking statements. Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on its business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statement. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this presentation may not occur and actual results could differ materially and adversely from those anticipated or implied. Except as required by law, neither we nor any other person assumes responsibility for the accuracy and completeness of the forward-looking statements. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations. We file reports, proxy statements, and other information with the SEC. Such reports, proxy statements, and other information concerning us can be read and copied at the SEC's Public Reference Room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549 or on the Internet at http://www.sec.gov. Please call the SEC at 1-800-SEC-0330 for further information on the Public Reference Room. Our common stock is listed on the NASDAQ Global Select Market, and these reports, proxy statements and other information are also available for inspection at the offices of the NASDAQ Stock Market, Inc. located at 1735 K Street, NW, Washington, D.C. 20006. We will provide without charge upon written or oral request a copy of any or all of the documents that are incorporated by reference into this prospectus, other than exhibits which are specifically incorporated by reference into such documents. Requests should be directed to our Investor Relations department at Natera, Inc., 201 Industrial Road, Suite 410, San Carlos, California 94070. Our telephone number is (650) 249-9090.

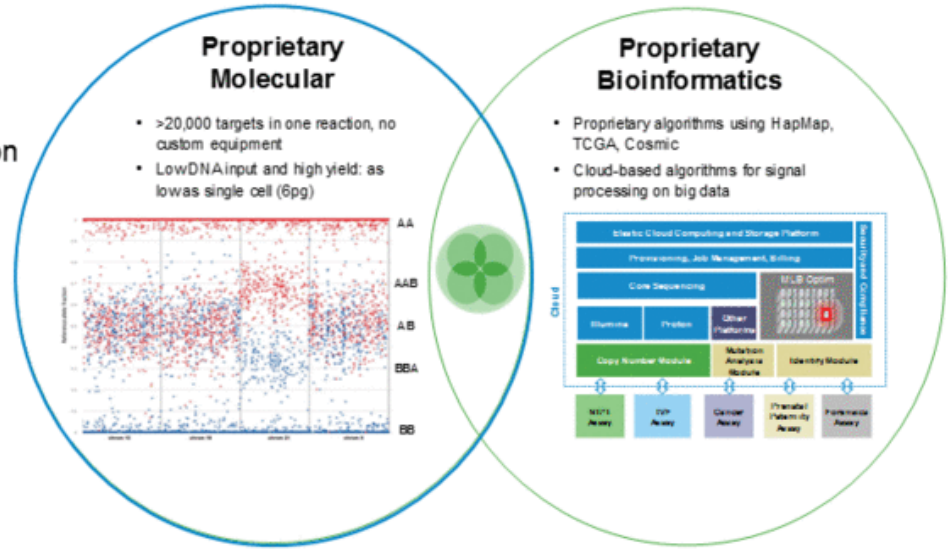
Agenda

- **Kidney transplant rejection**
  - New data from UCSF study demonstrates 92% sensitivity for acute rejection
  - Targets greater than $2bn market (estimated) with established CMS pricing at ~$2,800 per test

- **Breast cancer update**
  - Preliminary data very promising, to be submitted for peer review
  - Two additional studies in pipeline
  - Reinforces large pan-cancer market opportunity > $12bn

Natera's Technology Designed to Analyze Cell-Free DNA

- 10+ years of experience with cfDNA, over 1 million tests performed
- Single molecule sensitivity in a tube of blood
- COGS below $200 per sample



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Applications Across Multiple Indications

Prenatal Care	Oncology	Transplant
• Panorama • Horizon • Vistara • Spectrum • Anora	• Lung • Bladder • Colon • Breast • Additional indications	• Renal • Additional indications

Unmet Need in Renal Transplant Monitoring

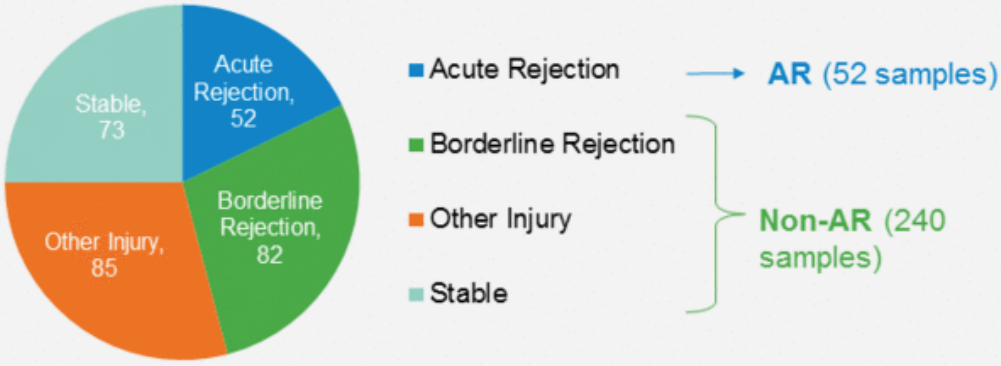
- ~190,000 living kidney transplant recipients in the U.S.
- ~20,000 kidney transplants performed in U.S. per annum[1]
- Approximately 15-20% suffer acute rejection in first year
- Patients must be monitored throughout their lifetime for graft rejection; patients often over-immunosuppressed
- Existing surveillance methods have significant limitations:
  Invasive/expensive (biopsy) or clinically inadequate (serum creatinine)
- Measurement of donor-derived cell free DNA emerging as a superior monitoring technology

[1] HTTPS://OPTN.transplant.hrsa.gov/ data/view-data/national data/#

UCSF Study Overview

292 samples from 187 patients were analyzed

Classified into 4 groups by biopsy:

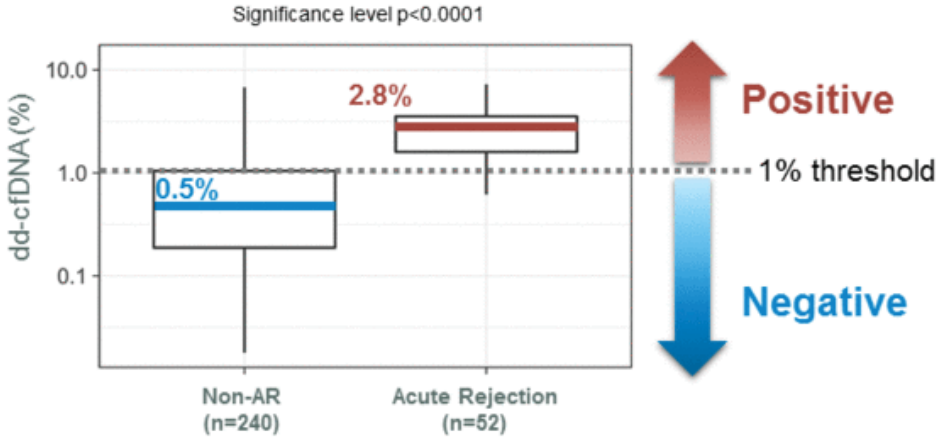


Levels of Donor DNA Significantly Higher in Patients Suffering Acute Rejection

Sensitivity: 92.3%

Specificity: 72.9%

Area Under Curve (AUC): 0.90



> 95% of positive results had clinically meaningful findings

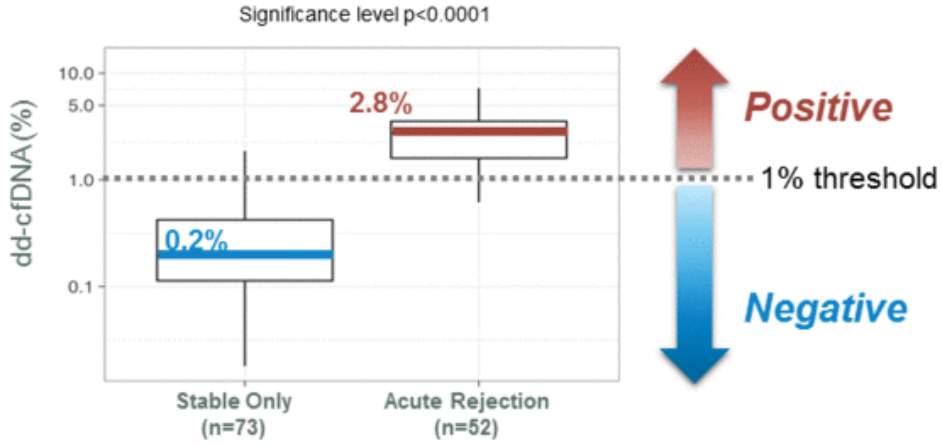
Boxes indicate inter-quartile range, horizonal lines represent medians.*Non-AR includes Stable, Borderline Rejection, and Other Injury

Specificity Among Stable Patients is Even Higher

Sensitivity: 92.3%

Specificity: 93.2%

Area Under Curve (AUC): 0.95



Boxes indicate inter-quartile range, horizonal lines represent medians

Natera Assay Outperforms Competition

	Natera study[1] (n=292 samples)	Bloom et al.[2] (n=107 samples)
Performance Metrics		
Sensitivity	92% (n=52)	59% (n=27)
Specificity	73% (n=240)	85% (n=80)
AUC	0.90	0.74
Assuming 25% Prevalence (higher risk population)		
NPV	97%	86%
PPV	53%	57%
Assuming 15% Prevalence (average risk population)		
NPV	98%	92%
PPV	38%	41%

[1] Based on SNP-based dd-cfDNA analyses described here (292 plasma specimens from 187 unique kidney transplant recipients).
[2] From Bloom RD, et al. Cell-Free DNA and Active Rejection in Kidney Allografts. J Am Soc Nephrol. 2017;28(7):2221-2232.

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Addressable Market in U.S. Estimated to Exceed $2bn

- ~190,000 living with kidney transplant
- ~20,000 new kidney transplants per year
- CMS rate for comparable test: $2,841
- Testing up to 7x in year 1, 4x tests per year thereafter

Commercialization Plan for Transplant Assay

~20,000 transplants annually

U.S. Kidney Transplants

- Natera scale and experience with NGS testing provides COGS advantage
- History of winning as fast follower with technical superiority
- Robust user experience
- Distributed model with Constellation™ platform

Patent-Protected Technology

- Natera approach does not use transplant-specific markers and does not require advance determination of donor or recipient genotypes
- Natera technology already protected by two granted European patents, one issued U.S. patent, and at least four pending EU and US patent applications
- Patents corresponding to the first-generation cfDNA-based approaches do not apply to us

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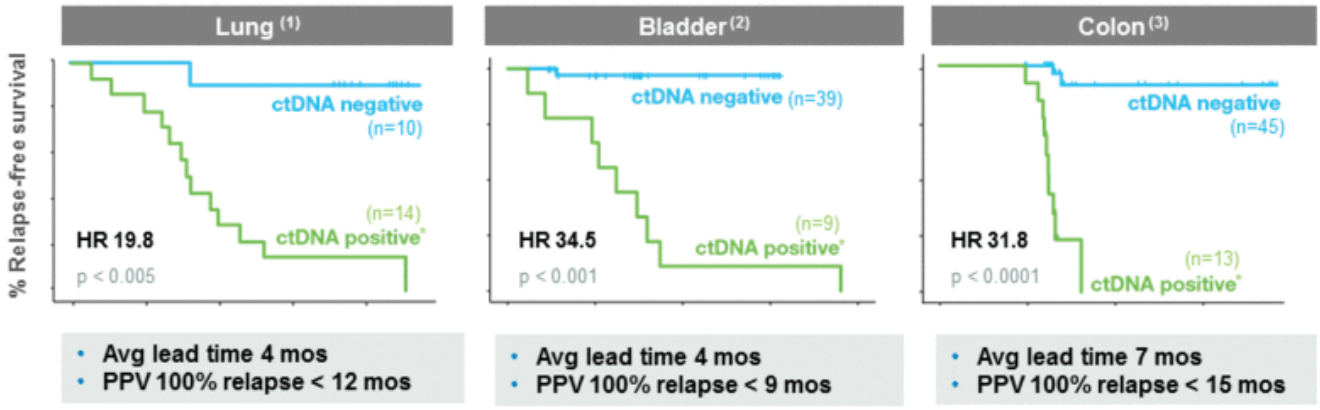
Signatera™(RUO) Highly Consistent Across Tumor Types

Positive result after treatment has always led to relapse



- Avg lead time 4 mos
- PPV 100% relapse < 12 mos

- Avg lead time 4 mos
- PPV 100% relapse < 9 mos

- Avg lead time 7 mos
- PPV 100% relapse < 15 mos

1.RFS post treatment. Abbosh C, et al. Nature. 2017 Apr 26;545(7655):446-451; 2. RFS post cystectomy. Birkenkamp-Demtroder K, et al. AACR; 2018. Abstract nr 3653.; 3.RFS post ACT treatment. Andersen C, et al. AACR; 2018 Abstract nr 1590.
* Positive at any time point at or before clinical relapse

3 Prospective Breast Cancer Studies for Different Indications

1 **ISPY-2: Neoadjuvant**	PI: Laura Esserman, MD, PhD 182 patients 327 plasma time points	**Objective:** • Evaluate Signatera as marker of *molecular response* to neoadjuvant therapy, in comparison with radiological and pathological response criteria	UCSF I-SPY
2 **Leicester/ICL: Adjuvant/RM**	PIs: Jacqui Shaw, MD, PhD Charles Coombes, MD, PhD 49 patients 218 plasma time points	**Objective:** • Evaluate Signatera as marker of *molecular relapse*, after completion surgery and adjuvant chemotherapy, in comparison to radiology	Imperial College London UNIVERSITY OF LEICESTER
3 **Jules Bordet: Neoadjuvant/RM**	PI: Michail Ignatiadis, MD,PhD 80 patients 300 plasma time points	**Objectives:** • Evaluate Signatera as marker of *molecular response* to neoadjuvant therapy, in comparison with radiological and pathological response criteria • Evaluate Signatera as marker of *molecular relapse*, after completion of neoadjuvant therapy and definitive surgery, in comparison to radiology	INSTITUT JULES BORDET INSTITUUT ULB UNIVERSITÉ LIBRE DE BRUXELLES

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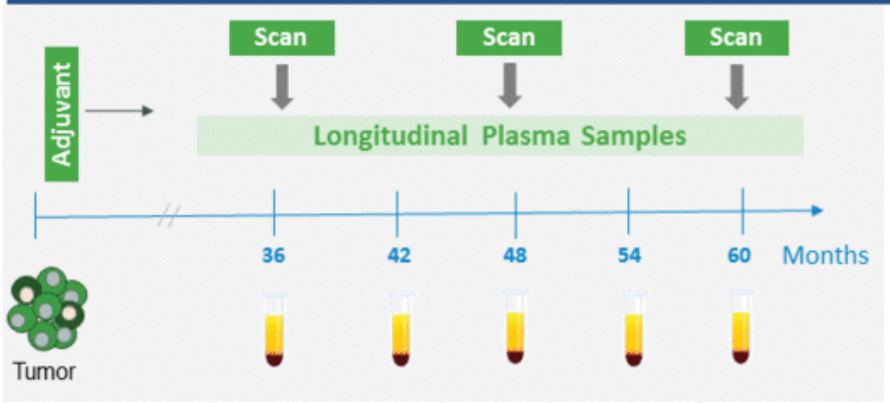
Study Design in Post-Treatment Setting

Collaboration with University of Leicester and Imperial College of London

- **Study design:** Blood collection every 6 months, in a cohort of 49 breast cancer patients starting at least 3 years after conclusion of treatment
- **Key output metrics:** relapse detection rate, lead time vs. imaging



Subtype	Patients
ER/PR+/HER2-	34
HER2+	8
TNBC	7
Total	49

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HER2+ Therapeutic Decision Making in the MRD Setting

- **Unmet need:** Neratinib recently approved for treatment in HER2+ patients after a full year of trastuzumab. Only 2% survival benefit with severe side effects.
- Patients: > 40,000 new diagnoses per year with HER2+ disease[1]
- Cost of neratinib treatment: $10,400 per month

> *"Use of neratinib could be considered in patients with early stage HER2-positive breast cancer and clinical features that indicate a higher likelihood of relapse."*[2]

Dr. Alexandra Zimmer, M.D.
Women's Malignancies Branch of
NCI Center for Cancer Research

[1] American Cancer Society. Breast Cancer Facts & Figures 2017-2018.
[2] https://www.cancer.gov/news-events/cancer-currents-blog/2017/neratinib-breast-cancer-fda

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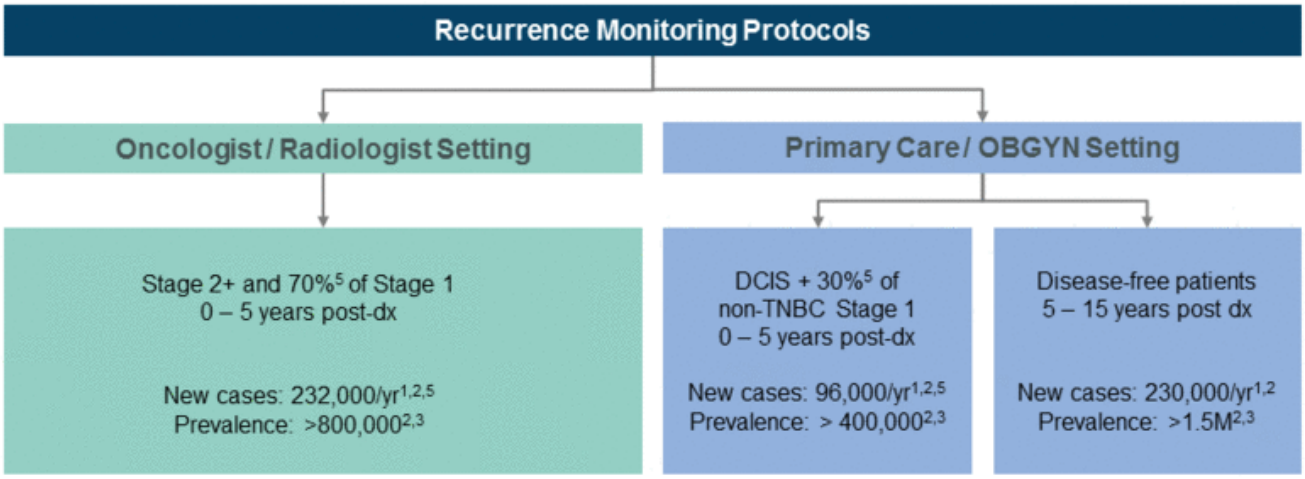
Establishing the Recurrence Monitoring Indication

Over 70% of relapses are distant, not local[2,4]



1. ACS Breast Cancer Facts & Figures 2017-2018
2. JAMA. 2015;313(2):165-173. doi:10.1001/jama.2014.17322
3. SEER database Prevalence Estimates: link
4. Del Turco. JAMA 1994;271:1593-1597
5. Internal estimates

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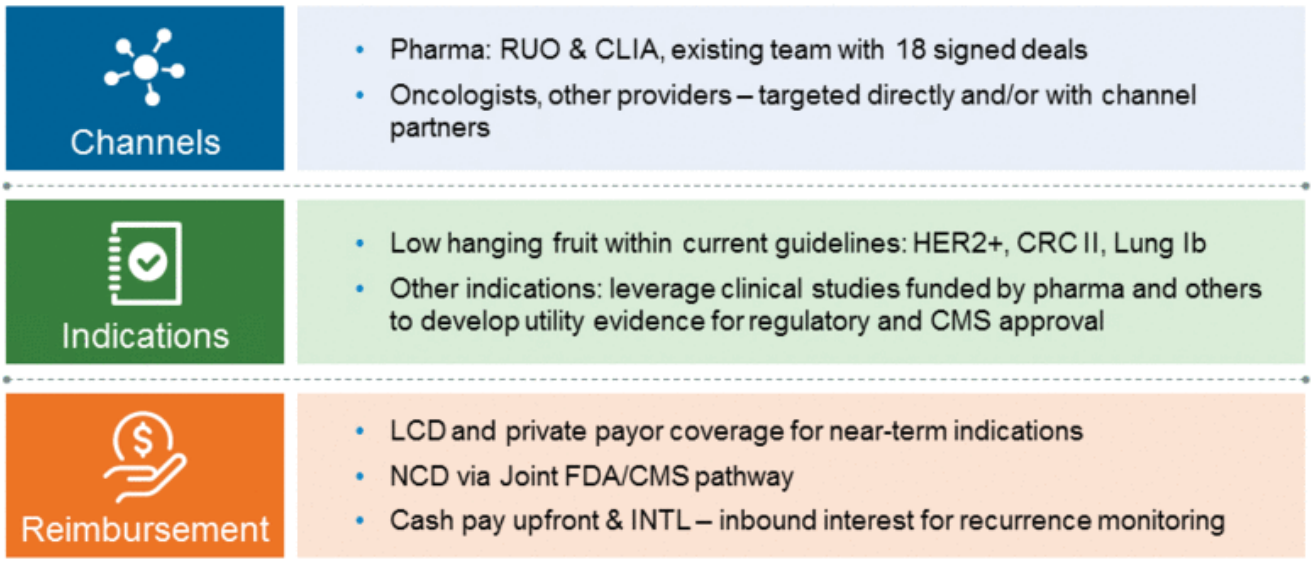
Commercialization Strategy

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horizon™
ADVANCED CARRIER SCREEN
spectrum®
PREIMPLANTATION GENETICS
anora®
MISCARRIAGE TEST (POC)
evercord™
NEWBORN STEM CELL BANKING
constellation™
TECHNOLOGY LICENSING

EXHIBIT 4

News Release

Natera Develops Powerful Kidney Transplant Rejection Biomarker

Data to be Presented at The Transplantation Society International Congress in Madrid on July 3, 2018

SAN CARLOS, Calif., June 21, 2018 /PRNewswire/ -- Natera, Inc. (https://www.natera.com/) (NASDAQ: NTRA), a leader in cell-free DNA analysis, announces a powerful new kidney transplant rejection biomarker and study results in collaboration with the University of California, San Francisco, a recognized leader in transplantation care. The data demonstrates superior performance of its massively-multiplexed PCR (mmPCR) technology for detecting acute rejection in kidney transplant patients.

In a blinded, retrospective study, Natera leveraged its validated SNP (Single Nucleotide Polymorphism) technology to measure donor-derived cell-free DNA levels (dd-cfDNA) in 300 plasma samples from 193 unique kidney transplant patients, including 52 patients experiencing acute rejection. The assay was designed based on years of experience in differentiating maternal DNA from fetal DNA in reproductive health. This is the largest patient cohort to date, comparing dd-cfDNA levels to organ biopsies, the current gold standard for organ status assessment.

Natera's dd-cfDNA assay demonstrated 92% sensitivity in detecting acute rejection, identifying 48 out of 52 affected cases based on a cutoff of 1% dd-cfDNA. This sensitivity compares favorably against competition, which reported only 59% sensitivity in a 2017 study.[1] This performance data suggests the potential of Natera's assay for use in both rule-in and rule-out applications.

There is a significant unmet need for more accurate non-invasive tools to monitor for allograft rejection. Natera's assay could help physicians detect rejection events earlier, avoid unnecessary biopsies, and safely optimize immunosuppression levels, potentially lowering the overall costs associated with transplant care. With over 190,000 people living with a kidney transplant in the United States[2] and roughly 20,000 new kidney transplant surgeries performed each year,[3] the kidney transplant market opportunity has been estimated at over $2 billion.[4,5] Similar dd-cfDNA tests are reimbursed at approximately $2,800. Natera expects to launch a CLIA-certified laboratory developed clinical test in 2019.

"We are very pleased with the results of this study," noted Dr. Paul Billings, Natera's Chief Medical Officer and Senior Vice President, Medical Affairs. "Natera's unique mmPCR technology has excellent clinical utility potential for patients living with renal and other organ transplants. I look forward to working with the medical community to introduce this rapidly into clinical practice."

About Natera

Natera (http://www.natera.com/) is a global leader in cell-free DNA testing. The mission of the company is to transform the diagnosis and management of genetic diseases. Natera operates an ISO 13485-certified and CAP-accredited laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) in San Carlos, Calif. It offers a host of proprietary genetic testing services to inform physicians who care for pregnant women, researchers in cancer and organ transplantation including biopharmaceutical companies, and genetic laboratories through its cloud-based software platform. Follow Natera on LinkedIn (https://www.linkedin.com/company/natera/) and Twitter (https://twitter.com/NateraGenetics).

Forward-Looking Statements

All statements other than statements of historical facts contained in this press release are forward-looking statements and are not a representation that Natera's plans, estimates, or expectations will be achieved. These forward-looking statements represent Natera's expectations as of the date of this press release, and Natera disclaims any obligation to update the forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual results to differ materially, including with respect to our efforts to develop and commercialize new product offerings, our ability to successfully increase demand for and grow revenues for our product offerings, whether the results of clinical studies will support the use of our product offerings, our expectations of the reliability, accuracy and performance of our screening tests, or of the benefits of our screening tests and product offerings to patients, providers and payers. Additional risks and uncertainties are discussed in greater detail in "Risk Factors" in Natera's recent filings on Forms 10-K and 10-Q and in other filings Natera makes with the SEC from time to time. These documents are available at www.natera.com/investors (http://www.natera.com/investors) and www.sec.gov (http://www.sec.gov/).

Contacts

Investor Relations: Mike Brophy, CFO, Natera, Inc., 650-249-9090
Media: Barbara Sullivan, Sullivan & Associates, 714-374-6174, bsullivan@sullivanpr.com (mailto:bsullivan@sullivanpr.com)

References

1. Bloom, et al. Cell-free DNA and active rejection in kidney allografts. J Am Soc Nephrol. 2017 Jul;28(7):2221-2232. doi: 10.1681/ASN.2016091034. Epub 2017 Mar 9.
2. Kidney Disease Statistics for the United States. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease (https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease). Published Dec. 1, 2016.
3. Organ Donation Statistics. U.S. Department of Health and Human Services. U.S. Government Information on Organ Donation and Transplantation. https://www.organdonor.gov/statistics-stories/statistics.html (https://www.organdonor.gov/statistics-stories/statistics.html). Published March 31, 2016.
4. Bromberg, et al. Biological variation of donor-derived cell-free DNA in renal transplant recipients: clinical implications. J Appl Lab Med. 2017;2:309-321.
5. Natera data on file. June 2018.

View original content with multimedia:http://www.prnewswire.com/news-releases/natera-develops-powerful-kidney-transplant-rejection-biomarker-300670431.html (http://www.prnewswire.com/news-releases/natera-develops-powerful-kidney-transplant-rejection-biomarker-300670431.html)

SOURCE Natera, Inc.

EXHIBIT 5

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Filed Pursuant to Rule 424(b)(5)
Registration Statement No. 333-214577

PROSPECTUS SUPPLEMENT
(To Prospectus dated November 28, 2016)

4,500,000 Shares

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NATERA, INC.

COMMON STOCK

We are offering 4,500,000 shares of our common stock. Our common stock is listed on The Nasdaq Global Select Market under the symbol "NTRA." The last reported sale price of our common stock on July 11, 2018 was $20.58 per share.

We are an "emerging growth company" as defined under the federal securities laws. Investing in our common stock involves risks. See "Risk Factors" beginning on page S-14.

	Price to Public	Underwriting Discounts and Commissions(1)	Proceeds to Natera, Inc.
Per Share	$20.00	$1.20	$18.80
Total	$90,000,000	$5,400,000	$84,600,000

(1) See "Underwriting" for a description of the compensation payable to the underwriters.

We have granted the underwriters the right to purchase up to an additional 675,000 shares at the public offering price, less underwriting discounts and commissions.

The Securities and Exchange Commission and state securities regulators have not approved or disapproved these securities, or determined if this prospectus supplement or the prospectus to which it relates is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares to purchasers on July 16, 2018.

J.P. Morgan **Morgan Stanley** **Cowen**

July 12, 2018.

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ABOUT THIS PROSPECTUS SUPPLEMENT AND THE ACCOMPANYING PROSPECTUS

We provide information to you about this offering of shares of our common stock in two separate documents that are bound together: (1) this prospectus supplement, which describes the specific details regarding this offering and certain other matters relating to us, our financial condition, which may also, where applicable, add to and update information contained in the accompanying prospectus; and (2) the accompanying prospectus, dated November 28, 2016, and included as part of our registration statement on Form S-3 (File No. 333-214577), which provides general information about the securities that we may offer from time to time, some of which may not apply to this offering (the "Registration Statement"). If information in this prospectus supplement is inconsistent with the accompanying prospectus, you should rely on this prospectus supplement. However, if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in this prospectus supplement—the statement in the document having the later date modifies or supersedes the earlier statement as our business, financial condition, results of operations and prospects may have changed since the earlier dates.

We have not authorized, nor have the underwriters authorized, anyone to provide you with any information or to make any representation, other than those contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus we have prepared by or on behalf of us or to which we have referred you. Neither we nor any of the underwriters take any responsibility for, or provide any assurance as to the reliability of, any other information that others may give you. Neither we nor any of the underwriters are making an offer to sell or soliciting an offer to buy our securities in any jurisdiction where an offer or solicitation is not authorized or in which the person making that offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference herein and therein, and in any free writing prospectus that we may authorize for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read carefully this prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we may authorize for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus supplement entitled "Where You Can Find More Information" and "Information Incorporated by Reference."

Neither we nor the underwriters are not offering to sell, or seeking offers to buy, shares of common stock in any jurisdictions where offers and sales are not permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

In this prospectus supplement and the accompanying prospectus, unless otherwise indicated or the context otherwise requires, the terms "Natera," "Company," "we," "us" and "our" refer to Natera, Inc.

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FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus, and the documents incorporated by reference therein contains forward-looking statements within the meaning of Section 27A of the Private Securities Litigation Reform Act. Forward-looking statements include information concerning our future results of operations and financial position, strategy and plans, and our expectations for future operations. Forward-looking statements include all statements that are not historical facts and, in some cases, can be identified by terms such as "believe," "may," "will," "estimate," "continue," "anticipate," "design," "intend," "expect," "could," "plan," "potential," "predict," "seek," "should," "would" or the negative version of these words and similar expressions.

Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including those described in "Risk Factors" and elsewhere in this prospectus supplement and in the documents that are incorporated by reference herein. Potential investors are urged to consider these factors carefully in evaluating the forward-looking statements. Also, forward-looking statements speak only as of the date of this prospectus supplement, the accompanying prospectus and the documents that are incorporated by reference herein and therein, respectively. We undertake no obligation to update any forward-looking statements for any reason, even if new information becomes available. You should read this prospectus supplement completely and with the understanding that our actual future results may be materially different from what we expect.

These forward-looking statements include, but are not limited to, statements concerning the following:

- our preliminary estimates of our financial performance for the three months ended June 30, 2018, including our preliminary estimate of total revenues and our preliminary estimate of operating loss;
- our expectation that, for the foreseeable future, a significant portion of our revenues will be derived from sales of Panorama;
- our ability to increase demand for Panorama, obtain favorable coverage and reimbursement determinations from third-party payers, and expand geographically;
- our expectation that Panorama will be adopted for broader use in average-risk pregnancies and for the screening of microdeletions and that third-party payer reimbursement will be available for these applications;
- our expectations of the reliability, accuracy, and performance of Panorama, as well as expectations of the benefits to patients, providers, and payers of Panorama;
- our ability to successfully develop additional revenue opportunities and expand our product offerings to include new tests, including our recently launched offerings;
- our efforts to translate our technology and expertise in prenatal testing into oncology and kidney transplant rejection applications;
- the effect of improvements in our cost of goods sold;
- our estimates of the total addressable markets for our current and potential product offerings;
- our ability and expectations regarding obtaining, maintaining and expanding third-party payer coverage of, and reimbursement for, our tests;
- the effect of changes in the way we account for our revenue;

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- our ability to successfully commercialize our products through strategic or commercial partnerships, such as our agreement with QIAGEN, and our ability to enter into additional such partnerships in the future;
- the scope of protection we establish and maintain for, and developments or disputes concerning, our intellectual property or other proprietary rights;
- competition in the markets we serve;
- our reliance on collaborators such as medical institutions, contract laboratories, laboratory partners, and other third parties;
- our ability to operate our laboratory facility and meet expected demand, and to successfully scale our operations;
- our reliance on a limited number of suppliers, including sole source suppliers, which may impact our ability to maintain a continued supply of laboratory instruments and materials and to run our tests;
- our expectations of the rate of adoption of Panorama and of any of our future tests by laboratories, clinics, clinicians, payers, and patients;
- our ability to successfully complete clinical studies and publish clinical data in peer-reviewed medical publications regarding Panorama and any of our future tests, including our SMART study and our ongoing trials in oncology and transplantation;
- our reliance on our partners to market and offer Panorama in the United States and in international markets;
- our estimates regarding our costs and risks associated with our international operations and international expansion;
- our ability to retain and recruit key personnel;
- our reliance on our direct sales efforts;
- our expectations regarding acquisitions and strategic operations;
- our ability to fund our working capital requirements;
- our compliance with federal, state, and foreign regulatory requirements;
- the factors that may impact our financial results; and
- anticipated trends and challenges in our business and the markets in which we operate.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. We have filed with the SEC a registration statement on Form S-3 (File No. 333-214577) under the Securities Act relating to the common stock offered by this prospectus supplement and accompanying prospectus. This prospectus supplement and the accompanying prospectus do not contain all of the information in the registration statement, parts of which we have omitted, as allowed under the rules and regulations of the SEC. You should refer to the registration statement for further information with respect to us and our common stock. Statements contained in this prospectus supplement and the accompanying prospectus as to the contents of any contract or other document are not necessarily complete and, in each instance, we refer you to the copy of each contract or document filed as an exhibit to the registration statement. Copies of the registration statement and the other documents we file with the SEC, including exhibits, may be inspected without charge at the SEC's

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Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549, and you may obtain copies from the Public Reference Room upon payment of the fees prescribed by the SEC. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. Our SEC filings are also available to the public over the Internet at the SEC's website at www.sec.gov.

INCORPORATION BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus supplement, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below (except the information contained in such documents to the extent "furnished" and not "filed") and any future filings we make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (except the information contained in such documents to the extent "furnished" and not "filed"):

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2017;
- the information in our Definitive Proxy Statement on Schedule 14A for the 2018 annual meeting of stockholders, but only to the extent incorporated by reference in our Annual Report on Form 10-K for the year ended December 31, 2017;
- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2018;
- our Current Report on Form 8-K filed with the SEC on May 22, 2018; and
- the description of our Common Stock contained in our Registration Statement File No. 001-37478 on Form 8-A as amended and filed with the SEC on June 26, 2015, including any amendment or report filed for the purpose of updating such description.

We will provide without charge upon written or oral request a copy of any or all of the documents that are incorporated by reference into this prospectus supplement, other than exhibits which are specifically incorporated by reference into such documents. Requests should be directed to our Investor Relations department at Natera, Inc., 201 Industrial Road, Suite 410, San Carlos, California 94070. Our telephone number is (650) 249-9090.

Any statement contained in a document incorporated or deemed to be incorporated by reference into this prospectus supplement or the accompanying prospectus shall be deemed to be modified or superseded for the purposes of this prospectus supplement or the accompanying prospectus to the extent that a statement contained in this prospectus supplement (or in any document incorporated by reference therein) or the accompanying prospectus or in any other subsequently filed document that is or is deemed to be incorporated by reference into this prospectus supplement modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus supplement or the accompanying prospectus.

To the extent that any information contained in any Current Report on Form 8-K, or any exhibit thereto, was furnished to, rather than filed with, the SEC, such information or exhibit is specifically not incorporated by reference in this prospectus supplement or the accompanying prospectus.

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PROSPECTUS SUPPLEMENT SUMMARY

You should read the following summary together with the entire prospectus supplement and accompanying prospectus and the documents incorporated by reference herein and therein, including our consolidated financial statements and related notes. You should carefully consider, among other things, the matters discussed in the section entitled "Risk Factors" in this prospectus supplement.

NATERA, INC.

Overview

We are a growing diagnostics company with proprietary molecular and bioinformatics technology that we are deploying to change the management of genetic disease worldwide. Our novel molecular assays reliably measure many informative regions across the genome from samples as small as a single cell. Our statistical algorithms combine these measurements with data available from the broader scientific community to identify genetic variations covering a wide range of serious conditions with best-in-class accuracy and coverage. Our goal is to develop and commercialize non- or minimally-invasive tests to evaluate risk, and thereby enable early detection, for a wide range of genetic conditions, such as Down syndrome. Our technology has been proven clinically and commercially in the prenatal testing space. We have begun translating this success into the liquid biopsy space, where we are leveraging our core expertise to develop products for oncology diagnostic applications, initially for research use and which we are developing as a Clinical Laboratory Improvement Amendments, or CLIA, test. We seek to enable even wider adoption of our technology through our global cloud-based distribution model. In addition to our direct sales force in the United States, we have a global network of close to 90 laboratory and distribution partners, including many of the largest international laboratories.

Since 2009, we have launched a comprehensive suite of ten products in women's health and prenatal testing—nine molecular diagnostic tests and a newborn stem cell banking offering to complement our prenatal testing portfolio—and our personalized liquid biopsy technology for research use only in oncology applications. We intend to continue to launch new products in the future.

We launched Panorama, our non-invasive prenatal test, or NIPT, in March 2013 and have since gone from being the fourth company to enter the NIPT market to being the market leader by volume in the United States. Panorama represented approximately 63% of our revenues, with approximately 343,700 Panorama tests accessioned, during the year ended December 31, 2017. Our revenues were $210.9 million in 2017, compared to $217.1 million in 2016 and $190.4 million in 2015. Our net losses increased to $136.3 million in 2017 from $95.8 million in 2016 and $70.3 million in 2015.

In both prenatal testing and oncology, the use of blood-based diagnostic tests offers significant advantages over older methods, but the significant technological challenge is that such testing requires the measurement of very small amounts of relevant genetic material circulating within a much larger blood sample. Our approach combines proprietary molecular biology and computational techniques to measure genomic variations in tiny amounts of DNA, as small as a single cell. Our molecular biology techniques are based on measuring thousands of single nucleotide polymorphisms, or SNPs, simultaneously using massively multiplexed polymerase chain reaction, or mmPCR, to multiplex, or target, many thousands of regions of the genome simultaneously in a single test reaction. Our method avoids losing molecules, which can happen when samples are split into separate reaction tubes, so that all relevant variants can be detected. We believe our approach represents a fundamental advance in molecular biology. This approach is distinct from the approach employed with other commercially available NIPTs, which use first-generation "quantitative", or counting, methods to compare the relative number of sequence reads from a chromosome of interest to a reference chromosome. Based on extensive data published in the journals *Obstetrics & Gynecology*, the *American Journal*

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of Obstetrics & Gynecology, Prenatal Diagnosis, and others, we believe Panorama is the most accurate NIPT commercially available in the United States.

Recent Developments

Preliminary Estimates for Three Months Ended June 30, 2018

Our consolidated financial statements for the three months ended June 30, 2018 are not yet available. Accordingly, the information presented below reflects our preliminary estimates subject to the completion of our financial closing procedures and any adjustments that may result from the completion of the quarterly review of our consolidated financial statements. As a result, these preliminary estimates may differ from the actual results that will be reflected in our consolidated financial statements for the quarter when they are completed and publicly disclosed. These preliminary estimates may change and those changes may be material.

Our expectations with respect to our unaudited results for the period discussed below are based upon management estimates and are the responsibility of management. Our independent registered public accounting firm has not audited, reviewed or performed any procedures with respect to these preliminary results and, accordingly, does not express an opinion or any other form of assurance about them.

We estimate total revenues for the three months ended June 30, 2018, will range from $61.3 million to $63.0 million. We estimate that operating loss for the three months ended June 30, 2018 will be generally similar to recent prior periods.

License, Development and Distribution Agreement with Qiagen

On March 9, 2018, we entered into a License, Development and Distribution Agreement (the "Agreement") with Qiagen LLC ("QIAGEN"), an indirect wholly-owned subsidiary of QIAGEN N.V., a Netherlands-based holding company, for the development and distribution of NGS-based genetic tests on our proprietary technology for use on QIAGEN's proprietary GeneReader® NGS sequencing platform in certain countries globally.

Under the Agreement, which has a ten (10) year term, we will receive an upfront license fee and prepaid royalties totaling $40 million. QIAGEN will owe us tiered royalties on a percentage basis based on net sales of its sequencers and reagent kits that are distributed by QIAGEN, as enabled by our technology. The tiers increase after the first and second years after commercial launch of such products. These royalties will initially be credited against the prepaid royalties and then paid quarterly to us once the prepaid royalties have been fully credited. QIAGEN has also committed to a minimum net sales requirement. We are also entitled to milestone payments from QIAGEN totaling $10 million upon the achievement of certain volume, regulatory, and commercial milestones.

For a certain period, QIAGEN is restricted from developing assays in prenatal screening competitive to the ones being developed based on our technology under this Agreement, and we are restricted from developing and selling certain in vitro diagnostic kits in prenatal screening independent of QIAGEN, unless such kits have been approved by regulatory authorities separately from a sequencing platform. These restrictions could be removed if QIAGEN fails to satisfy certain requirements related to the development and performance of its sequencing platform and to sales of the assays that are subject to the Agreement. In addition, if, in the future, QIAGEN satisfies certain requirements related to the development and performance of its sequencing platform for use with our prenatal screening assays, additional provisions related to an extended cooperation between both parties will apply.

The Agreement contains representations, warranties, covenants, termination provisions, and indemnification provisions that are generally customary for a transaction of this type.

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We must return up to $15 million of the prepaid royalties if the Agreement expires, or under termination of the Agreement in most circumstances, without such prepaid royalties having been earned. The remainder of the prepaid royalties, to the extent not yet earned, and the upfront license fee, are subject to return to QIAGEN by us only in the event of certain terminations of the Agreement.

As is typical for companies in our industry, we are in the process of pursuing additional strategic or commercial partnerships, relationships, or collaborations, some of which may involve the sale and issuance of our common stock, which could result in additional dilution of the percentage ownership of our stockholders and could cause the price of our common stock to decline.

Kidney Transplant Rejection Biomarker and Study Results

In June 2018, we announced a powerful new kidney transplant rejection biomarker and study results in collaboration with the University of California, San Francisco, a recognized leader in transplantation care. The data demonstrates strong performance of Natera's massively-multiplexed PCR (mmPCR) technology for detecting the likelihood of acute rejection in patient candidates for kidney transplants.

In a blinded, retrospective study, Natera leveraged its validated SNP (Single Nucleotide Polymorphism) technology to measure donor-derived cell-free DNA levels (dd-cfDNA) in 292 plasma samples from 187 unique kidney transplant patients, including 52 patients experiencing acute rejection. The assay was designed based on years of experience in differentiating maternal DNA from fetal DNA in reproductive health. This is the largest patient cohort to date, comparing dd-cfDNA levels to organ biopsies, the current gold standard for organ status assessment.

Natera's dd-cfDNA assay demonstrated 92% sensitivity in detecting acute rejection, identifying 48 out of 52 affected cases based on a cutoff of 1% dd-cfDNA. This sensitivity compares favorably against competition, which reported only 59% sensitivity in a 2017 study. This performance data suggests the potential of Natera's assay for use in both rule-in and rule-out applications.

Based on our internal estimates, we believe the total addressable market in the United States for tests such as ours that predict kidney transplant rejection is over $2 billion.

Oncology Studies

We have presented data from our previously disclosed research collaborations with Aarhus University in Denmark in locally advanced muscle invasive bladder cancer and in colorectal cancer. In both the bladder study and the colon study, blood was drawn prospectively at regular intervals over more than two years from initial diagnosis. The studies demonstrated the ability of our Signatera (RUO) test to stratify patients by high or low risk of recurrence based on post-treatment presence or absence of ctDNA in the blood. Signatera (RUO) detected molecular relapse an average of four months prior to clinical relapse in bladder cancer, and an average of over seven months in colorectal cancer. In addition to the data in recurrence monitoring, our Signatera technology showed promise in treatment response monitoring. In addition, in the bladder study, ctDNA analysis using Signatera (RUO) at the time of diagnosis predicted treatment outcome more accurately than other variables traditionally used for clinical staging, and was the only variable with statistical significance in predicting outcome in commercially available tests. Because our Signatera (RUO) test is currently for research use only in the United States, the test can only be promoted in the United States for research purposes.

Additionally, we have announced that our previously disclosed study with Cancer Research UK-funded researchers at Imperial College London and the University of Leicester, U.K. is now complete. In the study, which includes patients with all three of the key breast cancer subtypes,

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including ER+, HER2+, and Triple Negative, blood was prospectively collected every six months from patients who were relapse-free for at least three years after the completion of adjuvant treatment. We expect the key endpoints of this study will include relapse detection rate, and the lead time of molecular relapse versus clinical or radiographic relapse.

Based on our internal estimates, we believe that the total addressable market in the United States for recurrence monitoring for various types of cancer is over $12 billion.

Government Regulations

Our business is subject to and impacted by extensive and frequently changing laws and regulations in the United States (at both the federal and state levels) and internationally. These laws and regulations include regulations particular to our business and laws and regulations relating to conducting business generally (e.g., export controls laws, U.S. Foreign Corrupt Practices Act and similar laws of other jurisdictions). We also are subject to inspections and audits by governmental agencies. Set forth below are highlights of certain key regulatory schemes applicable to our business. Information regarding other regulatory schemes applicable to our business can be found in our Annual Report on Form 10-K for the year ended December 31, 2017, which is incorporated herein by reference.

Clinical Laboratory Improvement Amendments of 1988 and State Regulation

As a clinical laboratory, we are required to hold certain federal and state licenses, certifications and permits to conduct our business. As to federal certifications, in 1988, Congress passed the Clinical Laboratory Improvement Amendments of 1988, or CLIA, establishing more rigorous quality standards for all laboratories that perform testing on human specimens for the purpose of providing information for the diagnosis, prevention, or treatment of disease. CLIA requires such laboratories to be certified by the federal government and mandates compliance with various operational, personnel, facilities administration, quality and proficiency testing requirements intended to ensure the accuracy, reliability and timeliness of patient test results. CLIA certification is also a prerequisite to be eligible to bill state and federal healthcare programs, as well as many commercial third-party payers, for laboratory testing services.

Our laboratory located in San Carlos, California is CLIA certified. Our laboratory must comply with all applicable CLIA requirements.

CLIA provides that a state may adopt laboratory regulations that are more stringent than those under federal law, and a number of states have implemented their own more stringent laboratory regulatory requirements. State laws may require that laboratory personnel meet certain qualifications, specify certain quality control procedures or facility requirements, or prescribe record maintenance requirements. We are required to meet certain laboratory licensing requirements for those states in which we sell products who have adopted regulations beyond CLIA. For more information on state licensing requirements, see "—California Laboratory Licensing", "—New York Laboratory Licensing," and "—Other State Laboratory Licensing Laws."

Our laboratory has also been accredited by the College of American Pathologists, or CAP, which means that our laboratory has been certified as following CAP guidelines in operating the laboratory and in performing tests that ensure the quality of our results.

California Laboratory Licensing

In addition to federal certification requirements for laboratories under CLIA, we are required under California law to maintain a California state license for our San Carlos clinical laboratory and comply with California state laboratory laws and regulations. Similar to the federal CLIA regulations, the California state laboratory laws and regulations establish standards for the operation of a clinical

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laboratory and performance of test services, including the education and experience requirements of a laboratory director and personnel (including requirements for documentation of competency); equipment validations; and quality management practices. All testing personnel must maintain a California state license or be supervised by licensed personnel.

Clinical laboratories are subject to routine on-site inspections by the state. If a clinical laboratory is found to be out of compliance with California standards, the California Department of Health Services, or DHS, may suspend, restrict or revoke the California state laboratory license to operate the clinical laboratory (and exclude persons or entities from owning, operating, or directing a laboratory for two years following license revocation), assess civil money penalties, impose specific corrective action plans, among other sanctions.

New York Laboratory Licensing

Because we receive test specimens originating from New York State, our San Carlos clinical laboratory is required to obtain a New York state laboratory permit (CLEP) and comply with New York state laboratory laws and regulations. The New York state laboratory laws, regulations and rules are equal to or more stringent than the CLIA regulations and establish standards for the operation of a clinical laboratory and performance of test services, including education and experience requirements of a laboratory director and personnel; physical requirements of a laboratory facility; equipment validations; and quality management practices. The laboratory director must maintain a Certificate of Qualification issued by New York's DOH in the permitted categories.

Our clinical laboratory is subject to proficiency testing and on-site survey inspections conducted by the Clinical Laboratory Evaluation Program, or CLEP, of the New York State Department of Health, or DOH. If a laboratory is found to be out of compliance with New York's CLEP standards, the DOH, may suspend, limit, revoke or annul the New York laboratory permit, censure the holder of the license or assess civil money penalties. Statutory or regulatory noncompliance may result in a laboratory's operator, owners and/or laboratory director being found guilty of a misdemeanor under New York law.

Our clinical laboratory maintains a valid permit in the State of New York for molecular genetic testing services furnished by our clinical laboratory.

The DOH also must approve each Laboratory Developed Test (LDT) before the test is offered to patients located in New York. Our clinical laboratory has received approval from New York's DOH to offer our basic Panorama test to women with high-risk pregnancies and a conditional approval to offer both our basic Panorama and Panorama with the microdeletions panel to all pregnant women, regardless of risk. Our clinical laboratory also holds a permit from New York's DOH to offer our Horizon, Spectrum, Anora and non-invasive prenatal paternity tests, and provisional approval is pending for our Horizon test under our recently updated workflow.

Other State Laboratory Licensing Laws

In addition to New York and California, other states, including Florida, Maryland, Pennsylvania and Rhode Island, require licensing of out-of-state laboratories under certain circumstances. We have obtained licenses in these three additional states and believe we are in compliance with applicable state laboratory licensing laws. We also hold a Florida state laboratory license; however effective as of July 1, 2018, Florida no longer requires laboratories to obtain a Florida state laboratory license.

Potential sanctions for violation of state statutes and regulations include significant fines, the rejection of license applications and the suspension or loss of various licenses, certificates and authorizations, which could harm our business. CLIA does not preempt state laws that have established laboratory quality standards that are at least as stringent as federal law.

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State Genetic Testing Laws

Many states have implemented genetic testing and privacy laws imposing specific patient consent requirements and protecting test results. In some cases, we are prohibited from conducting certain tests without appropriate documentation of patient consent by the physician ordering the test. Requirements of these laws and penalties for violations vary widely.

HIPAA and Other Privacy Laws

The privacy and security regulations under the Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, establish uniform standards governing the conduct of certain electronic healthcare transactions and require certain entities, called covered entities, to comply with standards that include the privacy and security of protected health information, or PHI. HIPAA further requires business associates of covered entities—independent contractors or agents of covered entities that have access to protected health information in connection with providing a service to or on behalf of a covered entity—to enter into business associate agreements with the covered entity and to safeguard the covered entity's PHI against improper use and disclosure. In addition, certain of HIPAA's privacy and security standards are directly applicable to business associates.

As a covered entity and as a business associate of other covered entities (with whom we have therefore entered into business associate agreements), we have certain obligations regarding the use and disclosure of any PHI that may be provided to us, and we could incur significant liability if we fail to meet such obligations or if our business associates fail to meet such obligations. Among other things, HITECH imposes civil and criminal penalties against covered entities and business associates for noncompliance with privacy and security requirements and authorizes states' attorneys general to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions.

As noted above, we are required to comply with HIPAA standards promulgated by the U.S. Department of Health and Human Services, or HHS. First, we must comply with HIPAA's standards for electronic transactions, which establish standards for common healthcare transactions, such as claims information, plan eligibility, payment information and the use of electronic signatures. We must also comply with the standards for the privacy of individually identifiable health information, which limit the use and disclosure of most paper and oral communications, as well as those in electronic form, regarding an individual's past, present or future physical or mental health or condition, or relating to the provision of healthcare to the individual or payment for that healthcare, if the individual can or may be identified by such information. Additionally, we must comply with HIPAA's security standards, which require us to ensure the confidentiality, integrity and availability of all electronic protected health information that we create, receive, maintain or transmit, to protect against reasonably anticipated threats or hazards to the security of such information, and to protect such information from unauthorized use or disclosure.

Various states in the United States have implemented similar restrictive requirements regulating the use and disclosure of health information and other personally identifiable information that are not necessarily preempted by HIPAA, particularly if a state affords greater protection to individuals than HIPAA. For example, Massachusetts law requires that any company that obtains personal information of any resident of the Commonwealth of Massachusetts implement and maintain a security program that adequately protects such information from unauthorized use or disclosure.

There are also foreign privacy and security laws and regulations that impose restrictions on the access, use and disclosure of health information. In particular, the EU's General Data Protection Regulation, or GDPR, became effective in May 2018. The GDPR applies not only to organizations within the EU, but also applies to organizations outside of the EU, such as Natera, that offer goods or

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services to EU data subjects or that process or hold personal data of EU data subjects. The regulation specifies higher potential liabilities for certain data protection violations, and we anticipate that it will result in a greater compliance burden for us as we conduct our business, particularly through our Constellation cloud-based distribution model, in the European Union. Fines for non-compliance can range from the greater of 2% of annual global revenues or €10 million, up to the greater of 4% of annual global revenues or €20 million.

As a business that operates both internationally and throughout the United States, any unauthorized use or disclosure of personally identifiable information, even if it does not constitute PHI, by us or our third-party contractors, including disclosure due to data theft or unauthorized access to our or our third-party contractors' computer networks, could subject us to costs, fines or penalties that could adversely affect our business and results of operations, including the cost of providing notice, credit monitoring and identity theft prevention services to affected consumers.

Healthcare Fraud and Abuse Laws

The federal Anti-Kickback Statute makes it a felony for a provider or supplier, including a laboratory, to knowingly and willfully offer, pay, solicit or receive remuneration, directly or indirectly, in order to induce business that is reimbursable under any federal healthcare program. A violation of the federal Anti-Kickback Statute may result in imprisonment for up to five years and/or criminal fines of up to $25,000, civil assessments and fines up to $50,000, and exclusion from participation in Medicare, Medicaid and other federal healthcare programs. Although the federal Anti-Kickback Statute applies only to federal healthcare programs, a number of states have passed laws substantially similar to the federal Anti-Kickback Statute pursuant to which similar types of prohibitions are made applicable to all other health plans and third-party payers. Actions which violate the federal Anti-Kickback Statute or similar laws may also involve liability under the Federal False Claims Act, which prohibits knowingly presenting or causing to be presented a false, fictitious or fraudulent claim for payment to the U.S. Government.

Federal and state law enforcement authorities scrutinize arrangements between healthcare providers and potential referral sources to ensure that the arrangements are not designed as a mechanism to induce patient care referrals and opportunities. Law enforcement authorities, courts and Congress have demonstrated a willingness to look behind the formalities of a transaction to determine the underlying purpose of payments between healthcare providers and actual or potential referral sources. Generally, courts have taken a broad interpretation of the scope of the federal Anti-Kickback Statute, holding that the statute may be violated if merely one purpose of a payment arrangement is to induce future referrals.

The HHS Office of Inspector General, or OIG, has issued Special Fraud Alerts on arrangements for the provision of clinical laboratory services and relationships between laboratories and referring physicians. The Fraud Alerts set forth a number of practices allegedly engaged in by some clinical laboratories and healthcare providers that raise issues under the federal fraud and abuse laws, including the federal Anti-Kickback Statute. The OIG emphasized in the Special Fraud Alerts that when one purpose of such arrangements is to induce referrals of government program-reimbursed laboratory testing, both the clinical laboratory and the healthcare provider (e.g., physician) may be liable under the federal Anti-Kickback Statute, and may be subject to civil and/or criminal prosecution and exclusion from participation in the Medicare and Medicaid programs.

Recognizing that the federal Anti-Kickback Statute is broad and may technically prohibit many innocuous or beneficial arrangements within the healthcare industry, HHS has issued a series of regulatory "safe harbors" which provide confidence to healthcare providers and other parties that they may not be prosecuted under the federal Anti-Kickback Statute if they can demonstrate compliance with each element of the safe harbor. Although full compliance with these provisions ensures against

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prosecution under the federal Anti-Kickback Statute, the failure of a transaction or arrangement to fit within a specific safe harbor does not necessarily mean that the transaction or arrangement is illegal or that prosecution under the federal Anti-Kickback Statute will be pursued.

While we believe that we are in compliance with the federal Anti-Kickback Statute or similar laws, there can be no assurance that our relationships with physicians, hospitals and other customers will not be subject to scrutiny or will survive regulatory challenge under such laws. If imposed for any reason, sanctions under the federal Anti-Kickback Statute or any similar state statute could have a negative effect on our business.

Because our laboratory is located in California and licensed by California's DHS, California law is applicable to our business arrangements. California's state anti-kickback statutes, Business and Professions Code Section 650 (which applies to all categories of payors) and Insurance Code Section 754, and its Medi-Cal anti-kickback statute, Welfare and Institutions Code Section 14107.2, are analogous to, and have been interpreted by the California Attorney General and California courts in substantially the same way as the federal government and the courts have interpreted, the federal Anti-Kickback Statute. A violation of Section 650 is punishable by up to one year of imprisonment, a fine up to $50,000, or both imprisonment and a fine. A violation of Section 14107.2 is punishable by imprisonment and fines of up to $10,000. The California Insurance Code includes similar prohibitions against any consideration for the referral or procurement of patients if a claim is submitted to a commercial insurer, CA Ins. Code § 750, which is punishable by criminal penalties mirroring those that apply to violations of Business and Professions Code Section 650.

Because our laboratory holds a New York CLEP permit, we must comply with New York state laboratory statutes and regulations, which include anti-kickback provisions, Public Health Law Section 587, and Medicaid anti-kickback provisions, 18 NYCRR Section 515.2, related to laboratory services. The New York DOH may suspend, limit, revoke or annul the New York laboratory permit or otherwise discipline the permit holder for a violation.

In addition to the requirements that are discussed above, there are other healthcare fraud and abuse laws that could have an impact on our business. The federal False Claims Act prohibits a person from knowingly submitting or causing to be submitted false claims or making a false record or statement in order to secure payment by the federal government. In addition to actions initiated by the government itself, the statute authorizes actions to be brought on behalf of the federal government by a private party having knowledge of the alleged fraud sometimes referred to as a "whistleblower". Because the complaints are initially filed under seal, the action may be pending for some time before the defendant is even aware of the action. If the government is ultimately successful in obtaining redress in the matter or if the private party plaintiff succeeds in obtaining redress without the government's involvement, then the private party plaintiff will receive a percentage of the recovery. Violation of the federal False Claims Act may result in fines of up to three times the actual damages sustained by the government, plus mandatory civil penalties of up to approximately $22,000 for each separate false claim, imprisonment or both, and possible exclusion from Medicare or Medicaid.

We are also subject to a federal law directed at "self-referrals," commonly known as the Stark Law, which prohibits, with certain exceptions, payments made by a laboratory to a physician in exchange for the provision of clinical laboratory services, or presenting or causing to be presented claims to Medicare and Medicaid for laboratory tests referred by physicians who personally, or through a family member, have an investment interest in, or a compensation arrangement with, the clinical laboratory performing the tests. A person who engages in a scheme to circumvent the Stark Law's referral prohibition may be fined up to $100,000 for each such arrangement or scheme. In addition, any person who presents or causes to be presented a claim to the Medicare or Medicaid programs in violation of the Stark Law is subject to civil monetary penalties of up to $15,000 per claim submission, an assessment of up to three times the amount claimed, and possible exclusion from participation in

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federal governmental payer programs. Claims submitted in violation of the Stark Law may not be paid by Medicare or Medicaid, and any person collecting any amounts with respect to any such prohibited claim is obligated to refund such amounts.

Many states, including California, also have state "physician self-referral" prohibitions and other laws that are not limited to Medicare and Medicaid referrals, with which we must comply. We are subject to California's Physician Ownership and Referral Act, or PORA, under Article 6 of the California Business & Professions Code. PORA generally prohibits us from billing a patient or any governmental or private payer for any laboratory services when the physician ordering the service, or any member of such physician's immediate family, has a "financial interest" with us, unless the arrangement meets an exception. The term "financial interest" is defined broadly and includes any type of ownership interest, debt, loan, lease, compensation, remuneration, discount, rebate, refund, etc. between the ordering physician and the entity receiving the referral. The exceptions to PORA track certain of the Stark Law exceptions, including an exception for personal service arrangements and for ownership of publicly traded entities. A violation of PORA is punishable by civil and criminal penalties (civil penalties and criminal fines vary depending on the nature of the violation, but may reach up to $15,000 per violation).

Other states may have self-referral restrictions with which we have to comply that differ from those imposed by federal and California law.

We are also subject to applicable state client billing laws (also known as "pass through billing"), which specify whether a provider that did not perform the service is permitted to submit the claim for payment and if so, whether the non-performing provider is permitted to mark up the cost of the services in excess of the price the purchasing provider paid for such services. California has an anti-markup statute with which we must comply, which prohibits providers from charging for a laboratory test that it did not perform unless the provider (a) notifies the patient of the name, address, and charges of the laboratory performing the test, and (b) charges no more than what he or she was charged by the clinical laboratory which performed the test except for any other service actually rendered to the patient by the provider (Business and Professions Code Section 655.5). A violation of this provision can lead to imprisonment and/or a fine of up to $10,000. Other states have similar anti-markup prohibitions with which we must comply. In addition, many states also have "direct-bill" laws, which means that the services actually performed by an individual or entity must be billed by such individual or entity, thus preventing ordering physicians from purchasing services from a laboratory and billing for the services they order. For example, California has a direct bill rule specific to anatomic pathology services that prohibits any provider from billing for anatomic pathology services if those services were not actually rendered by that person or under his or her direct supervision with some exemptions (Business and Professions Code Section 655.7).

While we have attempted to comply with the federal fraud and abuse laws, California fraud and abuse laws and similar laws of other states and non-U.S. jurisdictions, it is possible that some of our arrangements could be subject to regulatory scrutiny at some point in the future, and we cannot provide assurance that we will be found to be in compliance with these laws following any such regulatory review.

Further, in addition to the privacy and security regulations stated above, HIPAA created two federal crimes: healthcare fraud and false statements relating to healthcare matters. The healthcare fraud statute prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private payers. A violation of this statute is a felony and may result in fines, imprisonment or exclusion from government sponsored programs. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare

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benefits, items or services. A violation of this statute is a felony and may result in fines or imprisonment.

Finally, federal law prohibits any entity from offering or transferring to a Medicare or Medicaid beneficiary any remuneration that the entity knows or should know is likely to influence the beneficiary's selection of a particular provider, practitioner or supplier of Medicare or Medicaid payable items or services, including waivers of copayments and deductible amounts (or any part thereof) and transfers of items or services for free or for other than fair market value. Entities found in violation may be liable for civil monetary penalties of up to $10,000 for each wrongful act. Although we believe that our sales and marketing practices are in material compliance with all applicable federal and state laws and regulations, relevant regulatory authorities may disagree, and violation of these laws or our exclusion from such programs as Medicaid and other governmental programs as a result of a violation of such laws could have a material adverse effect on our business, results of operations, financial condition and cash flows.

Corporate Information

We were initially formed in California as Gene Security Network, LLC in November 2003. We were incorporated in Delaware in January 2007, and we changed our name to Natera, Inc. in January 2012. Our principal executive offices are located at 201 Industrial Road, Suite 410, San Carlos, California 94070, and our telephone number is (650) 249-9090. Our website address is www.natera.com. We do not incorporate the information on, or accessible through, our website into this prospectus supplement, and you should not consider any information on, or accessible through, our website as part of this prospectus supplement.

Natera, Panorama and other trademarks or service marks of Natera appearing in this prospectus supplement are the property of Natera. This prospectus supplement contains additional trade names, trademarks and service marks of ours and of other companies. We do not intend our use or display of other companies' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

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THE OFFERING

Common stock offered by Natera	4,500,000 shares of common stock.
Common stock to be outstanding after this offering	58,749,507 shares of common stock (59,424,507 shares if the underwriters exercise their option to purchase additional shares in full).
Option to purchase additional shares	We have granted to the underwriters the option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 675,000 additional shares of our common stock.
Use of proceeds	We intend to use the net proceeds from this offering for working capital and general corporate purposes and continued investments in research and development for our core technology and development of our product offerings. In addition, we may use a portion of the net proceeds for acquisitions of complementary businesses, technologies or other assets. However, we have no current understandings, agreements or commitments for any material acquisitions at this time. See "Use of Proceeds."
Risk Factors	Investing in our common stock involves a high degree of risk. See "Risk Factors" in this prospectus supplement and other information included or incorporated into this prospectus supplement and the accompanying prospectus, for a discussion of the factors you should carefully consider before deciding to invest in our securities.
The Nasdaq Global Select Market Symbol	NTRA

The number of shares of common stock that will be outstanding after this offering is based on 54,249,507 shares outstanding as of March 31, 2018, and excludes:

- 376,691 shares of common stock issuable upon the exercise of warrants outstanding as of March 31, 2018, with a weighted-average exercise price of $2.32 per share;
- 1,013,903 shares of common stock issuable upon the vesting and settlement of restricted stock units outstanding as of March 31, 2018;
- 10,731,571 shares of common stock issuable upon the exercise of options outstanding as of March 31, 2018, with a weighted-average exercise price of $6.76 per share;
- 308,300 shares of common stock issuable upon the exercise of options granted after March 31, 2018, with an exercise price of $10.70 per share;
- 82,600 shares of common stock issuable upon the vesting and settlement of restricted stock units granted after March 31, 2018; and

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- 18,195,505 shares of common stock, subject to increase on an annual basis, reserved for future grant or issuance under our stock-based compensation plans, consisting of:
  - 16,518,565 shares of common stock as of March 31, 2018 reserved for future grants under our 2015 Equity Incentive Plan, or the 2015 Plan; and
  - 1,676,940 shares of common stock as of March 31, 2018 reserved for future issuance under our 2015 Employee Stock Purchase Plan, or the 2015 ESPP.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase additional shares.

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SUMMARY FINANCIAL DATA

The following tables set forth a summary of our historical financial data as at and for the periods presented. The summary historical financial data set forth below includes the results of operations and balance sheet data for the three months ended, and as of, March 31, 2018 and 2017 and the years ended, and as of, December 31, 2017, 2016 and 2015. The summary financial data for the three months ended March 31, 2018 and 2017 have been derived from our unaudited condensed financial statements included in our Quarterly Report on Form 10-Q for the quarter ended March 31, 2018, which is incorporated herein by reference. The summary historical financial data for each of the three years in the period ended December 31, 2017 have been derived from our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2017, which is incorporated herein by reference. The unaudited condensed financial data have been prepared on a basis consistent with our audited financial statements and, in the opinion of management, reflect all adjustments, consisting of normal recurring adjustments, considered necessary for a fair presentation. The results of operations for the three months ended March 31, 2018 are not necessarily indicative of the results that may be expected for the full year or for any future period.

The information below should be read in conjunction with (i) our financial statements (and notes thereto) contained in our Annual Report on Form 10-K for the year ended December 31, 2017 and our unaudited condensed financial statements (and notes thereto) contained in our Quarterly Report on Form 10-Q for the quarter ended March 31, 2018, and (ii) "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Part II, Item 7 in our Annual Report on Form 10-K for the year ended December 31, 2017 and Part I, Item 2 of our Quarterly Report on Form 10-Q for the quarter ended March 31, 2018, each incorporated by reference herein.

	For the three months ended March 31,		Year ended December 31,		
(in thousands, except per share data)	2018	2017[1]	2017	2016	2015
Selected Statement of Operations Data:					
Total revenues	$ 62,340	$ 49,382	$ 210,939	$ 217,074	$ 190,355
Total cost and expenses	92,857	83,932	344,966	313,562	250,193
Interest expense and other income (expense), net	(2,252)	1,117	(1,833)	865	(10,437)
Income tax expense	(104)	(47)	(454)	(142)	—
Net loss	(32,873)	(33,480)	(136,314)	(95,765)	(70,275)
Net loss per common share, basic	(0.61)	(0.63)	(2.56)	(1.86)	(2.68)
Net loss per common share, diluted	(0.61)	(0.65)	(2.56)	(1.86)	(2.68)

	As of March 31,		As of December 31,		
	2018	2017	2017[1]	2016	2015
Selected Balance Sheet Data:					
Cash, cash equivalents and restricted cash	$ 39,690	$ 10,203	$ 13,021	$ 16,690	$ 30,531
Short-term investments	80,023	106,692	106,247	130,860	201,586
Inventory	11,911	8,223	8,998	6,414	8,093

Property and equipment, net	26,878	31,752	29,667	32,289	12,710
Total assets	218,655	176,024	214,613	210,680	265,240
Debt	123,263	49,807	123,177	49,624	42,090
Total liabilities	222,531	102,352	189,196	104,204	80,475
Total stockholders' (deficit) equity	(3,876)	73,672	25,417	106,476	184,765

(1) Effective January 1, 2018, we adopted the requirements of Accounting Standards Update ("ASU") No. 2014-09, Revenue from Contracts with Customers retroactively to January 1, 2016. Amounts have been updated to comply with the new accounting standards.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. You should consider carefully the risks and uncertainties described below, together with all of the other information contained in this prospectus supplement and the accompanying prospectus, or incorporated by reference herein or therein. The risks described in this prospectus supplement and the accompanying prospectus, or incorporated by reference herein or therein, are not the only risks facing us. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial also may materially adversely affect our business, financial condition and/or operating results. If any of the unfavorable events or circumstances described in the risk factors actually occurs, our business may suffer, the trading price of our common stock and other securities could decline, and you could lose all or part of your investment.

Risks Related to Our Business and Industry

We derive most of our revenues from Panorama, and if our efforts to further increase the use and adoption of Panorama or to develop new products and services in the future do not succeed, our business will be harmed.

For the three months ended March 31, 2018 and the year ended December 31, 2017, 53% and 63%, respectively, of our revenues were derived from sales of our Panorama NIPT. Although we are growing our revenues from other products, in particular our Horizon carrier screen, we expect to continue to derive a significant portion of our revenues from the sales of Panorama. Continued and additional market demand for Panorama, and reimbursement for the average risk population and for microdeletions, are key elements to our future success. The market demand for NIPTs has grown in recent periods and is evolving, but this market trend may not continue or, even if it does continue, physicians may not recommend and order Panorama, and our laboratory distribution partners and licensees may not actively or effectively market Panorama.

Our ability to increase sales and establish significant levels of adoption and reimbursement for Panorama is uncertain, and it may be challenging for us to achieve profitability for many reasons, including, among others:

- the NIPT market may not grow as we expect, and NIPTs may not gain acceptance for use in the average-risk pregnancy population or as a screen for microdeletions, which would limit the market for Panorama, and we may fail to compete successfully in this market, whatever size;
- if we are unable to demonstrate that Panorama is superior to competing NIPTs, laboratories, clinics, clinicians, physicians, payers and patients may not adopt use of Panorama on a broad basis, and may not be willing to pay the price premium over other NIPTs that we have, to date, been able to achieve;
- third-party payers, such as commercial insurance companies and government insurance programs, may decide not to reimburse for Panorama, may not reimburse for uses of Panorama for the average-risk pregnancy population or for the screening of microdeletions, or may set the amounts of such reimbursements at prices that do not allow us to cover our expenses; in fact, many third-party payers currently have negative coverage determinations or otherwise do not reimburse for average-risk patient populations or for microdeletions screening and we expect low reimbursement rates for microdeletions screening to continue, at least in the near term; also, most state Medicaid programs currently either reimburse at low rates or do not reimburse for our tests;
- third-party payers are increasingly requiring that prior authorization be obtained prior to conducting genetic testing as a condition to reimbursing for it, which has reduced and/or delayed the reimbursement amounts we receive for Panorama or our other tests, which has impacted our results of operations since the fourth quarter of 2017, when these requirements began to take effect;

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- the results of our clinical trials and any additional clinical and economic utility data that we may develop, present and publish or that comes from the commercial use of Panorama may be inconsistent with prior data, may raise questions about the performance of Panorama, or may fail to convince laboratories, clinics, clinicians, physicians, payers or patients of the value of Panorama; furthermore, we may be unable to achieve stable reimbursement for microdeletions unless and until sufficient validation data on the sensitivity and specificity of our test for these conditions becomes available, which may take longer than we anticipate;

- we may experience supply constraints, including those due to the failure of our key suppliers to provide required sequencers and reagents in sufficient amounts or of adequate quality or disputes with our key suppliers, including those with respect to the required sequencers and reagents from our supplier, Illumina, Inc., or Illumina, which is also one of our main NIPT competitors through its subsidiary, Verinata Health Inc., or Verinata;

- we may experience increased cost of product, licensing and other revenues as a percentage of total revenues, as was the case for each of the years ended December 31, 2017, 2016 and 2015;

- the U.S. Food and Drug Administration, or the FDA, or other U.S. or foreign regulatory or legislative bodies may adopt new regulations or policies, or take other actions that impose significant restrictions on our ability to market and sell Panorama or our other tests, including requiring FDA clearance or approval for the sale of Panorama or of the sequencers, reagents, kits and other consumable products that we purchase from third parties in order to perform our testing;

- our laboratory partners may choose to develop their own tests that are competitive with ours or offer tests provided by our competitors due to pricing or other reasons as has happened in the past, or otherwise fail to effectively market Panorama; and competitors may develop and commercialize more effective and/or less expensive tests that deliver comparable results as our tests;

- we may fail to adequately protect or enforce our intellectual property relating to Panorama, leading to increased competition; or other parties may claim that the practice of our technology by us or our licensees and collaborators infringes such other party's intellectual property rights, as Illumina, Inc., or Illumina, has done in a lawsuit that it has filed against us, as discussed further in "Commitments and Contingencies—Legal Proceedings" in Note 7 to our Consolidated Financial Statements in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference; if we are required to pay license fees in order to license third-party intellectual property rights due to actual or alleged infringement based on our running Panorama, we may experience increased costs in running Panorama, and we may be unable to pass such costs on to our customers;

- we may be unable to dedicate adequate resources to the maintenance and further technological advancement of Panorama that are necessary for Panorama to be competitive in the marketplace because of the demands placed on our research and development and product teams with respect to our other products and programs, including our Horizon carrier screen product, our Signatera (RUO) cancer screening offering, and our Evercord cord blood banking service;

- in the event that it is in our commercial or financial interest or we are forced to transition sequencing platforms for Panorama, we may be unable to do so in a commercially sustainable way and that could survive claims of infringement of intellectual property rights of Illumina and other competitors, in a timely manner or at all; and

- we may not be successful in commercializing our cloud-based distribution model.

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If the market for Panorama or our market share fail to grow or grow more slowly than expected, our business, operating results and financial condition will be harmed.

We have incurred losses since our inception and we anticipate that we will continue to incur losses for the foreseeable future, which could harm our future business prospects.

We have incurred net losses each year since our inception in 2003. To date, we have financed our operations primarily through private placements of preferred stock, convertible debt and other debt instruments, and our initial public offering. Our net loss for the three months ended March 31, 2018 and 2017 was $32.9 million and $33.5 million, respectively. Our net loss for the years ended December 31, 2017, 2016 and 2015 was $136.3 million, $95.8 million and $70.3 million, respectively. As of March 31, 2018 and December 31, 2017, we had an accumulated deficit of $479.3 million and $446.4 million, respectively. Such losses may continue to increase in the future as we continue to devote a substantial portion of our resources to efforts to increase adoption of, and reimbursement for, Panorama and our other products, improve these products, and research and develop new products.

In addition, the rate of growth in our revenues has generally been negative, low or flat in recent periods, and this trend may continue in future periods. In particular, a significant element of our business strategy has been to maintain increased in-network coverage with third-party payers; however, the negotiated fees under our contracts with third-party payers are typically lower than the list price of our tests, and in some cases the third-party payers that we contract with have negative coverage determinations for some of our offerings, in particular Panorama for the average-risk pregnancy population and for microdeletions screening. Therefore, being in-network with third-party payers has had, and may continue to have, an adverse impact on our revenues if we are unable to continue to increase adoption of, and obtain favorable coverage determinations for reimbursement for, our products. Furthermore, a CPT code for microdeletions went into effect beginning January 1, 2017. We have experienced low average reimbursement rates thus far for microdeletions testing under this code, and we expect that this code will continue to cause our microdeletions reimbursement to remain low, at least in the near term, either due to reduced reimbursement, or third-party payers declining to reimburse, under the new code, which has had and will likely continue to have an adverse effect on our revenues. In addition, a new CPT code for expanded carrier screening has been approved and is expected to take effect beginning January 1, 2019, and may have a similar effect on our reimbursement rates for our broader Horizon carrier screening panel, which we currently primarily receive reimbursement for on a per-condition basis, as those tests will be reimbursed as a combined single panel instead of as multiple individual tests.

As further discussed in the risk factor entitled "*—We may not be successful in commercializing our cloud-based distribution model*", our results of operations may be adversely affected if we do not sell a sufficient volume of tests under our cloud-based distribution model to offset the lower revenues per test performed under that model. As a result of our limited operating history, our ability to forecast our future operating results, including revenues, cash flows and profitability, is limited and subject to a number of uncertainties. We have also encountered and will continue to encounter risks and uncertainties frequently experienced by growing companies in the life sciences and technology industry, such as those described in this report. If our assumptions regarding these risks and uncertainties are incorrect or these risks and uncertainties change due to changes in our markets, or if we do not address these risks successfully, our operating and financial results may differ materially from our expectations, and our business may suffer.

Uncertainty in the development and commercialization of our enhanced or new tests or services could materially adversely affect our business, financial condition and results of operations.

Our success will depend in part on our ability to effectively introduce enhanced or new tests. We continue to focus our research and development efforts on prenatal products, and are now expanding

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our platform and applying our expertise in processing and analyzing cell-free DNA in the fields of cancer diagnostics and transplant rejection. In 2017 we launched several new products or enhanced versions of existing products, including our first offering in oncology for research use only. The development and launch of enhanced or new tests requires the completion of certain clinical development and commercialization activities that are complex, costly, time-intensive and uncertain, and requires us to accurately anticipate patients', clinicians' and payers' attitudes and needs and emerging technology and industry trends. This process is conducted in various stages, and each stage presents the risk that we will not achieve our goals.

We may experience research and development, regulatory, marketing and other difficulties that could delay or prevent our introduction of enhanced or new tests and result in increased costs and the diversion of management's attention and resources from other business matters, such as from our Panorama and Horizon product offerings, which currently represent the significant majority of our revenues. For example, any tests that we may enhance or develop may not prove to be clinically effective in clinical trials or commercially, or may not meet our desired target product profile, be offered at acceptable cost and with the sensitivity, specificity and other test performance metrics necessary to address the relevant clinical need or commercial opportunity; our test performance in commercial experience may be inconsistent with our validation or other clinical data; we may not be successful in achieving market awareness and demand, whether through our own sales and marketing operations or entering into collaborative arrangements; healthcare providers may not order or use, or third-party payers may not reimburse for, any tests that we may enhance or develop; or we may otherwise have to abandon a test in which we have invested substantial resources. In particular, we are subject to the risk that the biological characteristics of the genetic mutations we seek to target, and upon which our technologies rely, are uncertain and difficult to predict. For example, in our efforts to detect and analyze circulating tumor DNA in plasma for cancer screening, our success depends on tumors shedding mutant DNA into the bloodstream in sufficient quantities such that our technology can detect such mutations. As further discussed in the risk factor entitled "*If our products do not perform as expected, our operating results, reputation and business will suffer*," we may also experience unforeseen difficulties when implementing updates to our processes, as we have occasionally experienced with Panorama and with Horizon, for which we recently launched a new workflow.

We cannot assure you that we can successfully complete the clinical development of any new or enhanced product, or that we can establish or maintain the collaborative relationships that may be essential to our clinical development and commercialization efforts. Clinical development requires large numbers of patient specimens and, for certain products, may require large, prospective, and controlled clinical trials. We may not be able to enroll patients or collect a sufficient number of appropriate specimens in a timely manner; or we may experience delays during clinical development due to slower than anticipated enrollment, which we experienced in the past with our SNP-based Microdeletions and Aneuploidy RegisTry (SMART) study, or due to changes in study design or other unforeseen circumstances, such as our decision to expand our SMART study to include a larger number of patients; or we may be unable to afford or manage the large-sized clinical trials that some of our planned future products may require. The data collected from any studies we complete may not be favorable or consistent with our existing data or may not be statistically significant or compelling to the medical community or to third-party payers seeking such data for purposes of determining coverage for our tests. This is particularly true with respect to testing in the average-risk pregnancy population and for microdeletions screening using our Panorama test. For example, in January 2017 we published data from our DNAFirst study showing that NIPT can be effectively and appropriately offered as a primary screen for all pregnant women regardless of risk due to maternal age or other factors; however, we cannot be certain whether or to what extent it will impact coverage or adoption of Panorama in the average-risk population.

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The publication of clinical data in peer-reviewed journals is a crucial step in commercializing and obtaining reimbursement for tests such as ours, and our inability to control when, if ever, results are published may delay or limit our ability to derive sufficient revenues from any test that is the subject of a study. Peer-reviewed publications regarding our tests may be limited by many factors, including delays in the completion of, poor design of, or lack of compelling data from, clinical studies, as well as delays in the review, acceptance and publication process. If our tests or the technology underlying our current tests or future tests do not receive sufficient favorable exposure in peer-reviewed publications, the rate of clinician adoption of our tests and positive reimbursement coverage determinations for our tests could be negatively affected.

In addition, as further described in the risk factor entitled "*—If the FDA were to begin actively regulating our tests, we could incur substantial costs and delays associated with trying to obtain premarket clearance or approval and incur costs associated with complying with post-market controls*," development of the data necessary to obtain regulatory clearance and approval of a test is time-consuming and carries with it the risk of not yielding the desired results. The performance achieved in published studies may not be repeated in later studies that may be required to obtain FDA premarket clearance or approval or regulatory approvals in foreign jurisdictions. Limited results from earlier-stage verification studies may not predict results from studies in larger numbers of subjects drawn from more diverse populations over longer periods of time. Unfavorable results from ongoing preclinical and clinical studies could result in delays, modifications or abandonment of ongoing analytical or future clinical studies, or abandonment of a product development program, or may delay, limit or prevent regulatory approvals or clearances or commercialization of our product candidates, which could have a material adverse effect on our business, operating results or financial condition.

These and other factors beyond our control could result in delays or other difficulties in the research and development, approval, production, launch, marketing or distribution of enhanced or new tests and could adversely affect our competitive position and results of operations.

Our quarterly results may fluctuate significantly, which could adversely impact the value of our common stock.

Our quarterly results of operations, including our revenues, gross margin, profitability and cash flows, may vary significantly in the future, and period-to-period comparisons of our operating results may not be meaningful. Accordingly, our quarterly results should not be relied upon as an indication of future performance. Our quarterly results may fluctuate as a result of a variety of factors, many of which are outside of our control. Factors that may cause fluctuations in our quarterly results include, without limitation, those listed elsewhere in this "Risk Factors" section. In addition, our quarterly results have historically fluctuated because we generally recognize costs as they are incurred, but, prior to 2018, recorded most revenue only upon receipt of payment, and as a result typically experienced a delay in the related revenue recognition. However, beginning in 2018, we are transitioning to accrual accounting in accordance with ASC 606 issued by the Financial Accounting Standards Board, as further described in "Note 2—Summary of Significant Accounting Policies—Recent Accounting Pronouncements—New Accounting Pronouncements Not Yet Adopted" in the Notes to Consolidated Financial Statements in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference. In addition, to the extent that we continue to spend considerably on our internal sales and marketing and research and development efforts, we expect to incur costs in advance of achieving the anticipated benefits of such efforts. Fluctuations in quarterly results and key metrics may cause those results to fall below our financial guidance or other projections, or the expectations of analysts or investors, which could cause the price of our common stock to decline. We also face competitive pricing and reimbursement pressures, and we may not be able to maintain our premium pricing in the future, which would adversely affect our operating results.

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If we are unable to compete successfully with respect to our current or future products or services, we may be unable to increase or sustain our revenues or achieve profitability.

We compete primarily in the molecular testing field, which is characterized by rapid technological changes, frequent new product introductions, reimbursement challenges, emerging competition, evolving industry standards, intellectual property disputes, price competition, aggressive marketing practices and changing customer preferences. Our principal competition in this field comes from existing testing methods, technologies and products that are used by OB/GYNs, MFM specialists or IVF centers. These include other NIPTs and carrier screening tests offered by our competitors, as well as established, traditional first-line prenatal screening methods, such as serum protein measurement, where doctors measure certain hormones in the blood, and invasive prenatal diagnostic tests like amniocentesis, which have been used for many years and are therefore difficult to displace or supplement. In addition, new testing methods may be developed which may displace or be preferred over NIPTs, such as whole genome sequencing or single cell analysis. We are new to the cord blood and tissue banking field and the field of cancer diagnostics and face competition in both of these business areas from other companies, many of which are larger, more established and have more experience and more resources than we do. Some of our competitors in the liquid biopsy field, in which clinical cancer diagnostic tests examine blood samples rather than solid tumor samples, are expanding their research and development efforts to include screening for other biomarkers instead of, or in addition to, ctDNA, on the basis that analyzing multiple biomarkers may result in improved sensitivity, lower costs and earlier detection than ctDNA-based tests such as ours. We cannot assure you that research, discoveries or other advancements by other companies will not render our existing or potential products and services uneconomical or result in products and services that are superior or otherwise preferable to our current or future products and services.

We compete with numerous companies in the genetic diagnostics space. Our primary competitors in NIPT include Sequenom, which was recently acquired by LabCorp; Illumina, through its subsidiary Verinata; Ariosa, a subsidiary of Roche; Counsyl, Inc.; Bio-Reference, a business unit of OKPO Health, Inc.; Quest; Premaitha Health PLC; BGI; Berry Genomics Co., Ltd.; Progenity; LifeCodexx AG; Synlab International GmbH; and Multiplicom N.V., which was recently acquired by Agilent Technologies Inc. All of our main NIPT competitors in the United States are owned or controlled by companies much larger than ours and with much greater resources for sales, marketing and research and development efforts. Our primary competitors in carrier screening include LabCorp; Counsyl, Inc.; Good Start Genetics, Inc., which has been acquired by Invitae Corp.; Progenity; Quest; Recombine Inc.; NxGen MDx LLC; Fulgent Genetics; and GenPath Diagnostics, a business unit of Bio-Reference. In cord blood and tissue banking, we compete with companies such as Cord Blood Registry, a subsidiary of AMAG Pharmaceuticals, Inc.; ViaCord, a division of PerkinElmer, Inc.; Cryo-Cell International, Inc.; CorCell Companies, Inc.; LifeBankUSA; AlphaCord LLC; StemCyte USA; and CariCord. In the field of cancer diagnostics through liquid biopsy tests, which are the same type of cancer diagnostic tests as Signatera (RUO) and other cancer diagnostic tests that we may seek to develop, we face competition from various companies that offer or seek to offer competing solutions, such as Roche Molecular Systems Inc. and Foundation Medicine, Inc., both subsidiaries of Roche, Grail, which was spun off from Illumina, Guardant Health, Inc., Personal Genome Diagnostics, Inc., and Genomic Health Inc. We expect that the number of competitors in this space will continue to increase as we conduct our development and commercialization activities.

Some of our competitors' products and services are sold at a lower price than ours, which could cause sales of our tests and services to decline or force us to reduce our prices. Our current and future competitors could have greater technological, financial, reputational and market access advantages than us, and we may not be able to compete effectively against them. Increased competition is likely to result in pricing pressures, which could harm our revenues, operating income or market share. If we

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are unable to compete successfully, we may be unable to increase or sustain our revenues or achieve profitability.

We may not be successful in commercializing our cloud-based distribution model.

We utilize a cloud-based distribution model to deploy our bioinformatics technology for use by other laboratories. Under this model, clinical laboratories around the world, including the U.S., license our technology to develop and run their own NIPT or other molecular testing assays in their own facilities, and then access our proprietary algorithms through our cloud-based Constellation software to analyze the assay results. In the diagnostics industry, the market for cloud-based solutions and services is not as mature as the market for on-premise enterprise software, and it remains uncertain whether and to what extent our cloud-based distribution model will achieve and sustain high levels of customer demand and market acceptance. As of May 1, 2018, our number of agreements with licensees under our cloud-based distribution model remains at 23, and only 12 are using Constellation commercially to market NIPT products and one is using Constellation commercially to market its non-invasive prenatal paternity test in the United States and internationally. The rate of adoption of our cloud-based distribution model continues to be slower than we anticipated, and depends on a number of factors, including the cost, performance and perceived value associated with our solution, as well as our ability to address security, privacy and regulatory requirements or concerns. In particular, all of our licensees under our cloud-based distribution model are required to use Illumina sequencers and reagents to run their tests that they develop based on our technology. As further described in the risk factor entitled "*—We rely on a limited number of suppliers or, in some cases, single suppliers, for some of our laboratory instruments and materials and may not be able to find replacements or immediately transition to alternative suppliers*", we are aware that Illumina has required our licensees to pay an additional license fee in certain jurisdictions in order to secure a supply agreement for the sequencers and reagents necessary to run NIPT under our cloud-based distribution model. Furthermore, Illumina competes with us through Verinata, and may not charge a similar license fee for Verinata's licensed-based offering to other laboratories. As a result, our potential or current licensees may be unable to commercially launch their tests under our cloud-based distribution model in a financially viable manner, which has dissuaded and could continue to dissuade potential or current licensees from licensing from us or launching a test based on our technology.

We also do not know whether, over the long term, this model will result in benefits or cost savings at the levels that we anticipate or at all. For example, to the extent that any of our laboratory customers for whom we currently perform our tests entirely in our laboratory transition to our cloud-based distribution model, our revenues from such customers will decrease because we are not able to charge as high an amount per test as when we perform the entire test ourselves. If the lower revenues per test performed is not offset by a sufficient increase in volume of tests sold, our overall revenues will be lower, and our results of operations may be adversely affected.

Among the risks to our business and results of operations from our Constellation model are the following:

- our and our licensees' ability to obtain required regulatory authorizations from the FDA and international regulatory agencies as further described in the risk factor entitled "*Reimbursement and Regulatory Risks Related to Our Business—Failure to obtain necessary regulatory approvals may adversely affect our ability to expand our operations internationally, including our ability to continue commercializing our cloud-based distribution model*";

- supply constraints, including with respect to the blood collection tubes that are used for our Panorama test and that are supplied by Streck, Inc., as further described in the risk factor entitled "*—We rely on a limited number of suppliers or, in some cases, single suppliers, for some of*

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our laboratory instruments and materials and may not be able to find replacements or immediately transition to alternative suppliers";

- allegations or potential third-party claims that the tests, based on our technology, developed by our licensees violate such third parties' intellectual property rights in the territories in which our licensees commercialize their tests;

- licensing portions of our proprietary technology to third parties that may not take the same security precautions as we do to protect this information; and

- an inability to achieve anticipated benefits and costs savings.

If we or other cloud-based solution providers experience security incidents, loss of customer data or disruptions in delivery or other problems, the market for cloud-based solutions in the diagnostics industry, including our solutions, may be adversely affected. Such events could also result in potential lawsuits and liability claims, which could have a material adverse effect on our business. If there is a reduction in demand for cloud-based solutions caused by technological challenges, weakening economic conditions, security or privacy concerns, competing technologies and products or other challenges, we may not be successful in executing our Constellation business model, and our results of operations may be adversely affected.

We may be subject to increased compliance risks as a result of our rapid growth, including our dependence on our sales, marketing and billing personnel.

Approximately 78% and 83% of our revenues for the three months ended March 31, 2018 and the year ended December 31, 2017, respectively, were attributable to our U.S. direct sales. We have had to expand our training and compliance efforts in line with our increasing reliance on personnel in our sales, marketing and billing functions; we continue to monitor our personnel, but we have in the past experienced, and may in the future experience, situations in which employees fail to strictly adhere to our policies. In addition, sales and marketing activities in the healthcare space are subject to various rules and regulations, as described in the risk factor entitled "*—Reimbursement and Regulatory Risks Related to Our Business—If we or our laboratory distribution partners, consultants or commercial partners act in a manner that violates healthcare fraud and abuse laws or otherwise engage in misconduct, we may be subject to civil or criminal penalties*"; moreover, our billing and marketing messaging can be complex and nuanced, and there may be errors or misunderstandings in our employees' communication of such messaging. Furthermore, we utilize text messaging, email, phone calls and other similar methods to communicate with patients who are existing or potential users of our products for various business purposes. These activities subject us to laws and regulations relating to communications with consumers, such as the CAN-SPAM Act and the Telephone Consumer Protection Act, violations of which could subject us to claims by consumers, who may seek actual or statutory damages, which could be material in the aggregate. As we continue to scale up our sales and marketing efforts in line with the growth in our business, in particular our increased pace of product launches as well as further geographical expansion, we face an increased need to continuously monitor and improve our policies, processes and procedures to maintain compliance with a growing number and variety of laws and regulations, including with respect to consumer marketing. To the extent that there is any violation, whether actual, perceived or alleged, of our policies or applicable laws and regulations, we may incur additional training and compliance costs, may receive inquiries from third-party payers or other third parties, or be held liable or otherwise responsible for such acts of non-compliance. Any of the foregoing could adversely affect our cash flow and financial condition.

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We rely on internal and third-party data centers and platforms to host our laboratory and cloud-based software, and any interruptions of service or failures may impair our laboratory operations or the delivery of our cloud-based services and harm our business.

We currently maintain a data center at our laboratory facilities in San Carlos, California. In addition, our proprietary bioinformatics algorithms are a crucial component of our test processing, and combine information derived from our mmPCR assay workflows with publicly available data from the broader scientific community to analyze and return test results. We host the significant majority of these algorithms on a cloud-based software platform pursuant to an agreement with DNAnexus, Inc., or DNAnexus, and both we and our Constellation licensees access our algorithms through the DNAnexus platform. The DNAnexus platform is hosted on third-party data center hosting facilities operated by Amazon Web Services, or AWS, located in the United States and in the European Union. These algorithms cannot currently be run other than through the DNAnexus platform; they are currently used to run our Panorama NIPT, NIPT analysis for our Constellation licensees, our Signatera (RUO) liquid biopsy technology, and for certain of our research and development activities, and we plan to utilize the platform for additional applications in the future. In the event of any technical problems that may arise in connection with our on-site data center, the DNAnexus platform or the AWS servers on which the DNAnexus platform is hosted, or difficulties in or termination of our relationship with DNAnexus, we could experience interruptions in our laboratory operations or our cloud-based services, and we and our Constellation licensees may be unable to access our proprietary algorithms and therefore be unable to process tests or conduct any other activities that require access to such algorithms. We do not have any backup platform, server or other means to host our algorithms, and may be unable to find and implement an alternative platform that is satisfactory for our needs on commercially reasonable terms, in a timely manner, or at all. These types of problems may be caused by a variety of factors, including infrastructure changes, human or software errors, viruses, security attacks, fraud, spikes in customer usage and denial of service issues. Interruptions in our operations or service may reduce our revenue, cause us to issue refunds, result in the loss of customers, cause laboratory licensees to terminate their contracts with us, adversely affect our ability to attract new laboratory licensees, or harm our reputation. We could also be exposed to potential lawsuits and liability claims.

If our products do not perform as expected, our operating results, reputation and business will suffer.

Our success depends on the market's confidence that we can provide reliable, high-quality genetic testing results. There is no guarantee that the accuracy and reproducibility we have demonstrated to date will continue as our test volumes increase and our product portfolio expands. We believe that our customers are particularly sensitive to test limitations and errors, including inaccurate test results and the need on occasion to perform second blood draws, or redraws, on patients, for which Panorama experiences a higher rate than advertised for other NIPTs. As a result, if our tests do not perform as expected or favorably in comparison to competitive tests, our operating results, reputation, and business will suffer. We may be subject to legal claims arising from such limitations, errors, or inaccuracies.

Panorama, Horizon and our other products use a number of complex and sophisticated biochemical and bioinformatics processes, many of which are highly sensitive to external factors. An operational or technological failure in one of these complex processes or fluctuations in external variables may result in sensitivity or specificity rates that are lower than we anticipate or that vary between test runs, a higher than anticipated number of tests that require redraws or fail to produce results, or longer than expected turnaround times, which we have experienced and will likely continue to experience on occasion as a result of issues with laboratory equipment, components or materials or otherwise. In addition, we regularly evaluate and refine our testing process, as we recently did in implementing significant updates to our Horizon workflow. Any refinements we make to our testing processes may not improve our tests as we expect and may result in unanticipated issues that may adversely affect our test performance as described above. For example, we have been experiencing

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longer than expected turnaround times under our updated Horizon workflow and are working to remedy these issues. Such operational and technical difficulties adversely affect test performance, may impact the commercial attractiveness of our products, and may increase our cost or divert our resources, including management's time and attention, from other projects and priorities. Furthermore, any changes to our testing process may require us to use new or different suppliers or materials with whom or which we are unfamiliar, and which may not perform as we anticipate.

In addition, as further discussed in the risk factor entitled "*If we are unable to successfully grow revenues for our current or future products or services in addition to Panorama, our business and results of operations may be adversely affected*," we have only recently launched our Evercord service, which is in an industry in which we previously had no experience; we also recently launched our Vistara NIPT and our Signatera (RUO) liquid biopsy technology for research use only. Any failure to meet consumer expectations could harm our reputation.

We rely on third-party laboratories to perform portions of our service offerings.

We and our subsidiaries outsource the portions of testing that we do not perform in-house to third-party CLIA certified laboratories. For example, a portion of our Horizon carrier screening testing and our Vistara single-gene mutations testing is performed by third-party laboratories. In addition, we contract with a third-party laboratory to perform the processing and storage of our Evercord customers' cord blood and cord tissue samples. These third-party laboratories are subject to contractual obligations to perform these services for us, but are not otherwise under our control. We therefore do not control the capacity and quality control efforts of these third-party laboratories other than through our ability to enforce contractual obligations on volume and quality systems, and we have no control over such laboratories' compliance with applicable legal and regulatory requirements. We also have no control over the timeliness of such laboratories' performance of their obligations to us, and the third-party laboratories that we contract with have in the past had issues with delivering results to us or resolving issues with us within the time frames we expected or established in our contracts with them. In the event of any adverse developments with these third-party laboratories or their ability to perform their obligations to us in a timely manner and in accordance with the standards that we and our customers expect, our ability to service our customers may be delayed, interrupted or otherwise adversely affected, which could result in a loss of customers and harm to our reputation. Furthermore, when these issues arise, we have had to expend time, management attention and other resources to address and remedy such issues.

We may not have sufficient alternative backup if one or more of the third-party laboratories that we contract with are unable to satisfy their obligations to us with sufficient performance, quality and timeliness. In particular, we do not have a backup laboratory for our Panorama, Vistara or Evercord offerings. Any natural or other disaster, acts of war or terrorism, shipping embargoes, labor unrest or political instability or similar events at one or more of our third-party laboratories' facilities that causes a loss of capacity would heighten the risks that we face. Changes to or termination of our agreements or inability to renew our agreements with these third-party laboratories or enter into new agreements with other laboratories that are able to perform such portions of our service offerings could impair, delay or suspend our efforts to market and sell these tests and services. In addition, certain third-party payers, including some state Medicaid payers, that we are under contract with may take the position that sending out testing to third-party laboratories and billing for such tests is contrary to the terms of our contract and may refuse to pay us for the testing. If any of these events occur, our business, financial condition and results of operations could suffer. Further, some state laws impose anti-markup restrictions that prevent an entity from realizing a profit margin on outsourced testing. If we or our subsidiaries are unable to markup outsourced testing, our revenues and operating margins would suffer.

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If we are unable to successfully grow revenues for our products or services in addition to Panorama, our business and results of operations may be adversely affected.

Our ability to successfully grow revenues for products or services in addition to Panorama, such as Horizon, Spectrum, Anora, Vistara, Evercord and Signatera (RUO), is uncertain and is subject to many of the risks we face with respect to Panorama. For example, the adoption and demand for such products or services may not grow as we expect; we may not be able to demonstrate that such products or services are equivalent to or superior to competing products or services; third-party payers may not reimburse for our tests, or may set the amounts of such reimbursements at prices that do not allow us to cover our expenses; we may fail to compete successfully in the relevant product markets, or our laboratory distribution partners may choose to more actively or exclusively market tests by competitors; we may experience supply constraints; and we may fail to adequately protect our intellectual property relating to our products or others may claim we infringe their intellectual property rights. If we are not able to increase adoption of and grow revenues for these products or services, our business and results of operations may be adversely affected.

We launched our Evercord cord blood and cord tissue banking service in April 2017; our Vistara single-gene mutations screening test in May 2017; our Signatera (RUO) recurrence monitoring liquid biopsy offering for research use only in August 2017; and our twin pregnancies screening capability for Panorama in October 2017. Our success with these offerings is subject to many of the risks affecting our business generally, as well as the inherent difficulty associated with launching a new offering. Moreover, our Evercord offering is in an industry that is new to us and that includes competitors who have been operating for many years. We may face unforeseen difficulties in a number of areas, including with Bloodworks Northwest, or Bloodworks, which is our partner providing the processing and storage services, and storage facility, for this offering; our other suppliers and service providers; our and Bloodworks' ability to maintain required regulatory registrations from the FDA or accreditations from AABB; or disruption of our business and distraction of our employees and management, as described in the risk factor entitled "*If we are unable to successfully scale our operations, our business could suffer*." Our Signatera (RUO) offering, while a molecular diagnostic technology, is in a field, oncology diagnostics, that is new to us; and Vistara is subject to the risks inherent in commercializing a product with a laboratory partner. We have had to review and, in some cases, revise our processes, procedures and agreements with our business partners to address unforeseen operational issues and other contingencies, and will likely continue to do so as these areas of our business grow. We cannot assure you that our Evercord, Vistara or Signatera (RUO) offerings will be successful.

If our sole CLIA-certified laboratory facility becomes inoperable, we will be unable to perform our tests and our business will be harmed.

We do not currently have redundant commercial laboratory facilities, other than third-party laboratories that we employ to perform a significant portion of our Horizon carrier screen testing, our Vistara single-gene mutations testing, and the processing and storage of cord blood and cord tissue for our Evercord offering. We have no backup or redundant facility to perform our main product and source of revenue, Panorama, which we perform at our San Carlos, California laboratory facility. This facility is situated near active earthquake fault lines. Our facility may be harmed or rendered inoperable, or samples could be damaged or destroyed, by natural or manmade disasters, including earthquakes, flooding, power outages and contamination, which may render it difficult or impossible for us to perform our tests for some period of time. The inability to perform our tests or the backlog of tests that could develop if our facility is inoperable for even a short period of time may result in the loss of customers or harm our reputation.

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We rely on a limited number of suppliers or, in some cases, single suppliers, for some of our laboratory instruments and materials and may not be able to find replacements or immediately transition to alternative suppliers.

We have sourced and will continue to source components of our technology, including sequencers, reagents, tubes and other laboratory materials, from third parties. In particular, our sequencers, many of our reagents, and our blood collection tubes are sole sourced. For example, our molecular diagnostics tests are currently only validated to perform on Illumina's sequencing platform; in addition, Illumina is currently the sole supplier of our sequencers and related reagents for Panorama and Signatera (RUO) and for our development activities relating to oncology diagnostics, along with certain hardware and software, pursuant to a supply agreement that expires in June 2026. Without sequencers and the related reagents, we would be unable to run our tests and commercialize our products. In addition, all of the licensees under our cloud-based distribution model do not have alternatives other than to use Illumina sequencers and reagents to run the tests that they develop based on our technology. In addition, Illumina and Sequenom, which has been acquired by LabCorp, have entered into a patent pooling agreement pursuant to which both parties have pooled their intellectual property directed to NIPT. We understand from public filings that under the patent pooling agreement, Illumina has the exclusive worldwide rights to, among other things, license third-party laboratories to develop and sell NIPTs utilizing the pooled intellectual property and to enforce the pooled intellectual property against suspected infringers. Under our supply agreement with Illumina, we do not have an express license to the pooled intellectual property for running our own tests or to grant rights under the pooled intellectual property to the licensees under our cloud-based distribution model. We are aware that Illumina has required our licensees, in order to secure a supply agreement for the sequencers and reagents necessary to run NIPT under our cloud-based distribution model, to pay an additional fee for a license under the pooled intellectual property in jurisdictions in which Illumina believes certain of the pooled intellectual property is enforceable. This additional fee has dissuaded and could continue to dissuade potential or current licensees from licensing from us or launching a test based on our technology. In addition, Illumina has filed a patent infringement lawsuit against us, as further described in "Commitments and Contingencies—Legal Proceedings" in Note 7 to our Consolidated Financial Statements in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference, alleging that our performance of part of our Panorama test infringes one of the patents in the patent pool. While we believe that our commercialization of Panorama in the United States does not infringe any valid patents included in the pooled intellectual property, we cannot be certain as to the outcome of this lawsuit, including based on further claims that could be brought during the course of a litigation, and the costs and distraction to management of defending against this lawsuit could be significant. In addition, Illumina directly competes with us in the NIPT market through its subsidiary, Verinata. We understand Illumina supplies the same or similar sequencers and consumables to Verinata. Because of Illumina's ownership of Verinata, we face increased risk and uncertainty regarding continuity of a successful working relationship with Illumina under our supply agreement, as well as in our ability to compete with Verinata in the marketplace in view of economic advantages enjoyed by Verinata with respect to the cost of sequencers and related consumables. Our failure to maintain a continued supply of the sequencers and reagents, along with the right to use certain hardware and software, would adversely impact our business, financial condition, and results of operations. In particular, while we are seeking to validate our tests on additional sequencing platforms, such as under our license, distribution and development agreement with Qiagen LLC, or Qiagen, we have not, to date, validated any alternative sequencing platform on which our testing could be run in a commercially viable manner. These efforts will require significant resources, expenditures and time and attention of management, and there is no guarantee that we will be successful in implementing any such sequencing platforms in a commercially sustainable way. We also cannot guarantee that we will appropriately prioritize or select alternative sequencing platforms on which to focus our efforts, in particular given our limited product and research and development

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resources and various business initiatives, which could result in increased costs and delayed timelines or otherwise impact our business and results of operations.

In addition, our Panorama test is currently only validated to be performed using Streck, Inc., or Streck's, blood collection tubes, and Streck is the sole supplier of the blood collection tubes included in our Panorama test under a supply arrangement with Streck under which we are required to exclusively use Streck tubes. Similarly, all of the licensees under our cloud-based distribution model also have no current alternative but to use these blood collection tubes to run the tests that they develop based on our technology. The blood collection tubes supplied by Streck are intended for research use only and are labeled as RUO. Our sequencers, sourced from Illumina, as well as certain other reagents we use for Panorama and our other tests, are also labeled as RUO. As discussed further in the risk factor entitled "*Reimbursement and Regulatory Risks Related to Our Business—Changes in the way the FDA regulates the reagents, other consumables, and testing equipment we use when developing, validating, and performing our tests could result in delay or additional expense in bringing our tests to market or performing such tests for our customers*," the FDA may determine that a product labeled RUO is, nonetheless, intended to be used diagnostically, and could take enforcement action against the supplier of the product. If this were to occur with respect to Streck, Illumina or any of our other suppliers of RUO products, we would be required to obtain one or more alternative sources of these products, and we may not be able to do so on commercially reasonable terms or at all. Furthermore, because our licensees under our cloud-based distribution model also exclusively use such sole-sourced components to run the tests they develop based on our technology, and our laboratory distribution partners must use certain of such sole-sourced components in order to utilize our tests, any enforcement action against the supplier by the FDA or any other regulatory authority in the jurisdictions in which our licensees and laboratory distribution partners are located could have an adverse impact on our business.

Because we rely on third-party manufacturers, we do not control the manufacture of these components, including whether such components will meet our quality control requirements, nor the ability of our suppliers to comply with applicable legal and regulatory requirements. In many cases, our suppliers are not contractually required to supply these components to the quality or performance standards that we require. If the supply of components we receive does not meet our quality control or performance standards, we may not be able to use the components, or if we use them not knowing that they are of inadequate quality, which occasionally occurs with respect to certain reagents, our tests may not work properly or at all, and we may be subject to significant delays caused by interruption in production or manufacturing or to lost revenue from such interruption or from spoiled tests. In addition, any natural or other disaster, acts of war or terrorism, shipping embargoes, labor unrest or political instability or similar events at our third-party manufacturers' facilities that cause a loss of manufacturing capacity would heighten the risks that we face.

In the event of any adverse developments with our sole suppliers, or if any of our sole suppliers modifies any of the components they supply to us, our ability to supply our products may be interrupted, and obtaining substitute components could be difficult or require us to re-design or re-validate our products. In addition, if we obtain FDA clearance or approval for any of our tests as an in vitro diagnostic, or IVD, such issues with suppliers or the components that we source from suppliers could affect our commercialization efforts for such an IVD, as further described in the risk factor entitled "*Reimbursement and Regulatory Risks Related to Our Business—If the FDA were to begin actively regulating our tests, we could incur substantial costs and delays associated with trying to obtain premarket clearance or approval and incur costs associated with complying with post-market controls*." Our failure to maintain a continued supply of components, or a supply that meets our quality control requirements, or changes to or termination of our agreements or inability to renew our agreements with these parties or enter into new agreements with other suppliers, particularly in the case of sole suppliers such as Streck and Illumina, could result in the loss of access to important components of our tests and impact our test performance or affect our ability to perform our tests in a timely manner or at all, which could

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impair, delay or suspend our commercialization activities. In the event that we transition to a new supplier from any of our sole suppliers, doing so could be time-consuming and expensive, may result in interruptions in our ability to supply our products to the market, could affect the performance specifications of our tests or could require that we re-validate Panorama and our other tests using replacement equipment and supplies, which could delay the performance of our tests and result in increased costs. Any of these occurrences could have a material adverse effect on our business, financial condition and results of operations.

We rely on commercial courier delivery services to transport samples to our facilities in a timely and cost-efficient manner and if these delivery services are disrupted, our business will be harmed.

Our core business depends on our ability to quickly and reliably deliver test results to our customers. We typically receive blood samples for analysis at our San Carlos, California facility within days of collection from the patient. Likewise, we rely on courier services to transport cord blood and tissue samples to Bloodworks' facility in which the samples will be processed and stored. Disruptions in delivery service, whether due to error by the courier service, labor disruptions, bad weather, natural disaster, terrorist acts or threats or for other reasons, could adversely affect specimen integrity, our ability to process or store samples in a timely manner and to service our customers, and ultimately our reputation and our business. In addition, if we are unable to continue to obtain expedited delivery services on commercially reasonable terms, our operating results may be adversely affected.

Security breaches, loss of data and other disruptions, including with respect to cybersecurity, could compromise sensitive information related to our business or prevent us from accessing critical information and expose us to liability, which could adversely affect our business and reputation.

In the ordinary course of our business, we collect and store sensitive data, including legally-protected personal information, such as test results and other patient health information, credit card and other financial information, insurance information, and personally identifiable information. We also store sensitive intellectual property and other proprietary business information, including that of our customers, payers and collaboration partners. We manage and maintain our applications and data utilizing a combination of on-site systems, managed data center systems and cloud-based data center systems. These applications and data encompass a wide variety of business-critical information, including research and development information, commercial information and business and financial information. We are highly dependent on information technology networks and systems, including the Internet, to securely process, transmit, and store this critical information. Although we take measures to protect sensitive information from unauthorized access or disclosure, our information technology and infrastructure, and that of our technology providers, may be vulnerable to cyber-attacks by hackers or viruses or breached due to employee error, malfeasance or other disruptions.

Any such breach or interruption could compromise our data security, and the information we store could be inaccessible by us or could be accessed by unauthorized parties, publicly disclosed, lost or stolen. Any such interruption in access, improper access, disclosure, modification, or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, such as the Health Insurance Portability and Accountability Act of 1996, or HIPAA, European data privacy regulations, such as the General Data Protection Regulation, or GDPR, and regulatory penalties. We may be required to comply with state breach notification laws, become subject to mandatory corrective action, or be required to verify the correctness of database contents. Unauthorized access, loss or dissemination could also disrupt our operations, including our ability to perform tests, provide test results, bill payers or patients, process claims and appeals, provide customer assistance services, conduct research and development activities, develop and commercialize tests, collect, process and prepare company financial information, provide information about our tests, and manage the administrative aspects of our business, any of which could damage our reputation and

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adversely affect our business. In addition, these breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may compound these adverse consequences. Any such breach could also result in the compromise of our trade secrets and other proprietary information, which could adversely affect our competitive position.

Our cloud-based distribution model adds additional data privacy risk, as certain personal health and other information may be sent to and stored in the cloud by our laboratory licensees. We contractually prohibit our licensees from sending personally-identifiable information to our cloud servers, and the vendor that hosts our software in the cloud is contractually required to comply with data privacy laws, such as HIPAA. However, we cannot be certain that these third parties will comply with the terms of our agreements, nor that they will not experience security breaches or other disruptions.

Damage to or loss of our Evercord customers' cord blood and cord tissue samples held in our custody could potentially result in significant legal liability and harm our reputation.

Our reputation among clients and the medical and birthing services community is extremely important to the commercial success of our Evercord service offering. This is due in significant part to the nature of the service we provide—as we are assuming custodial care of a child's umbilical cord blood stem cells entrusted to us by the parents for potential future use as a therapeutic for the child or a close relative. We believe that our reputation, and Bloodworks' reputation, enables us to market Evercord as a competitive cord blood and tissue preservation service in a crowded marketplace. However, we have occasionally and will likely continue to experience unforeseen issues, such as loss of or damage to a sample during transit, during the preservation process or while in storage. For example, if Bloodworks' facility or the equipment in the facility are significantly damaged or destroyed by natural or manmade disasters, including earthquakes, flooding or power outages, we could suffer a loss of some or all of the stored cord blood and tissue units. In addition, if we encounter problems during transportation, including while our customers' samples are in the possession of third-party commercial carriers that we contract with to transport the samples, some or all of the transported units could be damaged. Any such problems, particularly if publicized, could negatively impact our reputation, which could adversely affect our business and business prospects. If our Evercord offering does not meet customer or other public expectations, any resulting harm to our reputation could extend beyond Evercord to our core women's health and genetic testing business, which comprises the substantial portion of our revenue, because Evercord is promoted to the same OB/GYNs who prescribe and order many of our other products.

In addition to reputational damage, we face the risk of legal liability for loss of or damage to cord blood units. We do not own the cord blood units banked by our cord blood banking customers; instead, we act as custodian on behalf of the child-donor's parent or guardian. Loss of or damage to the units would be loss of or damage to the customer's property. We have included provisions in our enrollment agreement for this service, limiting our liability. However, we cannot be sure to what extent we could nevertheless be found liable for damages suffered as a result of harm to or loss of a cord blood unit, and if we are found liable, whether our insurance coverage will be sufficient to cover such damages.

We offer a quality service guarantee that provides that, subject to certain conditions, if an Evercord customer's cord blood and tissue sample is used for a transplant and fails to engraft, or begin to grow and develop, we will refund all service fees paid to us by the customer plus an additional $100,000. Failure to engraft can occur for a variety of reasons, and may occur more frequently than we anticipate. Frequent failures to engraft could result in many customers making claims under our quality service guarantee, which could adversely impact the profitability of this service offering.

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The marketing, sale, and use of Panorama and our other products could result in substantial damages arising from product liability or professional liability claims that exceed our resources.

The marketing, sale and use of Panorama and our other products could lead to product liability claims against us if someone were to allege that our test failed to perform as it was designed or as claimed in our promotional materials, was performed pursuant to incorrect or inadequate laboratory procedures, if we delivered incorrect or incomplete test results, or if someone were to misinterpret test results. In addition, we may be subject to liability for errors in, a misunderstanding of, or inappropriate reliance upon, the information we provide, or for failure to provide such information, in connection with our marketing and promotional activities or as part of the results generated by Panorama and our other products. For example, Panorama could provide a low-risk result which a patient or physician may rely upon to make a conclusion about the health of the fetus, which may, in fact, have the condition for which we delivered a low-risk result because the Panorama result was a so-called false negative. Even though Panorama is highly accurate, it is not 100% accurate and we may report false negative results. If the resulting baby with the condition is born, the family may file a lawsuit against us claiming product or professional liability. We were recently involved in a lawsuit by a patient alleging that we failed to perform a carrier screening test that was ordered. See "Commitments and Contingencies—Legal Proceedings" in Note 7 to our Consolidated Financial Statements in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference. A product liability or professional liability claim could result in substantial damages and be costly and time-consuming for us to defend. Although we maintain product and professional liability insurance, our insurance may not fully protect us from the financial impact of defending against product liability or professional liability claims or any judgments, fines or settlement costs arising out of any such claims. Any product liability or professional liability claim brought against us, with or without merit, could increase our insurance rates, cause our insurance coverage to be terminated or prevent us from securing insurance coverage in the future. Additionally, any product liability or professional liability lawsuit could harm our reputation, result in a cessation of our services or cause our partners to terminate our agreements with them, any of which could adversely impact our results of operations.

If we are unable to successfully scale our operations, our business could suffer.

Our overall test volumes grew from approximately 317,700 to 447,600 and further to 515,200 tests processed during the years ended December 31, 2015, 2016 and 2017, respectively, and since 2009 we have launched 11 product offerings, four of them in 2017 alone. In addition, we regularly evaluate and refine our testing process, often significantly updating our workflows, as with V3 of Panorama in 2017 and our new Horizon workflow earlier this year. As our test volumes and product offerings continue to grow, we will need to continue to ramp up our testing capacity and, with respect to our Evercord offering, storage capacity, and implement increases in scale. We will need additional or new equipment, laboratory space and qualified laboratory personnel, and will need to increase office space, expand our customer service capabilities, implement billing and systems process improvements, enhance our controls and procedures and expand our internal quality assurance program and technology platform. The value of Panorama and our other products depends on our ability to perform the tests on a timely basis and at an exceptionally high standard of quality, and on maintaining our reputation for such timeliness and quality. Failure to implement necessary procedures, transition to new facilities, equipment or processes or to hire the necessary personnel in a timely and effective manner could result in higher processing costs or an inability to meet market demand, or could otherwise affect our operating results, as has happened in the past when we experienced a delay in our claims submissions and processing as a result of transitioning most of our insurance billing operations from our headquarters in San Carlos, California to our facility in Austin, Texas. In addition, our efforts to scale our operations may be unable to keep pace with an increase in the frequency of our launches of new or enhanced products and services. We launched four new products in 2017 alone, two of which are in markets or industries that are new to us; as we continue to launch additional offerings and product

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enhancements, we will need to manage our resources among various initiatives, and such competing priorities could lead to delays in one or more of our business initiatives. Conversely, to the extent that we scale our operations, infrastructure and other resources but do not ultimately meet our anticipated timelines in our product development efforts, we will experience higher costs and expenses than necessary until our project timelines and operational resources become aligned. We may also, intentionally or unintentionally, allocate resources to new products or initiatives in a manner disproportionate to the amount of revenue that such initiatives generate compared to our existing or core offerings. We cannot assure you that our efforts to scale our commercial operations will not negatively affect the quality of our test process or results, or that we will be successful in managing the growing complexity of our business operations.

To execute our growth plan, we must attract and retain highly qualified personnel. Competition for these personnel is intense, especially for sales, scientific, medical, laboratory, research and development and other technical personnel, and especially in the San Francisco Bay Area where our headquarters and laboratory facilities are located, and the turnover rate of such personnel can be high. We have from time to time experienced, and we expect to continue to experience, difficulty in hiring and retaining employees with appropriate qualifications. Many of the companies with which we compete for highly qualified personnel have greater resources than we have. If we hire employees from competitors or other companies, their former employers may attempt to assert that these employees or we have breached their legal obligations to their former employers. In addition, job candidates and existing employees in the San Francisco Bay Area often consider the value of the equity awards they receive in connection with their employment. To the extent that our current or potential employees perceive the value of our equity awards to be low, our ability to recruit, retain and motivate highly skilled employees may be adversely affected, which could then have an adverse effect on our business and future growth prospects. Furthermore, to the extent that we are unable to retain our employees and they leave our company to join one of our competitors, we cannot assure you that any invention, non-disclosure or non-compete agreements we have in place will provide meaningful protection against a departing employee's unauthorized use or disclosure of our confidential information, as further discussed in "*—Risks Relating to our Intellectual Property—If we are not able to adequately protect our trade secrets and other proprietary information, the value of our technology and products could be significantly diminished.*"

In addition, our growth may place a significant strain on our management, operating and financial systems and our sales, marketing and administrative resources. As a result of our growth, our operating costs may escalate faster than we anticipate, we may face difficulties in obtaining additional office or laboratory space, and some of our internal systems may need to be enhanced or replaced. If we cannot effectively manage our expanding operations and our costs, we may not be able to grow successfully or we may grow at a slower pace, and our business could be adversely affected.

If our sales and distribution partnerships are not successful and we are not able to offset the resulting impact through our direct sales efforts or through agreements with new partners, our commercialization activities may be impaired and our financial results could be adversely affected.

While we have increased the focus of our commercial efforts on our U.S. direct sales force, we continue to rely on relationships with laboratory partners to sell Panorama and our other products, both in the United States and internationally. For example, we have recently entered into a license, distribution and development agreement with Qiagen pursuant to which, among others, we will rely on Qiagen for the distribution of an NIPT based on our Panorama test, on a new sequencing platform that has not yet been fully validated for our test to be run in a commercially viable manner. Distributing Panorama and our other products through partners reduces our control over our revenues, our market penetration and our gross margin on sales by the partner if we could have otherwise made that sale through our direct sales force. The financial condition of these laboratories could weaken, these laboratory partners could stop selling our products, reduce their marketing efforts in respect of our

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products, develop and commercialize or otherwise sell competing products, or otherwise breach their agreements with us. Furthermore, our laboratory partners may misappropriate our trade secrets or use our proprietary information in such a way as to expose us to litigation and potential liability. Disagreements or disputes with our laboratory partners, including disagreements over customers, proprietary rights or our or their compliance with contractual obligations, might cause delays or impair the commercialization of Panorama or our other tests, lead to additional responsibilities for us with respect to new tests, or result in litigation or arbitration, any of which would divert management attention and resources and be time-consuming and expensive. As is typical for companies in our industry, we are in the process of pursuing additional strategic or commercial partnerships, relationships, or collaborations, some of which may involve the sale and issuance of our common stock, which could result in additional dilution of the percentage ownership of our stockholders and could cause the price of our common stock to decline.

In addition, we face the risk of our laboratory partners terminating their relationship with us and completely suspending the sale of our products, which has happened in the past. Laboratory partners that are not bound by obligations of exclusivity or non-competition to us or our products could decide to develop their own product that competes with ours or sell a competing product, in addition to or in lieu of our tests. For example, we terminated our licensing and distribution agreement with Bio-Reference in January 2017, and Bio-Reference began selling a competing NIPT. Moreover, our partners could merge with or be acquired by a competitor of ours or a company that chooses to de-prioritize the efforts to sell our products.

If our partnerships are not successful, our ability to increase sales of Panorama and our other products and to successfully execute our strategy could be compromised.

Our financial condition and results of operations may be adversely affected by international regulatory and business risks.

As we expand our international operations and offer our tests in other countries, we are increasingly subject to varied and complex foreign and international laws and regulations due to operating, offering our products, or contracting with employees, contractors and other service providers in these other countries. Compliance with these laws and regulations often involves significant costs and may require changes in our business practices that may result in reduced revenues and profitability.

We are subject to the Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, which prohibits companies and their intermediaries from making payments in violation of law to non-U.S. government officials for the purpose of obtaining or retaining business or securing any other improper advantage. Our reliance on independent laboratories to sell Panorama and other products internationally demands a high degree of vigilance in maintaining our policy against participation in corrupt activity, because these distributors could be deemed to be our agents and we could be held responsible for their actions. Other U.S. companies in the medical device and pharmaceutical field have faced criminal penalties under the FCPA for allowing their agents to deviate from appropriate practices in doing business with foreign government officials. We are also subject to similar anti-bribery laws in the jurisdictions in which we operate, including the United Kingdom's Bribery Act of 2010, which also prohibits commercial bribery and makes it a crime for companies to fail to prevent bribery. These laws are complex and far-reaching in nature. Any violations of these laws, or allegations of such violations, could disrupt our operations, involve significant management distraction, involve significant costs and expenses, including legal fees, and we could be subject to severe penalties, including criminal and civil penalties, disgorgement, and other remedial measures, any of which could result in a material adverse effect on our business, prospects, financial condition, or results of operations.

In addition, our international activities are subject to U.S. economic and trade sanctions, which restrict or otherwise limit our ability to do business in certain designated countries. Other limitations,

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such as restrictions on the import into the United States or the export to other countries of tissue or genetic data necessary for us to perform our tests, or restrictions on importation and circulation of blood collection tubes or other equipment or supplies by countries outside of the United States, may limit our ability to offer our tests internationally. We may also face competition from companies located in the countries in which we or our partners or licensees offer our tests, and in which we may be at a competitive disadvantage because the country may favor a local provider or for other reasons.

By operating internationally, we may experience longer accounts receivable payment cycles and difficulties in collecting accounts receivable; realize lower margins due to lower pricing in many countries; incur potentially adverse tax consequences, including the complexities of foreign value added tax systems, tax inefficiencies related to our corporate structure and restrictions on the repatriation of earnings; experience financial accounting and reporting burdens and complexities; experience difficulties in staffing and managing foreign operations, including under labor and employment laws and regulations that are new or unfamiliar to us; be subject to trade barriers such as tariffs, quotas, preferential bidding or import or export licensing requirements; be exposed to political, social and economic instability abroad, including terrorist attacks and security concerns; be exposed to fluctuations in currency exchange rates; and experience reduced or varied protection for intellectual property rights and practical difficulties in enforcing intellectual property and other rights, including with respect to assignment of inventions to us by our consultants in foreign jurisdictions.

Outside of the United States we enlist local and regional laboratories, contract employees and other service providers to assist with blood draws, engineering, sales, marketing and customer support. Subject to regulatory clearance where required, we also contract with international licensees to run the molecular portion of our tests in their own labs and then access our algorithm for analysis of the resulting data through our cloud-based Constellation platform. Locating, qualifying and engaging additional distribution partners and local laboratories with local industry experience and knowledge is necessary to effectively market and sell our tests outside of the United States. We may not be successful in finding, attracting and retaining such distribution partners or laboratories, or we may not be able to enter into such arrangements on favorable terms. Sales practices and other activities utilized by our distribution partners, contract employees and other service providers that are locally acceptable may not comply with relevant standards required under United States laws that apply to our operations overseas, including through third parties, which could create additional compliance risk. Our training and compliance program and our other internal control policies and procedures may not always protect us from acts committed by our employees, contractors or agents abroad. Non-compliance by us or our employees, contractors or agents of these or any other applicable laws or regulations could result in fines or penalties, or adversely affect our ability to operate and grow our business. Even if we are able to effectively manage our international operations, if our distribution partners and local and regional laboratory licensees are unable to effectively manage their businesses, our business and results of operations could be adversely affected. Furthermore, the legal landscape governing advertising, promotional and other marketing activities can vary widely from jurisdiction to jurisdiction, and is often more complex, less clear or less developed than in the United States. If our marketing activities are found to be in violation of local laws, regulations or practices, we may be subject to fines and other penalties, and may be required to cease marketing or commercialization activities in such jurisdiction. If our sales and marketing efforts are not successful outside of the United States, we may not achieve market acceptance for our tests outside of the United States, which would harm our business.

Operating internationally requires significant management attention and financial resources. We cannot be certain that the investment and additional resources required to increase international revenues or expand our international presence will produce desired levels of revenues or profitability.

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If we lose the services of our founder and Chief Executive Officer or other members of our senior management team, we may not be able to execute our business strategy.

Our success depends in large part upon the continued service of our senior management team. In particular, our founder and Chief Executive Officer, Matthew Rabinowitz, is critical to our vision, strategic direction, culture, products and technology. Although Dr. Rabinowitz spends significant time with us and is highly active in our management, he has the ability to spend up to one business day per week on other commitments pursuant to his employment agreement. In addition, we do not maintain key-man insurance for Dr. Rabinowitz or any other member of our senior management team. The loss of our founder and Chief Executive Officer or one or more other members of our senior management team could have an adverse effect on our business.

We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.

In the future, we may enter into transactions to acquire other businesses, products or technologies. Because we have not made any acquisitions to date, our ability to do so successfully is unproven. Even if we identify suitable targets, we may not be able to make such acquisitions on favorable terms or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue shares of our common stock or other equity securities to the stockholders of the acquired company, which would cause dilution to our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by any indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and non-disruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

We may need to raise additional capital, and if we cannot do so when needed or on commercially acceptable terms, we may have to curtail or cease operations.

We may need to raise additional funds through public or private equity or debt financings, corporate collaborations or licensing arrangements to continue to fund or expand our operations.

Our actual liquidity and capital funding requirements will depend on numerous factors, including:

- our ability to achieve broader commercial success with Panorama, Horizon and our other products;
- the costs and success of our research, development, and commercialization efforts for potential new products;
- our ability to obtain more extensive coverage and reimbursement for our tests, including in the average-risk patient population and for microdeletions screening;
- our ability to generate sufficient revenues from our cloud-based distribution model;
- our ability to collect on our accounts receivable;
- our need to finance capital expenditures and further expand our clinical laboratory operations;
- our ability to manage our operating costs; and
- the timing and results of any regulatory authorizations that we are required to obtain for our tests.

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Additional capital, if needed, may not be available on satisfactory terms or at all. Furthermore, any additional capital raised through the sale of equity or equity-linked securities will dilute stockholders' ownership interests in us and may have an adverse effect on the price of our common stock. In addition, the terms of any financing may adversely affect stockholders' holdings or rights. Debt financing, if available, may include restrictive covenants, and may impose other constraints on us and our operations, as is the case under our 2017 Term Loan, as further described in the risk factor entitled "—*Our outstanding debt may impair our financial and operating flexibility*." To the extent that we raise capital through collaborations and licensing arrangements, it may be necessary to relinquish some rights to our technologies or grant licenses on terms that may not be favorable to us.

If we are not able to obtain adequate funding when needed, we may have to delay development programs or sales and marketing initiatives. In addition, we may have to work with a partner on one or more of our tests or market development programs, which could lower the economic value of those programs to our company.

Our outstanding debt may impair our financial and operating flexibility.

As of March 31, 2018 and December 31, 2017, we had approximately $125.1 million of debt outstanding with accrued interest. On August 8, 2017, we completed our 2017 Term Loan under which we borrowed $75.0 million. In addition, we have $50.1 million outstanding under our Credit Line with UBS. Except for operating leases, we do not have any off-balance sheet financing arrangements in place or available. Our 2017 Term Loan contains various restrictive covenants and is secured by substantially all of our assets, including our intellectual property. These restrictions could limit our ability to use operating cash flow in other areas of our business because we must use a portion of these funds to make principal and interest payments on our debt; conversely, our ability to make principal and interest payments on our indebtedness will depend on our ability to generate cash. If we default under the 2017 Term Loan or the Credit Line and if the default is not cured or waived, the lenders could terminate their commitments to lend to us and cause any amounts outstanding to be payable immediately. Under certain circumstances, they could also exercise their rights under the security agreements entered into in connection with the loans. Such a default could also result in cross defaults under other debt instruments. Moreover, any such default would limit our ability to obtain additional financing, which may have an adverse effect on our cash flow and liquidity.

We may incur additional indebtedness in the future. If we incur additional debt, a greater portion of our cash flows may be needed to satisfy our debt service obligations, and if we do not generate sufficient cash to meet our debt service requirements, we may need to seek additional financing. In that case, it may be more difficult, or we may be unable, to obtain financing on terms that are acceptable to us. As a result, we would be more vulnerable to general adverse economic, industry and capital markets conditions in addition to the risks associated with indebtedness described above.

Ethical, legal and social concerns related to the use of genetic information could reduce demand for our tests.

DNA testing, like that conducted using Panorama, Horizon, our Signatera (RUO) cancer diagnostic test, and our other products, has raised ethical, legal and social issues regarding privacy and the appropriate uses of the resulting information. Governmental authorities could, for social or other purposes, limit or regulate the use of genomic information or genomic testing or prohibit testing for genetic predisposition to certain conditions, particularly for those that have no known cure. Patients may also refuse to use genetic tests even if permissible, for similar reasons; they may also refuse genetic testing due to concerns regarding eligibility for life or other insurance. Ethical and social concerns may also influence U.S. and foreign patent offices and courts with regard to patent protection for technology relevant to our business. These and other ethical, legal and social concerns may limit market acceptance of our tests or reduce the potential markets for services and products enabled by our technology platform, either of which could harm our business.

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Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

We have a significant amount of net operating loss, or NOL, carryforwards that can be used to offset potential future taxable income and related income taxes. As of December 31, 2017, we had federal and state NOL carryforwards of approximately $319.6 million and $165.5 million, respectively, which, if not utilized, begin to expire in 2027 and 2028, respectively. We also had federal research and development credit carryforwards of approximately $11.7 million, which begin to expire in 2028, and state research and development credit carryforwards of approximately $8.1 million, which can be carried forward indefinitely. Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change" (generally defined as a greater than 50% change, by value, in equity ownership over any three-year period), the corporation's ability to use its pre-change NOL carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We may have experienced an "ownership change" upon our initial public offering; we may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may not be within our control. Our ability to use these carryforwards could be limited if we experience an "ownership change."

Our estimates of market opportunity and forecasts of market growth may prove to be inaccurate, and even if the market in which we compete achieves the forecasted growth, our business could fail to grow at similar rates.

Market opportunity estimates and growth forecasts are subject to significant uncertainty and are based on assumptions and estimates that may not prove to be accurate. Our publicly announced estimates and forecasts relating to the size and expected growth of our market may prove to be inaccurate. Even if the market in which we compete meets our size estimates and forecasted growth, our business could fail to grow at similar rates.

Reimbursement and Regulatory Risks Related to Our Business

If we are unable to expand or maintain third-party payer coverage and reimbursement for Panorama and our other tests, or if we are required to refund any reimbursements already received, our revenues and results of operations would be adversely affected.

Our business depends on our ability to obtain or maintain adequate reimbursement coverage from third-party payers and patients. Third-party reimbursement for our testing represents a significant portion of our revenues, and we expect third-party payers such as insurance companies and government healthcare programs to continue to be our most significant source of payments. In particular, we believe that the following will be necessary for us to continue to achieve commercial success: expanding insurance coverage from the high-risk to the average-risk pregnancy population, which represents roughly 80% of the United States pregnancy market, and for microdeletions screening, and obtaining positive coverage determinations and favorable reimbursement rates from commercial third-party payers, the Centers for Medicare and Medicaid, or CMS, and state reimbursement programs for our tests. We do not expect to receive reimbursement for a significant number of Panorama tests for average-risk patients and for microdeletions that we performed in the quarter ended March 31, 2018. In addition, we are working to develop our Signatera (RUO) liquid biopsy technology as a CLIA laboratory developed test, which is an oncology test, and it remains unclear whether and to what extent liquid biopsy or other oncology sequencing tests will be reimbursed. If we are unable to obtain or maintain adequate reimbursement coverage from, or achieve in-network status with, third-party payers for our existing tests or future tests, our ability to generate revenues will be limited. For example, physicians may be reluctant to order our tests due to the potential of a substantial cost to the patient if reimbursement coverage is unavailable or insufficient.

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In making coverage determinations, third-party payers often rely on practice guidelines issued by professional societies. The American College of Medical Genetics, or ACMG, has issued updated guidelines recommending informing pregnant women that NIPT is the most sensitive screening option for Patau, Edwards and Down syndromes, as well as of the availability of the expanded use of NIPT to screen for clinically relevant copy number variants, or CNVs, in the context of counseling that includes the risks/benefits and limitations of screening for CNVs. A CNV is a genetic mutation in which a segment of the genome has been deleted or duplicated, including microdeletions in which a small segment of a chromosome is deleted. The International Society for Prenatal Diagnosis, or ISPD, has issued guidelines that are supportive of performing NIPT in average-risk pregnancies, as well as high-risk pregnancies. However, the the Society for Maternal Fetal Medicine, or SMFM, has issued guidelines for NIPT stating that, while all pregnant women should be informed of the option to receive NIPT, conventional screening methods, such as traditional serum screening, rather than NIPT, remain the most appropriate choice for first-line screening for average-risk pregnancies. While we expect the ACMG and SMFM guidelines to result in an increase in the number of average-risk women who are informed of NIPT and that may request it as a result, not all third-party payers reimburse for NIPT for these average-risk patients. Currently, Aetna Inc., UnitedHealthcare Insurance Company and a number of other third-party payers have negative coverage determinations for NIPT in average-risk patient populations, meaning that their policy is not to reimburse for NIPT for patients in the average-risk population. The SMFM guidelines also echoed a previous statement from SMFM that routine screening for microdeletions should not be performed. Many third-party payers do not reimburse for microdeletions screening. While we have published data on the performance of Panorama for the 22q11.2 deletion syndrome, we have and may continue to experience a negative impact on third-party payers' reimbursement for Panorama for microdeletions, at least until additional validation data on the sensitivity and specificity of our tests becomes available. If we are unable to present satisfactory additional data on the performance of Panorama for 22q11.2 deletion syndrome, including from our SMART study, we may be unable to obtain positive coverage determinations for our test. If third-party payers do not reimburse for NIPT for average-risk pregnancies or microdeletions in the future, our future revenues and results of operations would be adversely affected, particularly to the extent that we continue to perform large volumes of tests for which third-party payors do not reimburse.

In addition, a CPT code for microdeletions took effect on January 1, 2017. We have experienced low average reimbursement rates thus far for microdeletions under this code, and we expect that this code will continue to cause our microdeletions reimbursement to remain low, at least in the near term, due to third-party payers declining to reimburse and as a result of reduced reimbursement, under the code, which has had, and we expect to continue to have, an adverse effect on our revenues. In addition, the American Medical Association, or AMA, has approved the use of a CPT code for expanded carrier screening tests, which is expected to take effect January 1, 2019. The new code may cause reimbursement rates for our broader Horizon carrier screening panel to decrease because those tests will be reimbursed as a combined single panel instead of as multiple individual tests.

The reimbursement environment, particularly for molecular diagnostics, is changing and our efforts to broaden reimbursement for our tests with third-party payers may not be successful. Third-party payers from whom we have received reimbursement may withdraw coverage or decrease the amount of reimbursement coverage for our tests at any time and for any reason. In some cases, our tests or their uses within certain populations, such as for microdeletions, are considered experimental by third-party payers and, as a result, some payers have decided not to reimburse for such tests. In addition, some third-party payers bundle payment for multiple tests, such as Horizon, that screen for multiple conditions, or our Panorama test and the separate Panorama screen for microdeletions, into a single payment rate, thereby limiting our reimbursement in those situations. Payers may also dispute our billing or coding. Based on any of the foregoing, third-party payers may also decide to deny payment or recoup payment for testing that they contend to have been not medically necessary, against their coverage determinations, or for which they have otherwise overpaid, and we may be required to refund

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reimbursements already received. We deal with requests for recoupment from third-party payers from time to time in the ordinary course of our business, and it is likely that we will continue to do so in the future. For example, a commercial payer has recently alleged that it has overpaid us and has demanded recoupment of the alleged overpayments. See "Commitments and Contingencies—Third-Party Payer Reimbursement Audits" in Note 7 to our Consolidated Financial Statements in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference. If a third-party payer denies payment for testing, reimbursement revenue for our testing could decline. If a third-party payer successfully proves that payment for prior testing was in breach of contract or otherwise contrary to law, they may recoup payment, which amounts could be significant and would impact our results of operations, and it may decrease reimbursement going forward. We may also decide to negotiate and settle with a third-party payer in order to resolve an allegation of overpayment. Any of these outcomes might require us to restate our financials from a prior period, which would likely cause our stock price to decline. As described in "Commitments and Contingencies—Legal Proceedings" in Note 7 to our Consolidated Financial Statements in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference, we recently reached a settlement with the United States Department of Justice to pay approximately $11.4 million to resolve claims under a qui tam complaint regarding past reimbursement submissions; although the settlement involved no admission of fault by us and no corporate integrity agreement, we cannot guarantee that we will not be subject to similar claims, resulting in additional settlements or repayments, in the future.

Furthermore, some of our contracts with third-party payers contain so-called most favored nation provisions, pursuant to which we have agreed that we will not bill the third-party payer more than we bill any other third-party payer. We must therefore monitor our billing and claims submissions to ensure that we remain in compliance with these contractual requirements with third-party payers. If we do not successfully manage these most favored nation provisions, we may need to forego revenues from some third-party payers or reduce the amount we bill to each third-party payor with a most-favored nation clause in its contract that is violated, which would adversely affect our revenues. This situation could also subject us to claims for recoupment, which could require the time and attention of our management, may be a distraction from development of our business, adversely impacting our operations. Such recoupment demands could also ultimately result in an obligation to repay amounts previously earned.

In addition, if a third-party payer denies coverage, it may be difficult for us to collect from the patient, and we may not be successful in doing so. In particular, we are often unable to collect the full amount of a patient's responsibility where we are an out-of-network provider and the patient is left with a large balance, despite our good faith efforts to collect. As a result, we cannot always collect the full amount due for our tests when third-party payers deny coverage, cover only a portion of the invoiced amount or the patient has a large deductible, which may cause payers to raise questions regarding our billing policies and patient collection practices. We believe that our billing policies and our patient collection practices are compliant with applicable laws. However, we have in the past received, and we may in the future receive, inquiries from third-party payers regarding our billing policies and collection practices. While we have addressed these inquiries as and when they have arisen, there is no guarantee that we will always be successful in addressing such concerns in the future, which may result in a third-party payer deciding to reimburse for our tests at a lower rate or not at all, seeking recoupment of amounts previously paid to us, or bringing legal action to seek reimbursement of previous amounts paid. Any of such occurrences could cause reimbursement revenue for our testing, which constitutes the large majority of our revenue, to decline. Additionally, if we were required to make a repayment, such repayment could be significant, this would impact our results of operations, and we might be required to restate our financials from a prior period, which would likely cause our stock price to decline.

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We are aware of policies and practices of our competitors to offer patients a set cap on their out-of-pocket responsibility, waive patient responsibility altogether, and, in some cases, to not send patients a bill at all, all of which we believe is not in accordance with third-party payers' policies and, in many cases, not compliant with the law. In contrast, it is our policy not to offer such caps or waivers and to send bills to patients for services rendered. Because of this discrepancy, our offerings may be perceived as less attractive to patients and their healthcare providers, who are concerned about patients having a large financial responsibility for these products. As a result, we believe that our revenues and results of operations have been adversely affected, and may continue to be so affected to the extent that our competitors continue such practices.

Our revenues may be adversely affected if we are unable to successfully obtain reimbursement from the Medicare program and state Medicaid programs.

Our revenues from Medicare are currently very small, given the population that Medicare covers, and the fact that our testing generally is not received by Medicare beneficiaries. As a result, we do not expect those revenues to increase materially with regard to NIPT. However, we expect that Medicare reimbursement will impact our ability to receive future revenue from our planned Signatera CLIA test. Medicare reimbursement can also affect both Medicaid reimbursement, which is relevant to NIPT, and reimbursement from commercial third-party payers. Specifically, fee-for-service Medicaid programs generally do not reimburse at rates that exceed Medicare's fee-for-service rates, and many commercial third-party payers set their payment rates at a percentage of the amounts that Medicare pays for testing services. Medicare reimbursement rates are typically based on the Clinical Laboratory Fee Schedule, or CLFS, set by CMS pursuant to a statutory formula established by the U.S. Congress. Our current Medicare Part B reimbursement was not set pursuant to a national coverage determination by CMS. Although we believe that coverage is available under Medicare Part B even without such a determination, we currently lack the certainty afforded by a formal national coverage determination by CMS. Thus, CMS could issue an adverse coverage determination as to Panorama which could influence other third-party payers, including Medicaid, and could have an adverse effect on our revenues.

It is estimated that nearly half of all births in the United States are to state Medicaid program recipients. Each state's Medicaid program has its own coverage determinations related to our testing, and many state Medicaid programs do not provide their recipients with coverage for our testing. Even if our testing is covered by a state Medicaid program, we must be recognized as a Medicaid provider by the state in which the Medicaid recipient receiving the services resides in order for us to be reimbursed by a state's Medicaid program. In addition, many Medicaid programs have entered into agreements with managed care plans to have the managed care plans manage the provision of healthcare to that Medicaid program's beneficiaries. In order for us to enter into contracts to provide our testing services to beneficiaries who are enrolled with a Medicaid managed care plan, we must first be recognized as a Medicaid provider in that state, and then contract with the applicable Medicaid managed care program. As of May 1, 2018, we are recognized by 47 states as a Medicaid provider. It is likely that we will not be able to be recognized as a provider by additional Medicaid programs because some states require that a provider maintain a physical laboratory in that state in order to be recognized; furthermore, some states have closed provider panels, which means that the state does not intend to expand its current provider network and therefore does not intend to recognize additional Medicaid providers. Even if we are recognized as a provider in a state, if Medicare's CLFS rate for our services and tests are low, the Medicaid reimbursement amounts are sometimes as low, or lower, than the Medicare reimbursement rate. In addition and as noted above, each state's Medicaid program has its own coverage determinations related to our testing, and many state Medicaid programs do not provide their recipients with coverage for our testing. As a result of all of these factors, our testing is not reimbursed or only reimbursed at a very low amount by many state Medicaid programs. In some cases, a state Medicaid program's reimbursement rate for our testing might be zero dollars. Low or zero dollar Medicaid reimbursement rates for our tests could have an adverse effect on our business and revenues.

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Our revenues may be adversely impacted if third-party payers withdraw coverage or provide lower levels of reimbursement due to changing policies, billing complexities or other factors.

We are in network, or under contract, with the significant majority of third-party payers from whom we receive reimbursement; this means that we have agreements with most third-party payers that govern approval or payment terms. However, these contracts do not guarantee reimbursement for all testing we perform. For example, many third-party payers with whom we have written agreements have policies that state they will not reimburse for use of NIPTs for average-risk pregnancies or for the screening of microdeletions, or don't have a policy in place to reimburse for microdeletions screening. In addition, the terms of certain of our agreements require a physician or qualified practitioner's signature on test requisitions or require other controls and procedures prior to conducting a test. In particular, third-party payers have been increasingly requiring prior authorization to be obtained prior to conducting a test, as a condition to reimbursing for the test. This has placed a burden on our billing operations as we have to dedicate resources to ensuring that these requirements are met and to conduct follow-up and address issues as they arise, and has also impacted our results of operations, including our gross margins, since the fourth quarter of 2017, when these requirements began to take effect. To the extent we or the physicians ordering our tests do not follow the prior authorization requirements, we may be subject to claims for recoupment of reimbursement amounts previously paid to us, or may not receive some or all of the reimbursement payments to which we would otherwise be entitled. This has occurred in some cases and may occur more frequently in the future, which does and would have an adverse impact on our revenues.

Where we are considered to be an out of network provider, which is the case with some third-party payers from whom we receive reimbursement, such third-party payers could withdraw coverage and decline to reimburse for our tests in the future, for any reason. Managing reimbursement on a case-by-case basis is time-consuming and contributes to an increase in the number of days it takes us to collect on accounts, which also increases our risk of non-payment. Negotiating reimbursement on a case-by-case basis also typically results in the receipt of reimbursement at a significant discount to the list price of our tests.

Even if we are being reimbursed for our tests, third-party payers may review and adjust the rate of reimbursement, require co-payments from patients or stop paying for our tests. Government healthcare programs and other third-party payers continue to increase their efforts to control the cost, utilization and delivery of healthcare services by demanding price discounts or rebates and limiting coverage of, and amounts they will pay for, molecular diagnostic tests. These measures have resulted in reduced payment rates and decreased utilization in the clinical laboratory industry. Because of these cost-containment measures, governmental and commercial third-party payers may reduce, suspend, revoke or discontinue payments or coverage at any time, including payors that currently provide reimbursement for our tests. Reduced reimbursement of our tests may harm our business, financial condition or results of operations.

Billing for clinical laboratory testing services is complex. We perform tests in advance of payment and without certainty as to the outcome of the billing process. In cases where we expect to receive a fixed fee per test due to our reimbursement arrangements, we may nevertheless encounter disputes over pricing and billing. Each third-party payer typically has different billing requirements, and the billing requirements of many payers have become increasingly difficult to meet. Among the factors complicating our billing of third-party payers are:

- disparity in coverage among various payers;
- disparity in information and billing requirements among payers, including with respect to prior authorization requirements and procedures and establishing medical necessity; and

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- incorrect or missing billing information, which is required to be provided by the ordering healthcare practitioner.

These risks related to billing complexities, and the associated uncertainty in obtaining payment for our tests, could harm our business, financial condition and results of operations.

In the United States, the AMA generally assigns specific billing codes for laboratory tests under a coding system known as Current Procedure Terminology, or CPT, which we and our ordering healthcare providers must use to bill and receive reimbursement for our diagnostic tests. Once the CPT code is established, CMS establishes payment levels and coverage rules under Medicare while private payers independently establish rates and coverage rules. A CPT code specific to NIPT for aneuploidies was implemented in January 2015, and a CPT code for microdeletions was implemented in January 2017. CMS has established a pricing benchmark of $802 for aneuploidy and microdeletions testing. However, our microdeletions reimbursement has decreased under this new code because third-party payers are declining to reimburse under this new code or reimbursing at a much lower rate than we had previously received. Furthermore, we cannot guarantee that we will be able to negotiate favorable rates for this code or receive reimbursement at all if we are unable to collect and publish additional data and obtain positive coverage determinations for Panorama for microdeletions. In addition, the AMA has approved the use of a CPT code for expanded carrier screening tests, which will be published later this year, and may similarly cause reimbursement for our Horizon expanded carrier screening tests to decline. We do not currently have assay-specific CPT codes assigned for all of our tests, and there is a risk that we may not be able to obtain such codes or, if obtained, we may not be able to negotiate favorable rates for such codes. We currently submit for reimbursement using CPT codes based on the guidance of outside coding experts and legal counsel. There is a risk that the codes we currently submit may be rejected or withdrawn or that third-party payers will seek refunds of amounts that they claim were inappropriately billed based on either the CPT code used, or the number of units billed. In addition, third-party payers may not establish positive coverage policies for our tests or adequately reimburse for any CPT code we may use, or seek recoupment for testing previously performed, which have occurred in the past.

If the FDA were to begin actively regulating our tests, we could incur substantial costs and delays associated with trying to obtain premarket clearance or approval and incur costs associated with complying with post-market controls.

We currently offer a number of prenatal genetic tests, including Panorama, and each of those tests is an LDT. In addition, we anticipate initially commercializing our planned Signatera CLIA laboratory test as an LDT. An LDT is generally considered to be a test that is designed, developed, validated and used within a single laboratory. The FDA takes the position that it has the authority to regulate such tests as medical devices under the Federal Food, Drug, and Cosmetic Act, or FDC Act, but it has generally exercised enforcement discretion with regard to LDTs. This means that even though the FDA believes it can impose regulatory requirements on LDTs, such as requirements to obtain premarket approval or clearance of LDTs, it has generally chosen not to enforce those requirements to date.

The regulation by the FDA of LDTs remains uncertain. In October 2014, the FDA issued draft guidances outlining its plan to actively regulate LDTs using a risk-based approach. In November 2016, the FDA announced that it no longer plans to finalize the 2014 draft guidances. In January 2017, the FDA issued a discussion paper that laid out elements of a possible revised future LDT regulatory framework, but did not establish any regulatory requirements. The FDA's efforts to regulate LDTs prompted the drafting of legislation governing diagnostic products and services that sought to substantially revamp the regulation of both LDTs and IVDs. Congress may still act to provide further direction to the FDA on the regulation of LDTs.

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In the meantime, the FDA could require us to seek premarket clearance or approval to offer our tests for clinical use even before it finalizes any future guidance. If FDA premarket clearance or approval is required for any of our existing or future tests, we may be forced to stop selling our tests or we may be required to modify claims or make other changes to our tests while we work to obtain FDA clearance or approval. Our business would be adversely affected while such review is ongoing and if we are ultimately unable to obtain premarket clearance or approval. For example, the regulatory premarket clearance or approval process may involve, among other things, successfully completing analytical, pre-clinical and/or clinical studies beyond the studies we have already performed for each of our products and would involve submitting a premarket notification, or 510(k), a de novo application, or filing a PMA application with the FDA. As further described in the risk factor entitled "*Uncertainty in the development and commercialization of our enhanced or new tests or services could materially adversely affect our business, financial condition and results of operations*," completing such studies requires the expenditure of time, attention and financial and other resources, and may not yield the desired results, which may delay, limit or prevent regulatory approvals. In addition, we may require cooperation in our filings for FDA clearance or approval from third-party manufacturers of the components of our tests. If we are unable to obtain such required cooperation, we may be unable to achieve the desired regulatory clearances or approvals, or may be delayed or be required to expend additional costs and other resources in doing so. For example, while we recently entered into a licensing, development and distribution agreement with Qiagen to develop NIPT and potentially other tests based on our technology, including for FDA approval, on Qiagen's sequencer, Illumina currently is our sole sequencer and sequencing reagent supplier. If we seek to achieve regulatory clearance or approval for Panorama, to the extent that Panorama incorporates Illumina's sequencer or sequencing reagents, we may require Illumina's cooperation in demonstrating safety and efficacy with respect to such components of our test. We may face difficulty obtaining cooperation from Illumina because Illumina is the parent company of Verinata, a direct competitor of ours in the NIPT field. In addition, we are party to certain litigation with Illumina as described in "Note 7—Commitments and Contingencies—Legal Proceedings" in the Notes to Unaudited Interim Condensed Consolidated Financial Statements, in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference. Furthermore, if FDA premarket clearance or approval is required, our cash flows may be adversely affected until we obtain such clearance or approval, as most third-party payers, including Medicaid, will not reimburse for use of medical devices which are required to be cleared or approved but which have not been.

We cannot assure you that Panorama or any of our other tests for which we decide to pursue or are required to obtain premarket clearance or approval by the FDA will be cleared or approved on a timely basis, if at all. In addition, if a test has been approved through a PMA, certain changes that we may make to improve the test, or as a result of issues with suppliers of the components of the test or if a supplier modifies its component upon which our approval relies, may need to be approved by the FDA before we can implement them, which could increase the time and expense involved in rolling such changes out to the commercial market. Ongoing compliance with FDA regulations would increase the cost of conducting our business and subject us to heightened regulation by the FDA and penalties for failure to comply with these requirements, any of which may adversely impact our business and results of operations.

Furthermore, the FDA or the Federal Trade Commission may object to the materials and methods we use to promote the use of our current tests or other LDTs we may develop in the future, including with respect to the product claims in our promotional materials, and may initiate enforcement actions against us. Enforcement actions by the FDA may include, among others, untitled or warning letters; fines; injunctions; civil or criminal penalties; recall or seizure of current or future tests, products or services; operating restrictions and partial suspension or total shutdown of production.

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Failure to obtain necessary regulatory approvals may adversely affect our ability to expand our operations internationally, including our ability to continue commercializing our cloud-based distribution model.

An important part of our business strategy is to expand and offer our tests internationally, either by providing our testing services directly or through our laboratory partners, or through our licensees under our Constellation cloud-based distribution model. As we do so, we will become increasingly subject to or impacted by the regulatory requirements of foreign jurisdictions, which are varied and complex. Our tests, and certain components of our tests, may be subject to the regulatory approval requirements in each foreign country in which they are sold by us or a laboratory partner, or by our licensees under our cloud-based distribution model, and our future performance would depend on us or our partners or licensees obtaining any necessary regulatory approvals in a timely manner. For example, while we have obtained a CE Mark from the European Commission for our Constellation software and the key reagents required for our licensees to run their NIPT based on our technology, we have not obtained a CE Mark for our Panorama test as a whole. Therefore, while we are able to offer Constellation in the European Union and other countries that accept a CE Mark, we are unable to offer Panorama as an IVD directly in these jurisdictions. This, coupled with our use of our Panorama brand name under our Constellation model, has caused regulatory authorities to question whether we, our laboratory partners or our licensees may be marketing, commercializing or otherwise offering our tests without required approvals. We have in the past addressed inquiries from regulatory authorities in the European Union regarding the regulatory status of our Panorama offering, and expect that we will continue to face questions from regulatory authorities in various countries with respect to Panorama or Constellation. If we do not continue to satisfactorily address any such questions in the future, we may be required to cease offering our products, either directly or through our partners or licensees, in the relevant country. This may in turn result in similar concerns, and subsequent cessation of our sources of revenue, in other countries.

Our cloud-based distribution model has raised similar concerns in some countries outside of the European Union; as a result, we have had to address inquiries from international regulatory authorities from time to time, and it is likely that we will continue to do so in the future regarding the regulatory status of Panorama and Constellation. We may also be at a competitive disadvantage in the European Union to our competitors who have obtained a CE Mark for their end to end NIPT. In addition, as further described in the risk factor entitled "*Risks Related to Our Business and Industry—We rely on a limited number of suppliers or, in some cases, single suppliers, for some of our laboratory instruments and materials and may not be able to find replacements or immediately transition to alternative suppliers*," blood collection tubes sourced solely from Streck are required to run our tests. These blood collection tubes are CE Marked by the European Commission; however, if such blood collection tubes are not registered in jurisdictions that do not accept a CE Mark, we may be unable to expand our business in such jurisdictions.

We may also need to obtain regulatory clearance or approval in the United States for our Constellation software in order for it to be used by third parties in the development and commercialization of their diagnostic tests based on our technology. We have engaged in discussions with the FDA regarding the regulatory status of a portion of our Constellation software, the copy number calculator, or CNC, to make calls of copy number variants, which are genetic mutations in which relatively large regions of the genome have been deleted or duplicated. In those discussions, the FDA indicated that the CNC may be appropriate for review under the *de novo* classification process, which is less burdensome than the premarket approval, or PMA, process. The FDA stated that it would not prevent us from marketing Constellation in the United States while we discuss with the FDA how it will be regulated; however, it is possible that the FDA may reverse itself either on the appropriate regulatory review path or on the issue of our ability to continue to market Constellation. In addition, the 21st Century Cures Act, enacted in 2016, included a number of changes to FDA's regulatory approach to software that may have bearing on the regulatory status of our Constellation software. If

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necessary, we intend to seek regulatory clearance or approval for our Constellation software; however, we cannot guarantee that we will obtain such clearance or approval. If clearance or approval is required by the FDA and we are unable to obtain it, we would be unable to commercialize our cloud-based distribution model in the United States.

If our Constellation software requires regulatory clearance or approval in the United States, we will be subject to ongoing FDA obligations and continued regulatory oversight and review, including compliance with requirements such as the quality system regulation, or QSR, which establishes extensive requirements for quality assurance and control as well as manufacturing procedures; the listing of our devices with the FDA; adverse event and malfunction reporting; corrections and removals reporting; and labeling and promotional requirements. We may also be subject to additional FDA post-marketing obligations. If we are not able to maintain regulatory compliance to the extent required, we may not be permitted to offer our Constellation software and may be subject to enforcement action by the FDA, such as the issuance of warning or untitled letters, fines, injunctions and civil penalties; recall or seizure of products; operating restrictions and criminal prosecution. In addition, if a test developed by any of our licensees under our cloud-based distribution model in the United States is found not to be a laboratory developed test, or LDT, or that licensee has difficulty obtaining the reagents and sequencing equipment for any regulatory, supply chain, or other reason, the licensee may not be able to market its test, we would not receive the anticipated revenues from that licensee, and potential or other current licensees may be dissuaded from utilizing our Constellation software.

Regulatory approval can be a lengthy, expensive and uncertain process. In addition, regulatory processes are subject to change, and new or changed regulations can result in unanticipated delays and cost increases. For example, the European Commission has published new directives regulating, among others, IVDs, which are expected to become effective in 2022. The new regulations will require companies providing genetic testing services to obtain a CE Mark for what will be considered IVDs, or a CE-IVD; in addition to requiring notified body approval for various classes of devices, including prenatal tests such as Panorama, companies will also be required to submit clinical evidence and post-market performance data to regulators after their tests have been approved and are commercialized. We or our partners or licensees may not be able to obtain regulatory approvals on a timely basis, if at all, which may cause us to incur additional costs or prevent us from marketing our tests in the United States or in foreign countries.

Changes in laws and regulations, or in their application, may adversely affect our business, financial condition and results of operations.

The clinical laboratory testing industry is highly regulated, and failure to comply with applicable regulatory, supervisory, accreditation, registration or licensing requirements may adversely affect our business, financial condition and results of operations. In particular, the laws and regulations governing the marketing and research of clinical diagnostic testing are extremely complex and in many instances there are no clear regulatory or judicial interpretations of these laws and regulations, which increases the risk that we may be found to be in violation of these laws.

Furthermore, the molecular diagnostics industry as a whole is a growing industry and regulatory agencies such as the United States Department of Health and Human Services, or HHS, or FDA may apply heightened scrutiny to new developments in the field. While we have taken steps to ensure compliance with the current regulatory regime in all material respects, given its nature and our geographical diversity, there could be areas where we are non-compliant. Any change in the federal or state laws or regulations relating to our business may require us to implement changes to our business or practices, and we may not be able to do so in a timely or cost-effective manner. Should we be found to be non-compliant with current or future regulatory requirements, we may be subject to sanctions which could include changes to our operations, adverse publicity, substantial financial penalties and criminal proceedings, which may adversely affect our business, financial condition and results of

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operations by increasing our cost of compliance or limiting our ability to develop, market and commercialize our tests.

In addition, there has been a recent trend of increased U.S. federal and state regulation of payments made to physicians, which are governed by laws and regulations including the Stark law, the federal anti-kickback statute, and the federal False Claims Act as well as state equivalents of such laws. Among other requirements, the Stark law requires laboratories to track, and places a cap on, non-monetary compensation provided to referring physicians.

While we have a compliance plan to address compliance with government laws and regulations, including applicable fraud and abuse laws and regulations such as those described in this risk factor, the evolving commercial compliance environment and the need to build and maintain robust and scalable systems to comply with regulations in multiple jurisdictions with different compliance and reporting requirements increases the possibility that we could inadvertently violate one or more of these requirements.

If we fail to comply with federal, state and foreign laboratory licensing requirements, we could lose the ability to perform our tests or experience disruptions to our business.

We are subject to CLIA, a federal law that regulates clinical laboratories that perform testing on specimens derived from humans for the purpose of providing information for the diagnosis, prevention or treatment of disease. CLIA regulations require clinical laboratories to obtain a certificate and mandate specific standards in the areas of personnel qualifications, administration, participation in proficiency testing, patient test management and quality assurance. CLIA certification is also required in order for us to be eligible to bill state and federal healthcare programs, as well as many private third-party payers, for our tests. To renew these certifications, we are subject to survey and inspection every two years. Moreover, CLIA inspectors may conduct a random inspection of our clinical laboratory or conduct an inspection as a result of a complaint or reported incident.

Some states require that we hold licenses to test samples from patients in those states and as a result we are also required to maintain standards related to state licensure to conduct testing in our laboratories under state law. California state laboratory laws and regulations establish standards for the operation of our clinical laboratory and performance of test services in San Carlos, California, including the education and experience requirements for laboratory directors and personnel (including requirements for documentation of competency); equipment validations; and quality management practices. All personnel involved in testing must maintain a California state license or be supervised by licensed personnel. We maintain a license in good standing with the California Department of Health Services, or DHS. In addition, because we receive test specimens originating from New York, we have obtained a state laboratory permit for our San Carlos laboratory from the New York Department of Health, or DOH, which mandates proficiency testing regardless of whether the laboratory is located in New York. The New York state laboratory laws, regulations and rules are equal to or more stringent than the CLIA regulations and establish standards for the operation of a clinical laboratory and performance of test services, including education and experience requirements for laboratory directors and personnel; physical requirements of a laboratory facility; equipment validations; and quality management practices. The laboratory director must maintain a Certificate of Qualification issued by New York's DOH in permitted categories. In addition, we are subject to routine on-site inspections under both California and New York state laboratory laws and regulations. If we are found to be out of compliance with either California or New York requirements, DHS or DOH may suspend, restrict or revoke our license or laboratory permit, respectively (and, with respect to California, may exclude persons or entities from owning, operating or directing a laboratory for two years following such license revocation), assess civil monetary penalties, or impose specific corrective action plans, among other sanctions. Any such actions could materially and adversely affect our business by prohibiting or limiting our ability to offer testing.

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As noted above, a number of states require that we hold licenses to test samples from patients in those states. We have also obtained licenses from states that we believe require us to do so, including Florida, Pennsylvania, Maryland, and Rhode Island, and we intend to comply with similar requirements for other states of which we may become aware. However, we cannot assure you that the regulators in each state will at all times find us to be in compliance with the applicable laws of their respective state, which may result in suspension, limitation, revocation or annulment of our laboratory's license for that state or negative impact to our CLIA license, censure, or civil monetary penalties, and would result in our inability to test samples from patients in that state. Any such actions could materially and adversely affect our business.

CMS also has the authority to impose a wide range of sanctions, including revocation of a laboratory's CLIA certification along with a bar on the ownership or operation of any CLIA-certified laboratory by any owners or operators of the deficient laboratory. If we fail to maintain our CLIA certification or any required state license or accreditation, or if any sanction were imposed upon us under CLIA, its implementing regulations, or state or foreign laws or regulations governing licensure, we would not be able to operate our clinical laboratory and offer our testing services in the affected states or countries, which would materially and adversely impact our business and results of operations.

Our cord blood and tissue banking activities are subject to regulations that may impose significant costs and restrictions on us.

Our Evercord cord blood and tissue banking service is subject to FDA regulatory oversight. Pursuant to FDA regulations, an individual or entity that performs any of the manufacturing steps in banking stem cells from peripheral and cord blood (recovery, processing, donor screening, donor testing, storage, labeling, packaging, or distribution) must register with the FDA unless an exception applies. Based on our direct activities, we are subject to FDA requirements and we may be subject to FDA inspection. We have registered with the FDA as an establishment engaged in specific manufacturing steps, including collecting cord blood and tissue samples, donor screening and distribution of cord blood HPCs, or hematopoietic progenitor cells, which are the blood-forming stem cells that are routinely used to treat patients with cancers such as leukemia or lymphoma, and other disorders of the blood and immune systems. We plan to register with the FDA for the storage of cord blood HPCs. We have contracted with Bloodworks, another FDA-registered establishment, to perform other manufacturing steps in the process on our behalf, which we may do as a registered establishment. As the contractor establishment, we remain responsible for ensuring that our subcontractors perform each manufacturing step in compliance with applicable requirements, and are required to terminate any arrangement if our subcontractor is non-compliant. While we are not required to validate and oversee the processes of our subcontractor registered establishments, we are required to make an initial determination that the subcontractor is compliant, and to have policies and procedures in place to ensure that the subcontractor remains compliant throughout the term of the arrangement. We have made this determination with respect to Bloodworks and have put such procedures in place. We are also responsible for any manufacturing step performed on our behalf by an individual or entity that is not required to register with the FDA, such as the doctors and midwives who perform the collection of the cord blood and tissue.

We are also required to comply with good tissue practice regulations, or GTPs, that establish a comprehensive regulatory program for human cellular and tissue-based products. We believe that we currently comply with GTP standards. However, the FDA may determine that we are not compliant or, even if we are currently compliant, we may not be able to maintain this compliance or comply with future regulatory requirements that may be imposed on us.

In certain states, manufacturing steps in banking stem cells from cord blood and tissue are subject to state licensure or registration and compliance with state requirements. Certain states regulate private cord blood and/or tissue banking activities, and may require us and our subcontractors engaged in

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specific manufacturing steps to become licensed, permitted or registered in such states. We believe that we are licensed, permitted or registered to operate in such states as required. If other states adopt similar requirements, we would have to obtain licenses, permits or registrations to continue providing services in those states.

Changes in government healthcare policy could increase our costs and negatively impact coverage and reimbursement for our tests by governmental and other third-party payers.

The U.S. government has shown significant interest in pursuing healthcare reform and reducing healthcare costs. Government healthcare policy has been and will likely continue to be a topic of extensive legislative and executive activity in the U.S. federal government and many U.S. state governments. As a result, our business could be affected by significant and potentially unanticipated changes in government healthcare policy, such as changes in reimbursement levels by government third-party payers. Any such changes could substantially impact our revenues, increase costs and divert management attention from our business strategy. Going forward, we cannot predict the full impact of governmental healthcare policy changes on our business, financial condition and results of operations.

In the United States, the Patient Protection and Affordable Care Act, as amended by the Healthcare and Education Reconciliation Act of 2010, or collectively, the PPACA, was signed into law in March 2010 and significantly impacted the U.S. pharmaceutical and medical device industries, including the diagnostics sector, in a number of ways. Among other things, the PPACA expanded healthcare fraud and abuse laws such as the False Claims Act and the Anti-Kickback Statute, including but not limited to required disclosures of financial arrangements with physician customers, required reporting of discovered overpayments, lower thresholds for violations, new government investigative powers, and enhanced penalties for such violations. The PPACA restricts insurers from charging higher premiums or denying coverage to individuals with pre-existing conditions, and requires insurers to cover certain preventative services without charging any copayment or coinsurance, including screening for lung, breast, colorectal and cervical cancers. However, there have been multiple attempts to repeal PPACA or significantly scale back its applicability, which could negatively impact reimbursement for our testing. This could adversely affect our test volumes and adversely affect our business, financial condition, results of operations, and cash flows. An example of an attempt to scale back PPACA came through the passing of the Tax Cuts and Jobs Act of 2017, or the Tax Act. The Tax Act repeals the individual mandate under PPACA, which required consumers to buy insurance or pay a penalty unless they qualified for an applicable exemption. The repeal of this mandate means that less consumers will carry insurance coverage and therefore may be less likely to elect to receive our testing because they would be required to pay out of pocket for such tests. This could also impact our test volumes and adversely affect our business, financial condition, results of operations, and cash flows. The PPACA also created a new system of health insurance "exchanges" designed to make health insurance available to individuals and certain groups through state- or federally-administered marketplaces in addition to existing channels for obtaining health insurance coverage. In connection with such exchanges, certain "essential health benefits" are intended to be made more consistent across plans, setting a baseline coverage level. The states (and the federal government) have some discretion in determining the definition of "essential health benefits" and we do not know whether Panorama or our other tests will fall into a benefit category deemed "essential" for coverage purposes across the plans offered in any or all of the exchanges. If Panorama or any of our other tests are not covered by plans offered in the health insurance exchanges, our business, financial condition and results of operations could be adversely affected. Furthermore, there have been a number of proposed legislative initiatives with respect to the PPACA, including possible repeal of the PPACA. These attempts have resulted in considerable uncertainty and concern regarding, for example, a patient's election to undergo genetic screening and whether doing so may impact health insurance eligibility. Because it is unclear whether or how the PPACA may change, and whether and to what extent NIPT, cancer screening or other genetic screening may be affected, we are uncertain how our business may be impacted.

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In addition to the PPACA, various healthcare reform proposals have also emerged from federal and state governments. The Protecting Access to Medicare Act of 2014, or PAMA, introduced a multi-year pricing program for services payable under the CLFS that is designed to bring Medicare allowable amounts in line with the amounts paid by private payers. The rule issued by CMS to implement PAMA required certain laboratories to report third-party payer rates and test volumes. Since January 1, 2018, the Medicare payment rate for these tests is equal to the weighted median private payer rate reported to CMS, which for many tests is lower than the previous CLFS payment rates due to the often lower negotiated private payer rates applicable to large commercial laboratories that were required to report data to CMS. While we believe that the new rates will have minimal impact on our business, the rates have been the subject of controversy in the industry, including a lawsuit by the American Clinical Laboratory Association, and it is unclear whether and to what extent the new rates may change. The implementation of the PAMA rates have negatively impacted overall pricing and reimbursement for many clinical laboratory testing services. In addition, federal budgetary limitations and changes in healthcare policy, such as the creation of broad limits for our tests and requirements that beneficiaries of government health plans pay for, or pay for higher portions of, clinical laboratory tests or services received, could substantially diminish the utilization of our tests, increase costs and adversely affect our ability to generate revenues and achieve profitability.

We cannot predict whether future healthcare initiatives will be implemented at the federal or state level or how any such future legislation, regulation or initiative may affect us. Current or potential future federal legislation and the expansion of government's role in the U.S. healthcare industry, as well as changes to the reimbursement amounts paid by third-party payers for our current and future tests, may adversely affect our test volumes and adversely affect our business, financial condition, results of operations, and cash flows.

If we or our laboratory distribution partners, consultants or commercial partners act in a manner that violates healthcare fraud and abuse laws or otherwise engage in misconduct, we may be subject to civil or criminal penalties.

We are subject to healthcare fraud and abuse regulation and enforcement by both the U.S. federal government and the states in which we conduct our business, including:

- HIPAA, which created federal civil and criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters and also imposes significant obligations with respect to maintenance of the privacy and security, and transmission, of individually identifiable health information;
- federal and state laws and regulations governing informed consent for genetic testing and the use of genetic material;
- federal and state laws and regulations governing the submission of claims, as well as billing and collection practices, for healthcare services;
- the federal Anti-Kickback Statute, which prohibits, among other things, the knowing and willful solicitation, receipt, offer or payment of remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as Medicare;
- the federal False Claims Act which prohibits, among other things, the presentation of false or fraudulent claims for payment from Medicare, Medicaid, or other government-funded third-party payers;
- federal laws and regulations governing the Medicare program, providers of services covered by the Medicare program, and the submission of claims to the Medicare program, as well as the

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Medicare Manuals issued by CMS and the local medical policies promulgated by the Medicare Administrative Contractors with respect to the implementation and interpretation of such laws and regulations;

- the federal Stark law, also known as the physician self-referral law, which, subject to certain exceptions, prohibits a physician from making a referral for certain designated health services covered by the Medicare program (and according to case law in some jurisdictions, the Medicaid program as well), including laboratory and pathology services, if the physician or an immediate family member has a financial relationship with the entity providing the designated health services;

- the federal Civil Monetary Penalties Law, which, subject to certain exceptions, prohibits, among other things, the offer or transfer of remuneration to a Medicare or state healthcare program beneficiary if the person knows or should know it is likely to influence the beneficiary's selection of a particular provider, practitioner or supplier of services reimbursable by Medicare or a state healthcare program;

- the prohibition on reassignment by the program beneficiary of Medicare claims to any party; and

- state law equivalents of the above U.S. federal laws, such as the Stark law, Anti-Kickback Statute and false claims laws, which may apply to items or services reimbursed by any third-party payer, including commercial insurers, and state data privacy and security laws and which may be more stringent than HIPAA.

Furthermore, a development affecting our industry is the increased enforcement of the federal False Claims Act and, in particular, actions brought pursuant to the False Claims Act's "whistleblower" or "qui tam" provisions. The False Claims Act imposes liability for, among other things, knowingly presenting, or causing to be presented, a false or fraudulent claim for payment by a federal governmental payer program. The qui tam provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government for violations of the False Claims Act and permit such individuals to share in any amounts paid by the defendant to the government in fines or settlement. When an entity is determined to have violated the False Claims Act, it is subject to mandatory damages of three times the actual damages sustained by the government, plus mandatory civil penalties of up to approximately $22,000 for each false claim. In addition, various states have enacted false claim laws analogous to the federal False Claims Act, and in some cases go even further because many of these state laws apply where a claim is submitted to any third-party payer and not merely a governmental payer program. As described further in Note 7—"Commitments and Contingencies—Legal Proceedings" in the Notes to Consolidated Financial Statements in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference, we have recently reached a settlement with the United States Department of Justice to resolve claims under a qui tam complaint regarding past reimbursement submissions. Although the settlement involved no admission of fault by us and no corporate integrity agreement, we cannot guarantee that we will not be subject to similar claims in the future.

Many of these laws and regulations have not been fully interpreted by regulatory authorities or the courts, and their provisions are open to a variety of interpretations. We have adopted policies and procedures designed to comply with these laws, and in the ordinary course of our business, we conduct internal reviews of our compliance with these laws. However, the rapid growth and expansion of our business both within and outside of the United States may increase the potential for violating these laws or our internal policies and procedures, and the uncertainty around the interpretation of these laws and regulations increases the risk that we may be found in violation of these or other laws and regulations, or of allegations of such violations, including pursuant to private qui tam actions brought by individual whistleblowers in the name of the government as described above. If our operations, including the conduct of our employees, distributors, consultants and commercial partners, are found to

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be in violation of any laws or regulations that apply to us, we may be subject to penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement of profits, exclusion from participation in government programs, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of pre-marketing product approvals, contractual damages, reputational harm, diminished profits and future earnings and the curtailment or restructuring of our operations, any of which could materially and adversely affect our business, financial condition and results of operations.

Failure to comply with privacy and security laws and regulations could result in fines, penalties and damage to our reputation and have a material adverse effect on our business.

The federal HIPAA privacy and security regulations, including the expanded requirements under the Health Information Technology for Economic and Clinical Health Act, or HITECH, which was enacted as part of the American Recovery and Reinvestment Act of 2009, establish comprehensive federal standards with respect to the use and disclosure of protected health information by health plans, healthcare providers, and healthcare clearinghouses, in addition to setting standards to protect the confidentiality, integrity and security of protected health information. The regulations establish a complex regulatory framework on a variety of subjects, including patient authorization of the use and disclosure of, administrative, technical and physical safeguards for, and analysis of security incidents and breach notification requirements with respect to, protected health information.

We have implemented policies and procedures related to compliance with the HIPAA regulations. The HIPAA privacy and security regulations establish minimum requirements, and do not supersede state laws that are more stringent. A number of states include medical information in the definition of personal information and have implemented requirements or standards more stringent than HIPAA. Therefore, we are required to comply with federal as well as various state privacy and security laws and regulations. HIPAA, as amended by HITECH, provides for significant fines and other penalties for wrongful use or disclosure of protected health information in violation of privacy and security regulations, including potential civil and criminal fines and penalties. We could also incur penalties, compliance costs as a result of non-compliance or damages under state laws pursuant to an action brought by a private party for the wrongful use or disclosure of confidential health information or other private personal information. In addition, other federal and state laws that protect the privacy and security of patient information may be subject to enforcement and interpretation by various governmental authorities and courts, resulting in complex compliance issues.

The European Union's new data privacy regulations, the General Data Protection Regulation, or GDPR, will become subject to enforcement in May 2018. These regulations comprehensively reform the prior data protection rules of the European Union, and are more stringent, provide for higher potential liabilities, and apply to a broader range of personal data than those in the United States. The GDPR is applicable to U.S.-based companies, such as ours, that do business or offer services in, or that process or hold personal data of data subjects in, the European Union. Our current processes and practices do not yet fully comply with the GDPR, and we are currently expending considerable time and resources, including management attention, to revise our practices and bring them into compliance. Furthermore, the GDPR enables EU member states to enact jurisdiction-specific requirements in key areas, which could require us to modify our plans to comply with the GDPR, or otherwise to implement multiple policies unique to the jurisdictions in which we operate, which could make it more difficult and resource-intensive to continue to operate in the European Union.

As we continue to expand and grow our business, our overall compliance with applicable laws and regulations may result in increased costs and attention of management, and failure to comply may result in significant fines, penalties and damage to our reputation. Additionally, the interpretation and application of health-related, privacy and data protection laws are often uncertain, contradictory and in flux, and it is possible that these laws may be interpreted and applied in a manner that is inconsistent

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with our practices. As a result, we could be subject to government-imposed fines or orders requiring that we change our practices, which could cause us to incur substantial costs and may adversely affect our business and our reputation.

Changes in the way the FDA regulates the reagents, other consumables, and testing equipment we use when developing, validating, and performing our tests could result in delay or additional expense in bringing our tests to market or performing such tests for our customers.

Many of the sequencers, reagents, kits and other consumable products used to perform our testing, as well as the instruments and other capital equipment that enable the testing, are offered for sale as analyte specific reagents, or ASRs, or for research use only, or RUO. In addition, we have recently launched Signatera (RUO) as a research use only offering. ASRs are medical devices and must comply with QSR provisions and other device requirements, but most are exempt from 510(k) and PMA premarket review. Products that are intended for research use only and are labeled as RUO are exempt from compliance with FDA requirements, including the approval or clearance and other product quality requirements for medical devices. A product labeled RUO but which is actually intended for clinical diagnostic use may be viewed by the FDA as adulterated and misbranded under the FDC Act and subject to FDA enforcement action. The FDA has said that when determining the intended use of a product labeled RUO, it will consider the totality of the circumstances surrounding distribution and use of the product, including how the product is marketed and to whom. The FDA could disagree with a supplier's assessment that the supplier's products are ASRs, or could conclude that products labeled as RUO are actually intended for clinical diagnostic use, and could take enforcement action against the supplier, such as us with respect to Signatera (RUO), including requiring the supplier to cease offering the product while it seeks clearance or approval. Suppliers of RUO products that we employ in our other tests may cease selling their respective products, and we may be unable to obtain an acceptable substitute on commercially reasonable terms or at all, which could significantly and adversely affect our ability to provide timely testing results to our customers or could significantly increase our costs of conducting business.

The sequencers and reagents supplied to us by Illumina and the blood collection tubes supplied to us by Streck are labeled as RUO in the United States. We are using these sequencers, reagents and blood collection tubes for clinical diagnostic use. If the FDA were to require clearance or approval for the sale of Illumina's sequencers and if Illumina does not obtain such clearance or approval, we would have to find an alternative sequencing platform for Panorama. We currently have not validated an alternative sequencing platform on which Panorama could be run in a commercially viable manner. If we were not successful in selecting, acquiring on commercially reasonable terms and implementing an alternative platform on a timely basis, our business, financial condition and results of operations would be adversely affected. Similarly, a decision by the FDA to require clearance or approval for the sale by Streck of the blood collection tubes used for Panorama, or a finding that any of our other suppliers failed to comply with applicable requirements, could result in interruptions in our ability to supply our products to the market and adversely affect our operations.

Our use of hazardous materials in the development of our tests exposes us to risks related to accidental contamination or injury and requires us to comply with regulations governing hazardous waste materials.

Our research and development activities involve the controlled use of hazardous materials and chemicals. We cannot eliminate the risk of accidental contamination or injury to employees or third parties from the use, storage, handling or disposal of these materials. In the event of contamination or injury, we could be held liable for any resulting damages, and any liability could exceed our resources or any applicable insurance coverage we may have. In addition, we are subject on an ongoing basis to federal, state and local regulations governing the use, storage, handling and disposal of these materials

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and specified hazardous waste materials. An increase in the costs of compliance with such laws and regulations could harm our business and results of operations.

If the validity of an informed consent from a patient intake for Panorama or our other tests is challenged, we could be precluded from billing for such testing, forced to stop performing such tests, or required to repay amounts previously received, which would adversely affect our business and financial results.

All clinical data and blood samples that we receive are required to have been collected from individuals who have provided appropriate informed consent for us to perform our testing, both commercially and in clinical trials. We seek to ensure that the individuals from whom the data and samples are collected do not retain or have conferred any proprietary or commercial rights to the data or any discoveries derived from them. Our partners operate in a number of different countries in addition to the United States, and, to a large extent, we rely upon them to comply with the individual's informed consent and with U.S. and international laws and regulations. The collection of data and samples in many different states and foreign countries results in complex legal questions regarding the adequacy of informed consent and the status of genetic material under a large number of different legal systems. The individual's informed consent obtained in any particular country could be challenged in the future, and those informed consents could be deemed invalid, unlawful or otherwise inadequate for our purposes. Any findings against us, or our partners, could deny us access to, or force us to stop testing samples in, a particular country or could call into question the results of our clinical trials. We could also be precluded from billing third-party payers for tests for which informed consents are challenged, or could be requested to refund amounts previously paid by third-party payers for such tests. We could become involved in legal challenges, which could require significant management and financial resources and adversely affect our revenues and results of operations.

Risks Related to Our Intellectual Property

Third-party claims of intellectual property infringement could result in litigation or other proceedings, which would be costly and time-consuming, and could limit our ability to commercialize our products or services.

Our success depends in part on our non-infringement of the patents or intellectual property rights of third parties. We operate in a crowded technology area in which there has been substantial litigation and other proceedings regarding patent and other intellectual property rights in the genetic diagnostics industry. Certain third parties, including our competitors, have asserted and may in the future assert that we are employing their proprietary technology without authorization or that we are otherwise infringing their intellectual property rights. In particular, Illumina has filed a patent infringement lawsuit against us alleging that our Panorama test infringes certain claims under U.S. Patent 9,493,831, as further described in "Commitments and Contingencies—Legal Proceedings" in Note 7 to our Consolidated Financial Statements in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference. We have in the past also been engaged in patent infringement litigation with Sequenom. The number of contested intellectual property proceedings may increase as the number of products and the level of competition in our industry segments grows. Defending against infringement claims is costly and may divert the attention of our management and technical personnel. If we are unsuccessful in defending against patent infringement claims, we could be required to stop developing or commercializing products or services; pay potentially substantial monetary damages; and/or obtain licenses from third parties, which we may be unable to do on acceptable terms, if at all, and which may require us to make substantial royalty payments. In addition, we could encounter delays in product introductions while we attempt to develop alternative non-infringing products. Any of these or other adverse outcomes could prevent us from offering our tests, which would have a material adverse effect on our business, financial condition and our results of operations.

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As we move into new markets and applications for our products, competitors in such markets may assert their patents and other proprietary rights against us as a means of blocking or slowing our entry into such markets or as a means to extract substantial license and royalty payments from us. Our competitors and others may have significantly stronger, larger and/or more mature patent portfolios than we have. In addition, future litigation may involve patent holding companies or other patent owners or licensees who have no relevant product revenues and against whom our own patents may provide little or no deterrence or protection.

In addition, our agreements with some of our customers, suppliers, and other entities with whom we do business require us to defend or indemnify these parties to the extent they become involved in infringement claims, including the types of claims described above. We could also voluntarily agree to defend or indemnify third parties if we determine it to be in the best interests of our business relationships. If we are required or agree to defend or indemnify third parties in connection with any infringement claims, we could incur significant costs and expenses that could adversely affect our business, financial condition and results of operations.

Any inability to effectively protect our proprietary technologies could harm our competitive position.

Our success and ability to compete depend to a large extent on our ability to develop proprietary products and technologies and to maintain adequate protection of our intellectual property in the United States and other countries. The laws of some foreign countries do not protect proprietary rights to the same extent as the laws of the United States, and many companies have encountered significant challenges in establishing and enforcing their proprietary rights outside of the United States. These challenges can be caused by the absence of rules and methods for the establishment and enforcement of intellectual property rights outside of the United States. In addition, the proprietary positions of companies developing and commercializing tools for molecular diagnostics, including ours, generally are uncertain and involve complex legal and factual questions. This uncertainty may materially affect our ability to defend or obtain patents or to address the patents and patent applications owned or controlled by our collaborators and licensors.

We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that our proprietary technologies are covered by valid and enforceable patents or are effectively maintained as trade secrets. Any finding that our patents or patent applications are unenforceable could harm our ability to prevent others from practicing the related technology. We cannot be certain that we were the first to invent the inventions covered by pending patent applications or that we were the first to file such applications, and a finding that others have claims of inventorship or ownership rights to our patents and applications could require us to obtain certain rights to practice related technologies, which may not be available on favorable terms, if at all. In addition, our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from practicing our technologies or from developing similar or alternative competing products or design around our patented technologies, and may therefore fail to provide us with any competitive advantage. Furthermore, as our issued patents expire, we may lose some competitive advantage as others develop competing products that would have been covered by the expired patents, and, as a result, we may lose revenue.

We may be required to file infringement lawsuits to protect our interests, which can be expensive and time-consuming. We cannot assure you that we would be successful in proving any such infringement by a third party, and we may become subject to counterclaims by such third parties. Our patents may be declared invalid or unenforceable, or narrowed in scope, as a result of such litigation. Some third-party infringers may have substantially greater resources than us and may be able to sustain the costs of complex infringement litigation more effectively than we can. Even if we prevail in an infringement action, we cannot assure you that we would be fully or partially financially compensated for any harm to our business. We may be forced to enter into a license or other agreement with the

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infringing third party on terms less profitable or otherwise less commercially acceptable to us than those negotiated between a willing licensee and a willing licensor. Any inability to stop third-party infringement could result in loss in market share of some of our products or lead to a delay, reduction and/or inhibition of our development, manufacture or sale of some of our products. A product produced and sold by a third-party infringer may not meet our or other regulatory standards or may not be safe for use, which could cause irreparable harm to the reputation of our products, which in turn could result in substantial loss in our market share and profits.

There is also the risk that others may independently develop similar or alternative technologies or design around our patented technologies, and our competitors or others may have filed, and may in the future file, conflicting patent claims covering technology similar or identical to ours. The costs associated with challenging conflicting patent claims could be substantial, and it is possible that our efforts would be unsuccessful and may result in a loss of our patent position and the issuance or validation of the competing claims. Should such competing claims cover our technology, we could be required to obtain rights to those claims at substantial cost

Certain of our intellectual property was partly supported by a U.S. government grant awarded by the National Institutes of Health, and the government accordingly has certain rights in this intellectual property, including a non-exclusive, non-transferable, irrevocable worldwide license to use applicable inventions for any governmental purpose. Such rights also include "march-in" rights, which refer to the right of the U.S. government to require us to grant a license to the technology to a responsible applicant if we fail to achieve practical application of the technology or if action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U.S. industry.

Any of these factors could adversely affect our ability to obtain commercially relevant or competitively advantageous patent protection for our products.

If we are not able to adequately protect our trade secrets and other proprietary information, the value of our technology and products could be significantly diminished.

We rely on trade secret protection and proprietary know-how protection for our confidential and proprietary information, and we have taken security measures to protect this information. These measures, however, may not provide adequate protection for our trade secrets, know-how, or other confidential information. For example, although we have a policy of requiring our consultants, advisors and collaborators to enter into confidentiality agreements and our employees to enter into invention, non-disclosure and non-compete agreements, we cannot assure you that such agreements will provide for a meaningful protection of our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure of information, including as a result of breaches of our physical or electronic security systems, or as a result of our employees failing to abide by their confidentiality obligations during or upon termination of their employment with us. Any action to enforce our rights is likely to be time-consuming and expensive, and may ultimately be unsuccessful, or may result in a remedy that is not commercially valuable. These risks are heightened in countries where laws or law enforcement practices may not protect proprietary rights as fully as in the United States or Europe. Any unauthorized use or disclosure of, or access to, our trade secrets, know-how or other proprietary information, whether accidentally or through willful misconduct, could have a material adverse effect on our programs and our strategy, and on our ability to compete effectively.

If our trademarks and trade names are not adequately protected, we may not be able to build name recognition in our markets of interest, and our business may be adversely affected.

Failure to maintain our trademark registrations, or to obtain new trademark registrations in the future, could limit our ability to protect our trademarks and impede our marketing efforts in the

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countries in which we operate. We may not be able to protect our rights to trademarks and trade names which we may need to build name recognition with potential partners or customers in our markets of interest. As a means to enforce our trademark rights and prevent infringement, we may be required to file trademark claims against third parties or initiate trademark opposition proceedings. This can be expensive, particularly for a company of our size, and time-consuming, and we may not be successful. Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented, declared generic or determined to be infringing on other marks.

Our pending trademark applications in the United States and in other foreign jurisdictions where we may file may not be allowed or may subsequently be opposed. Even if these applications result in registration of trademarks, third parties may challenge our use or registration of these trademarks in the future. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or diagnostic companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or willfully used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that our employees' former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims, and if we are unsuccessful, we could be required to pay substantial damages and could lose rights to important intellectual property. Even if we are successful, litigation could result in substantial costs to us and could divert the time and attention of our management and other employees.

Risks Related to Ownership of Our Common Stock

The market price of our common stock has been and may be volatile, which could subject us to litigation.

The trading prices of the securities of life sciences companies, including ours, have been and may continue to be highly volatile. Accordingly, the market price of our common stock is likely to be subject to wide fluctuations in response to numerous factors, many of which are beyond our control, such as those in this "Risk Factors" section and others including:

- actual or anticipated variations in our and our competitors' results of operations, as well as how those results compare to analyst and investor expectations;
- announcements by us or our competitors of new products, significant acquisitions, strategic and commercial partnerships and relationships, joint ventures, collaborations or capital commitments;
- changes in reimbursement practices by current or potential payers; for example, third-party payers are increasingly requiring that prior authorization be obtained prior to conducting genetic testing as a condition to reimbursing for it, which has reduced and/or delayed the reimbursement amounts we receive for Panorama or our other tests, which impacted our results of operations since the fourth quarter of 2017, when these requirements began to take effect;
- failure of analysts to initiate or maintain coverage of our company, issuance of new securities analysts' reports or changed recommendations for our stock;
- forward-looking statements related to our financial guidance or projections, our failure to meet or exceed our financial guidance or projections or changes in our financial guidance or projections;

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- periodic fluctuations in our revenue, due in part to the way in which we recognized revenue prior to transitioning to accrual accounting under ASC 606;
- actual or anticipated changes in regulatory oversight of our products;
- developments or disputes concerning our intellectual property or other proprietary rights;
- commencement of, or our involvement in, litigation;
- announcement or expectation of additional debt or equity financing efforts;
- sales of our common stock by us, our insiders or our other stockholders;
- any major change in our management; and
- general economic conditions and slow or negative growth of our markets.

In addition, if the market for life sciences stocks or the stock market in general experiences uneven investor confidence, the market price of our common stock could decline for reasons unrelated to our business, operating results or financial condition. The market price of our common stock might also decline in reaction to events that affect other companies within, or outside, our industry even if these events do not directly affect us. Some companies that have experienced volatility in the trading price of their stock have been the subject of securities class action litigation. For example, as described in Note 7—Commitments and Contingencies—Legal Proceedings" in the Notes to Consolidated Financial Statements, in our Quarterly Report on Form 10-Q for the three months ended March 31, 2018, which is incorporated by reference; a purported securities class action lawsuit had been filed against us, our directors and certain of our officers and stockholders. Under certain circumstances, we have contractual and other legal obligations to indemnify and to incur legal expenses on behalf of current and former directors and officers, and on behalf of our current or former underwriters, in connection with the litigation described in Note 7 in the Notes to Consolidated Financial Statements and in connection with any future lawsuits. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our offerings or business practices. Defending against litigation is costly and time-consuming, and could divert our management's attention and resources. Furthermore, during the course of litigation, there could be negative public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a material adverse effect on the market price of our common stock.

As a public company, we will continue to incur significantly increased costs and devote substantial management time.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. For example, we are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and are required to comply with the applicable requirements of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and the Dodd-Frank Wall Street Reform and Consumer Protection Act, as well as rules and regulations subsequently implemented by the SEC and the Nasdaq Global Select Market, including the establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. We expect that compliance with these requirements will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly. Our management and other personnel have limited experience managing a public company and preparing public filings. In addition, we expect that our management and other personnel will need to divert attention from operational and other business matters to devote substantial time to these public company requirements. In particular, we have incurred and expect to continue to incur

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significant expenses and devote substantial management effort toward ensuring compliance with the requirements of Section 404 of the Sarbanes-Oxley Act, which will increase when we are no longer an emerging growth company, as defined by the Jumpstart Our Businesses Act of 2012, or the JOBS Act. We hired, and we expect that we will need to continue to hire, additional accounting and financial staff with appropriate public company experience and technical accounting knowledge and may need to establish an internal audit function. We cannot predict or estimate the amount of additional costs we may incur as a public company or the timing of such costs. Additional compensation costs and any future equity awards will increase our compensation expense, which would increase our general and administrative expense and could adversely affect our profitability. Also, as a public company it is more expensive for us to obtain director and officer liability insurance on reasonable terms. As a result, it may be more difficult for us to attract and retain qualified people to serve on our board of directors, our board committees or as executive officers.

We are an emerging growth company and we cannot be certain if the reduced disclosure requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an emerging growth company. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

For as long as we continue to be an emerging growth company, we intend to take advantage of certain other exemptions from various reporting requirements that are applicable to other public companies including, but not limited to, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We cannot predict whether investors will find our common stock less attractive because we rely on these exemptions, which could result in a less active trading market for our common stock and increased volatility in our stock price.

We will remain an emerging growth company until the earliest of (a) the end of the fiscal year (i) following the fifth anniversary of the closing of our IPO, or December 31, 2020, (ii) in which the market value of our common stock that is held by non-affiliates exceeds $700 million and (iii) in which we have total annual gross revenues of $1.07 billion or more during such fiscal year, and (b) the date on which we issue more than $1 billion in non-convertible debt in a three-year period.

If we are unable to implement and maintain effective internal controls over financial reporting in the future, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our common stock could be adversely affected.

As a public company, we are required to maintain internal controls over financial reporting and to report any material weaknesses in such internal controls. Section 404 of the Sarbanes-Oxley Act requires that we evaluate and determine the effectiveness of our internal controls over financial reporting and provide a management report on internal controls over financial reporting. The Sarbanes-Oxley Act also requires that our management report on internal controls over financial reporting be attested to by our independent registered public accounting firm, to the extent we are no longer an emerging growth company. We do not expect to have our independent registered public accounting firm attest to our management report on internal controls over financial reporting for so long as we are an emerging growth company.

Although we have determined that our internal control over financial reporting was effective as of December 31, 2017, we must continue to monitor and assess our internal controls over financial

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reporting. If we have a material weakness in our internal controls over financial reporting, we may not detect errors on a timely basis and our financial statements may be materially misstated. If we identify material weaknesses in our internal controls over financial reporting, if we are unable to comply with the requirements of Section 404 in a timely manner, if we are unable to assert that our internal controls over financial reporting are effective, or, when required in the future, if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal controls over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our common stock could be adversely affected, and we could become subject to investigations by the stock exchange on which our securities are listed, the SEC, or other regulatory authorities.

We do not intend to pay dividends on our capital stock so any returns will be limited to changes in the value of our common stock.

We have never declared or paid any cash dividends on our capital stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. In addition, our ability to pay cash dividends on our capital stock may be prohibited or limited by the terms of any current or future debt financing arrangement. Any return to stockholders will therefore be limited to the increase, if any, in the price of our common stock.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans or in connection with acquisitions or strategic or commercial transactions, could result in additional dilution of the percentage ownership of our stockholders and could cause the price of our common stock to decline.

In the future, we may issue additional securities or sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. We also expect to issue common stock to employees and directors pursuant to our equity incentive plans. If we sell or issue common stock, convertible securities or other equity securities in subsequent transactions, or common stock is issued pursuant to equity incentive plans, investors may be materially diluted. We may decide to issue common stock or other equity securities in connection with an acquisition or a strategic or commercial transaction, which could cause dilution to our existing stockholders. New investors in such subsequent transactions could gain rights, preferences and privileges senior to those of holders of our common stock.

Sales of a substantial number of shares of our common stock in the public markets could cause the price of our common stock to decline.

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

Certain holders of shares of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act of 1933, as amended, or the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares held by our affiliates as defined in Rule 144 under the Securities Act. Any sales of securities by these stockholders could adversely affect the trading price of our common stock.

We may issue our shares of common stock or securities convertible into our common stock from time to time in connection with a financing, acquisition, investments or otherwise. Any such issuance

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could result in substantial dilution to our existing stockholders and cause the trading price of our common stock to decline.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our stock price and trading volume could decline.

The trading market for our common stock depends in part on the research and reports that securities or industry analysts publish about us or our business. Currently, only a small number of securities analysts cover our stock. If more analysts do not commence coverage of us, or if industry analysts cease coverage of us or fail to publish reports on us regularly, the trading price for our common stock could be adversely affected. If one or more of the analysts who cover us downgrade our common stock or publish inaccurate or unfavorable research about our business, our common stock price would likely decline.

Insiders have substantial control over us and will be able to influence corporate matters.

As of March 31, 2018, our directors and executive officers and their affiliates beneficially own, in the aggregate, approximately 47.6% of our outstanding capital stock. As a result, these stockholders will be able to exercise significant influence over all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions, such as a merger or other sale of our company or its assets. This concentration of ownership could limit stockholders' ability to influence corporate matters and may have the effect of delaying or preventing a third party from acquiring control over us.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws and Delaware law might discourage, delay or prevent a change in control of our company or changes in our management and, therefore, depress the market price of our common stock.

Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could depress the market price of our common stock by acting to discourage, delay or prevent a change in control of our company or changes in our management that the stockholders of our company may deem advantageous. These provisions, among other things:

- authorize the issuance of "blank check" preferred stock that our board of directors could use to implement a stockholder rights plan;
- prohibit stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders;
- eliminate the ability of our stockholders to call special meetings of stockholders;
- establish advance notice requirements for nominations for election to our board of directors or for proposing matters that can be acted upon by stockholders at annual stockholder meetings;
- establish a classified board of directors so that not all members of our board are elected at one time;
- permit the board of directors to establish the number of directors;
- provide that directors may only be removed "for cause" and only with the approval of 75% of our stockholders;
- require super-majority voting to amend some provisions in our amended and restated certificate of incorporation and amended and restated bylaws; and
- provide that the board of directors is expressly authorized to make, alter or repeal our amended and restated bylaws.

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In addition, Section 203 of the Delaware General Corporation Law may discourage, delay or prevent a change in control of our company. Section 203 imposes certain restrictions on mergers, business combinations and other transactions between us and holders of 15% or more of our common stock.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law or any action asserting a claim against us that is governed by the internal affairs doctrine. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees and may discourage these types of lawsuits. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, financial condition and results of operations.

Risks Relating to This Offering

Our management team may invest or spend the net proceeds of this offering in ways with which you may not agree or in ways which may not yield a significant return.

Our management will have broad discretion over the use of the net proceeds from this offering. We intend to use the net proceeds from the sale of common stock offered by this prospectus supplement for working capital and general corporate purposes and continued investments in research and development for our core technology and development of our product offerings. We do not currently have any commitments with regard to any such acquisitions or other strategic transactions. Our management will have considerable discretion in the application of the net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. The net proceeds may be used for working capital and corporate purposes that do not increase our operating results or enhance the value of our ordinary shares.

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USE OF PROCEEDS

We estimate that the net proceeds to us from the issuance of our common stock in this offering, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, will be approximately $83.9 million, or approximately $96.6 million if the underwriters exercise their option to purchase additional shares in full.

We currently intend to use the net proceeds from this offering for working capital and general corporate purposes and continued investments in research and development for our core technology and development of our product offerings. In addition, we may use a portion of the net proceeds for acquisitions of complementary businesses, technologies or other assets. However, we have no current understandings, agreements or commitments for any material acquisitions at this time. We have not yet determined the manner in which we will allocate the net proceeds from this offering, and as a result, management will have broad discretion in the allocation and use of the net proceeds. Pending the application of the net proceeds, we intend to invest the net proceeds in short-term, interest-bearing, investment-grade securities.

PRICE RANGE OF OUR COMMON STOCK

Our common stock is listed on The Nasdaq Global Select Market under the symbol "NTRA." The following table summarizes the high and low closing sales prices for our common stock as reported by The Nasdaq Global Select Market for the period indicated:

	High	Low
Year Ended December 31, 2016		
First quarter	$ 10.46	$ 6.61
Second quarter	$ 13.79	$ 9.37
Third quarter	$ 13.28	$ 9.53
Fourth quarter	$ 12.86	$ 8.02
Year Ended December 31, 2017		
First quarter	$ 11.90	$ 7.86
Second quarter	$ 11.94	$ 7.50
Third quarter	$ 13.33	$ 8.02
Fourth quarter	$ 14.31	$ 8.99
Year Ended December 31, 2018		
First quarter	$ 12.06	$ 11.57
Second quarter	$ 19.98	$ 8.79
Third quarter (through July 11, 2018)	$ 21.04	$ 18.82

The last reported sale price for our common stock on The Nasdaq Global Select Market on July 11, 2018 was $20.58. As of December 31, 2017, we had 30 holders of record of our common stock.

DIVIDEND POLICY

No cash dividends have ever been paid or declared on our common stock. We currently intend to retain all future earnings, if any, for use in our business and do not anticipate paying any cash dividends on our common stock in the foreseeable future. Any future determination to declare cash dividends will be made at the discretion of our board of directors, subject to applicable laws, and will depend on our financial condition, results of operations, capital requirements, general business conditions and other factors our board of directors may deem relevant. Our credit agreement with OrbiMed Royalty Opportunities II, LP, or OrbiMed, restricts our ability to pay cash dividends on our common stock, and we may also enter into credit agreements or other borrowing arrangements in the future that may further restrict our ability to declare or pay cash dividends on our common stock.

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CAPITALIZATION

The following table sets forth our cash and cash equivalents, short-term debt financing and capitalization as of March 31, 2018, as follows:

- on an actual basis; and
- on an as adjusted basis to give effect to the issuance and sale by us of 4,500,000 shares in this offering, and the receipt of the net proceeds from our sale of these shares, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us (assuming no exercise of the underwriters' option to purchase additional shares).

You should read this table in conjunction with the sections titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our condensed financial statements and related notes appearing in our Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and our Annual Report on Form 10-K for the year ended December 31, 2017, each of which is incorporated by reference in this prospectus supplement.

	As of March 31, 2018	
	Actual	As Adjusted
	(in thousands, except share and per share data) (unaudited)	
Cash and cash equivalents	$ 33,674	$ 117,574
Short-term debt financing	$ 50,125	$ 50,125
Long-term debt financing	$ 73,138	$ 73,138
Stockholders' equity		
Preferred stock, par value $0.0001 per share: 50,000,000 shares authorized, no shares issued and outstanding, actual and as adjusted	—	—
Common stock, par value $0.0001 per share: 750,000,000 shares authorized, 54,249,507 shares issued and outstanding, actual and 750,000,000 shares authorized, 58,749,507 shares issued and outstanding, as adjusted	6	6
Additional paid-in capital	476,270	560,170
Accumulated deficit	(479,248)	(479,248)
Accumulated other comprehensive loss	(904)	(904)
Total stockholders' (deficit) equity	(3,876)	80,024
Total capitalization	$ 69,262	$ 153,162

The number of shares in the table above excludes as of March 31, 2018:

- 376,691 shares of common stock issuable upon the exercise of warrants outstanding as of March 31, 2018, with a weighted-average exercise price of $2.32 per share;
- 1,013,903 shares of common stock issuable upon the vesting and settlement of restricted stock units outstanding as of March 31, 2018;
- 10,731,571 shares of common stock issuable upon the exercise of options outstanding as of March 31, 2018, with a weighted-average exercise price of $6.76 per share;
- 308,300 shares of common stock issuable upon the exercise of options granted after March 31, 2018, with an exercise price of $10.70 per share;
- 82,600 shares of common stock issuable upon the vesting and settlement of restricted stock units granted after March 31, 2018; and

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- 18,195,505 shares of common stock, subject to increase on an annual basis, reserved for future grant or issuance under our stock-based compensation plans, consisting of:

  - 16,518,565 shares of common stock as of March 31, 2018 reserved for future grants under our 2015 Equity Incentive Plan, or the 2015 Plan; and

  - 1,676,940 shares of common stock as of March 31, 2018 reserved for future issuance under our 2015 Employee Stock Purchase Plan, or the 2015 ESPP.

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CERTAIN MATERIAL U.S. FEDERAL INCOME TAX CONSIDERATIONS FOR NON-U.S. HOLDERS

The following is a discussion of certain material U.S. federal income tax considerations with respect to the ownership and disposition of shares of common stock applicable to non-U.S. holders who acquire such shares in this offering and hold such shares as a capital asset within the meaning of Section 1221 of the Internal Revenue Code of 1986, as amended, or the Code, (generally, property held for investment). For purposes of this discussion, a "non-U.S. holder" means a beneficial owner of our common stock (other than an entity or arrangement that is treated as a partnership for U.S. federal income tax purposes) that is not, for U.S. federal income tax purposes, any of the following:

- an individual citizen or resident of the United States;
- a corporation (or other entity treated as a corporation for U.S. federal income tax purposes) created or organized in the United States or under the laws of the United States, any state thereof or the District of Columbia, or any other corporation treated as such;
- an estate, the income of which is includable in gross income for U.S. federal income tax purposes regardless of its source; or
- a trust if (i) a court within the United States is able to exercise primary supervision over the administration of the trust and one or more "U.S. persons," as defined under the Code, have the authority to control all substantial decisions of the trust or (ii) such trust has made a valid election to be treated as a U.S. person for U.S. federal income tax purposes.

This discussion is based on current provisions of the Code, Treasury regulations promulgated thereunder, judicial opinions, published positions of the Internal Revenue Service and other applicable authorities, all of which are subject to change (possibly with retroactive effect). This discussion does not address all aspects of U.S. federal income taxation that may be important to a particular non-U.S. holder in light of that non-U.S. holder's individual circumstances, nor does it address any aspects of the unearned income Medicare contribution tax pursuant to the Health Care and Education Reconciliation Act of 2010, any U.S. federal estate and gift taxes, any U.S. alternative minimum taxes or any state, local or non-U.S. taxes. This discussion may not apply, in whole or in part, to particular non-U.S. holders in light of their individual circumstances or to holders subject to special treatment under the U.S. federal income tax laws (such as insurance companies, tax-exempt organizations, financial institutions, brokers or dealers in securities, "controlled foreign corporations," "passive foreign investment companies," non-U.S. holders that hold our common stock as part of a straddle, hedge, conversion transaction or other integrated investment and certain U.S. expatriates).

If a partnership (or other entity or arrangement treated as a partnership for U.S. federal income tax purposes) holds our common stock, the tax treatment of a partner therein will generally depend on the status of the partner and the activities of the partnership. Partners of a partnership holding our common stock should consult their tax advisor as to the particular U.S. federal income tax consequences applicable to them.

THIS SUMMARY IS NOT INTENDED TO CONSTITUTE A COMPLETE DESCRIPTION OF ALL TAX CONSEQUENCES FOR NON-U.S. HOLDERS RELATING TO THE OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK. PROSPECTIVE HOLDERS OF OUR COMMON STOCK SHOULD CONSULT WITH THEIR TAX ADVISORS REGARDING THE TAX CONSEQUENCES TO THEM (INCLUDING THE APPLICATION AND EFFECT OF ANY STATE, LOCAL, FOREIGN INCOME AND OTHER TAX LAWS) OF THE OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK.

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Dividends

In general, the gross amount of any distribution we make to a non-U.S. holder with respect to its shares of common stock will be subject to U.S. withholding tax at a rate of 30% to the extent the distribution constitutes a dividend for U.S. federal income tax purposes, unless the non-U.S. holder is eligible for a reduced rate of withholding tax under an applicable tax treaty and the non-U.S. holder provides proper certification of its eligibility for such reduced rate. A distribution will constitute a dividend for U.S. federal income tax purposes to the extent of our current or accumulated earnings and profits as determined for U.S. federal income tax purposes. To the extent any distribution does not constitute a dividend, it will be treated first as reducing the adjusted basis in the non-U.S. holder's shares of common stock and then, to the extent it exceeds the adjusted basis in the non-U.S. holder's shares of common stock, as gain from the sale or exchange of such stock. Any such gain will be subject to the treatment described in "—Gain on Sale or Other Disposition of Common Stock."

Dividends we pay to a non-U.S. holder that are effectively connected with its conduct of a trade or business within the United States (and, if required by an applicable tax treaty, are attributable to a U.S. permanent establishment of such non-U.S. holder) will not be subject to U.S. withholding tax, as described above, if the non-U.S. holder complies with applicable certification and disclosure requirements. Instead, such dividends generally will be subject to U.S. federal income tax on a net income basis, at regular U.S. federal income tax rates. Dividends received by a foreign corporation that are effectively connected with its conduct of trade or business within the United States may be subject to an additional branch profits tax at a rate of 30% (or such lower rate as may be specified by an applicable tax treaty).

Gain on Sale or Other Disposition of Common Stock

In general, a non-U.S. holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other disposition of the non-U.S. holder's shares of common stock unless:

- the gain is effectively connected with a trade or business carried on by the non-U.S. holder within the United States (and, if required by an applicable tax treaty, is attributable to a U.S. permanent establishment of such non-U.S. holder);
- the non-U.S. holder is an individual and is present in the United States for 183 days or more in the taxable year of disposition and certain other conditions are met; or
- we are or have been a U.S. real property holding corporation for U.S. federal income tax purposes at any time within the shorter of the five-year period preceding such disposition or such non-U.S. holder's holding period of our common stock.

Gain that is effectively connected with the conduct of a trade or business in the United States (or so treated) generally will be subject to U.S. federal income tax on a net income tax basis, at regular U.S. federal income tax rates. If the non-U.S. holder is a foreign corporation, the branch profits tax described above also may apply to such effectively connected gain. An individual non-U.S. holder who is subject to U.S. federal income tax because the non-U.S. holder was present in the United States for 183 days or more during the year of sale or other disposition of our common stock will be subject to a flat 30% tax on the gain derived from such sale or other disposition, which may be offset by U.S.-source capital losses. We believe that we are not, and we do not anticipate becoming, a U.S. real property holding corporation for U.S. federal income tax purposes.

Withholdable Payments to Foreign Financial Entities and Other Foreign Entities

Under the Foreign Account Tax Compliance Act, or FATCA, withholding tax of 30% applies to certain payments to foreign financial institutions, investment funds and certain other non-U.S. persons that fail to comply with certain information reporting and certification requirements pertaining to their

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direct and indirect U.S. securityholders and/or U.S. accountholders and do not otherwise qualify for an exemption. Such payments include dividends with respect to our common stock and, beginning after December 31, 2018, the gross proceeds from the sale or other disposition of our common stock. Prospective investors are encouraged to consult with their own tax advisors regarding the possible implications of FATCA on their investment in our common stock.

Backup Withholding, Information Reporting and Other Reporting Requirements

We must report annually to the Internal Revenue Service and to each non-U.S. holder the amount of dividends paid to, and the tax withheld with respect to, each non-U.S. holder. These reporting requirements apply regardless of whether withholding was reduced or eliminated by an applicable tax treaty. Copies of this information reporting may also be made available under the provisions of a specific tax treaty or agreement with the tax authorities in the country in which the non-U.S. holder resides or is established.

A non-U.S. holder will generally be subject to backup withholding for dividends on our common stock paid to such holder unless such holder certifies under penalties of perjury that, among other things, it is a non-U.S. holder (and the payer does not have actual knowledge or reason to know that such holder is a U.S. person) or otherwise establishes an exemption.

Information reporting and backup withholding generally are not required with respect to the amount of any proceeds from the sale or other disposition of our common stock by a non-U.S. holder outside the United States through a foreign office of a foreign broker that does not have certain specified connections to the United States. However, if a non-U.S. holder sells or otherwise disposes of its shares of common stock through a U.S. broker or the U.S. offices of a foreign broker, the broker will generally be required to report the amount of proceeds paid to the non-U.S. holder to the Internal Revenue Service and also backup withhold on that amount unless such non-U.S. holder provides appropriate certification to the broker of its status as a non-U.S. person (and the payer does not have actual knowledge or reason to know that such holder is a U.S. person) or otherwise establishes an exemption. Information reporting will also apply if a non-U.S. holder sells its shares of common stock through a foreign broker deriving more than a specified percentage of its income from U.S. sources or having certain other connections to the United States, unless such broker has documentary evidence in its records that such non-U.S. holder is a non-U.S. person (and the payer does not have actual knowledge or reason to know that such holder is a U.S. person) and certain other conditions are met, or such non-U.S. holder otherwise establishes an exemption.

Backup withholding is not an additional income tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder generally can be credited against the non-U.S. holder's U.S. federal income tax liability, if any, or refunded, provided that the required information is furnished to the Internal Revenue Service in a timely manner. Non-U.S. holders should consult their tax advisors regarding the application of the information reporting and backup withholding rules to them.

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UNDERWRITING

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom J.P. Morgan Securities LLC, Morgan Stanley & Co. LLC and Cowen and Company, LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

Name	Number of Shares
J.P. Morgan Securities LLC	1,800,000
Morgan Stanley & Co. LLC	1,800,000
Cowen and Company, LLC	900,000
Total:	4,500,000

The underwriters and the representatives are collectively referred to as the "underwriters" and the "representatives," respectively. The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus supplement are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus supplement if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus supplement and part to certain dealers. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives. Sales of shares made outside of the United States may be made by affiliates of the underwriters.

We have granted to the underwriters an option to purchase additional shares, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 675,000 additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. To the extent the option to purchase additional shares is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional 675,000 shares of common stock.

		Total	
	Per Share	No Exercise	Full Exercise
Public offering price	$ 20.00	$ 90,000,000	$ 103,500,000
Underwriting discounts and commissions	$ 1.20	$ 5,400,000	$ 6,210,000
Proceeds, before expenses, to us	$ 18.80	$ 84,600,000	$ 97,290,000

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately $0.7 million.

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Our common stock is listed on the Nasdaq Global Select Market under the trading symbol "NTRA."

We and our directors and officers and certain holders of our outstanding stock and stock options have agreed that, without the prior written consent of J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC on behalf of the underwriters, we and they will not, during the period ending 60 days after the date of this prospectus supplement (the "restricted period"):

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for shares of common stock; or

- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise. In addition, without the prior written consent of J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC on behalf of the underwriters, (i) our directors and officers and such holders will not, during the restricted period, make any demand for, or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock and (ii) we will not file any registration statement with the Securities and Exchange Commission relating to the offering of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock. In addition, our directors and officers and such holders agreed and consented to the entry of stop transfer instructions with our transfer agent and registrar against the transfer of each such person's shares of common stock except in compliance with the below restrictions.

The restrictions described in the immediately preceding paragraph to do not apply to:

- the sale of shares pursuant to the underwriting agreement;

- the issuance of common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of and disclosed in this prospectus supplement;

- our issuance of common stock or restricted stock units pursuant to employee benefit plans described in this prospectus supplement; provided that if such shares or other securities vest during the restricted period, the recipient signs and delivers a lock-up agreement;

- transactions by a securityholder relating to shares of common stock or other securities acquired in open market transactions after the completion of the offering of the shares; provided that no filing under Section 16(a) of the Securities Exchange Act of 1934, as amended, or (the "Exchange Act"), is required or voluntarily made in connection with subsequent sales of the common stock or other securities acquired in such open market transactions;

- the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required or voluntarily made by or on behalf of the person or us regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period;

- the sale of shares of common stock pursuant to a 10b5-1 trading plan (provided that such plan was established prior to the execution of the lockup agreement); provided that any filing under Section 16(a) of the Exchange Act that is made in connection with any such sales during the

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restricted period shall state that such sales have been executed under a 10b5-1 trading plan and shall also state the date such 10b5-1 trading plan was adopted;

- transfers of shares of common stock or any security convertible into or exercisable or exchangeable for common stock (i) as a bona fide gift, charitable contribution, will, or intestacy (ii) to an immediate family member or a trust for the direct or indirect benefit of the transferor or such immediate family of the transferor, (iii) to any corporation, partnership, or business entity controlled or managed, or under common control or management by the transferor or the immediate family of the transferor, or (iv) by a stockholder that is a trust to a trustor or beneficiary of the trust or to the estate of a beneficiary of such trust, provided in each case that (a) each donee, transferee or distributee signs and delivers a lock-up agreement and (b) no filing under Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of shares shall be required or voluntarily made during the restricted period (other than a filing on a Form 5);

- the exercise of options to purchase common stock granted under any stock incentive plan or stock purchase plan described in this prospectus supplement, provided that the underlying shares shall continue to be subject to the restrictions on transfer set forth in the lock-up agreement and provided further that if any filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made during the restricted period (other than a filing on a Form 5) such filing shall clearly indicate in the footnotes thereto that no shares were sold by the transferor and that the shares received upon exercise of the stock option are subject to a lock-up agreement with the underwriters;

- the transfer of common stock or any security convertible into common stock to us upon a vesting event of our securities or upon the exercise of options to purchase our securities on a "cashless" or "net exercise" basis or to cover tax withholding obligations of the transferor in connection with such vesting or exercise, provided that if any filing under Section 16(a) of the Exchange Act reporting a disposition of shares of common stock or other public announcement shall be required or shall be made voluntarily in connection with such vesting or exercise, such filing shall clearly indicate in the footnotes thereto that such disposition of shares was solely to us;

- the sale of shares of common stock underlying restricted stock units that are vested and settled to satisfy income tax withholding and remittance obligations in connection with the vesting of such restricted stock units that are outstanding as of the date of the prospectus supplement; provided that any filing required under Section 16 of the Exchange Act required in connection with such sale indicates that the transfer is to satisfy income tax withholding and remittance obligations in connection with the vesting of restricted stock units, provided that the aggregate number of shares of common stock that may be sold pursuant to this paragraph will not exceed 15,000 shares;

- the transfer of common stock or any security convertible into common stock pursuant to agreements under which we have the option to repurchase such shares or a right of first refusal with respect to transfers of such shares;

- the transfer of common stock or any security convertible into common stock that occurs pursuant to a qualified domestic order or in connection with a divorce settlement, provided that each transferee signs and delivers a lock-up agreement and provided further that any filing required to be made under Section 16(a) of the Exchange Act shall state that such transfer is by operation of law, pursuant to a qualified domestic order or in connection with a divorce settlement;

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- the transfer of shares of common stock or any security convertible into common stock pursuant to a bona fide third party tender offer, merger, consolidation or other similar transaction made to all holders of the common stock involving a involving a change of control of the company, provided that in the event that the tender offer, merger, consolidation or other such transaction is not completed, the common stock owned by the signatory shall remain subject to the restrictions on transfer set forth in the lock-up agreement; and

- our sale or issuance of or entry into an agreement to sell or issue shares of common stock in connection with our acquisition of one or more businesses, products or technologies or in connection with joint ventures, commercial relationships or other strategic transactions; provided that (i) the aggregate number of shares of common stock that we may sell or issue or agree to sell or issue may not exceed 5% of the total number of shares of common stock outstanding immediately following the closing of the offering and (ii) each recipient of these shares of common stock executes and delivers a lock-up agreement.

J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above at any time.

In order to facilitate this offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the option to purchase additional shares. The underwriters can close out a covered short sale by exercising the option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the option to purchase additional shares. The underwriters may also sell shares in excess of the option to purchase additional shares, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

In addition, in connection with this offering certain of the underwriters (and selling group members) may engage in passive market making transactions in our common stock on The Nasdaq Global Select Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on The Nasdaq Global Select Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are generally limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of these transactions. If passive market making is commenced, it may be discontinued at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

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A prospectus supplement in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The representatives may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus supplement in any jurisdiction where action for that purpose is required. The securities offered by this prospectus supplement may not be offered or sold, directly or indirectly, nor may this prospectus supplement or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus supplement comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus supplement. This prospectus supplement does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus supplement in any jurisdiction in which such an offer or a solicitation is unlawful.

Selling Restrictions

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State") an offer to the public of any shares of our common stock may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of any shares of our common stock may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Member State:

(a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

(b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares of our common stock shall result in a requirement for the

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publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer to the public" in relation to any shares of our common stock in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of our common stock to be offered so as to enable an investor to decide to purchase any shares of our common stock, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression "Prospectus Directive" means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State, and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

United Kingdom

This document is only being distributed to and is only directed at (i) persons who are outside the United Kingdom or (ii) to investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the "Order") or (iii) high net worth entities, and other persons to whom it may lawfully be communicated, falling with Article 49(2)(a) to (d) of the Order (all such persons together being referred to as "relevant persons"). The securities are only available to, and any invitation, offer or agreement to subscribe, purchase or otherwise acquire such securities will be engaged in only with, relevant persons. Any person who is not a relevant person should not act or rely on this document or any of its contents.

Hong Kong

The shares may not be offered or sold by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), or (ii) to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Singapore

This prospectus supplement and the accompanying prospectus have not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA"), (ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

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Where the shares are subscribed or purchased under Section 275 by a relevant person which is: (a) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest in that trust shall not be transferable for six months after that corporation or that trust has acquired the shares under Section 275 except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275 (1A), and in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is given for the transfer; or (3) by operation of law.

Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (the "Financial Instruments and Exchange Law") and the underwriter has agreed that it not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission (the "ASIC"), in relation to the offering. This prospectus supplement does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001 (the "Corporations Act"), and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the securities may only be made to persons (the "Exempt Investors") who are "sophisticated investors" (within the meaning of section 708(8) of the Corporations Act), "professional investors" (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the securities without disclosure to investors under Chapter 6D of the Corporations Act.

The securities applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring securities must observe such Australian on-sale restrictions.

This prospectus supplement contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this prospectus supplement is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

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Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange (the "SIX") or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company, the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes ("CISA"). The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Dubai International Financial Centre

This prospectus supplement and the accompanying prospectus relate to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority (the "DFSA"). This prospectus supplement and the accompanying prospectus are intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus supplement or the accompanying prospectus nor taken steps to verify the information set forth herein and has no responsibility for this prospectus supplement or the accompanying prospectus. The shares to which this prospectus supplement and the accompanying prospectus relate may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus supplement and the accompanying prospectus you should consult an authorized financial advisor.

Notice to Prospective Investors in Canada

The shares of our common stock may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of the shares of our common stock must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting*

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Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

LEGAL MATTERS

The validity of the shares of common stock offered by this prospectus supplement will be passed upon for us by Gunderson Dettmer Stough Villeneuve Franklin & Hachigian, LLP, Redwood City, California. Davis Polk & Wardwell LLP, Menlo Park, California is representing the underwriters in this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2017, as set forth in their report, which is incorporated by reference in this prospectus supplement and the accompanying prospectus. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

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PROSPECTUS

NATERA, INC.

COMMON STOCK
PREFERRED STOCK
DEPOSITARY SHARES
DEBT SECURITIES
WARRANTS
UNITS

We may offer and sell from time to time, in one or more offerings, in amounts, at prices and on terms determined at the time of any such offering, (1) shares of our common stock, (2) shares of our preferred stock, which we may issue in one or more series, (3) depositary shares representing preferred stock, (4) debt securities, which may be senior debt securities or subordinated debt securities, (5) warrants or (6) units.

Our common stock is listed on the NASDAQ Global Select Market under the symbol "NTRA."

We urge you to read carefully this prospectus and the accompanying prospectus supplement, which will describe the specific terms of the securities being offered to you, before you make your investment decision.

INVESTING IN OUR SECURITIES INVOLVES SIGNIFICANT RISKS. SEE "RISK FACTORS" ON PAGE 3 OF THIS PROSPECTUS AND IN THE APPLICABLE PROSPECTUS SUPPLEMENT AND IN THE OTHER DOCUMENTS INCORPORATED BY REFERENCE HEREIN BEFORE INVESTING IN ANY SECURITIES.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS OR THE ACCOMPANYING PROSPECTUS SUPPLEMENT IS TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

This prospectus may not be used to sell securities unless accompanied by a prospectus supplement.

The date of this prospectus is November 28, 2016.

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Unless otherwise indicated or the context otherwise requires, all references in this prospectus to "Natera," "the company," "we," "our," "us" or similar terms refer to Natera, Inc., together with its subsidiaries.

ABOUT THIS PROSPECTUS

This prospectus is part of a "shelf" registration statement that we filed with the Securities and Exchange Commission (the "Commission" or "SEC"). By using a shelf registration statement, we may sell, from time to time, in one or more offerings, any combination of the securities described in this prospectus.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The accompanying prospectus supplement may also add, update or change information contained in this prospectus. References to the "applicable prospectus supplement" are to the prospectus supplement to this prospectus that describes the specific terms and conditions of the applicable security. You should read both this prospectus and the accompanying prospectus supplement together with additional information described under the heading "Where You Can Find More Information."

We may include agreements as exhibits to the registration statement of which this prospectus forms a part. In reviewing such agreements, please remember that they are included to provide you with information regarding their terms and are not intended to provide any other factual or disclosure information about us or the other parties to the agreements. The agreements may contain representations and warranties by each of the parties to the applicable agreement. These representations and warranties have been made solely for the benefit of the other parties to the applicable agreement and:

- should not in any instance be treated as categorical statements of fact, but rather as a way of allocating the risk to one of the parties if those statements prove to be inaccurate;
- may have been qualified by disclosures that were made to the other party in connection with the negotiation of the applicable agreement, which disclosures would not necessarily be reflected in the agreement;
- may apply standards of materiality in a way that is different from what may be viewed as material to you or other investors; and
- were made only as of the date of the applicable agreement or such other date or dates as may be specified in the agreement and are subject to more recent developments.

Accordingly, these representations and warranties may not describe the actual state of affairs as of the date they were made or at any other time. Additional information about us may be found elsewhere in the registration statement of which this prospectus forms a part and our other public filings, which are available without charge through the SEC's website at http://www.sec.gov.

We have not authorized any other person, including any dealer, salesperson or other individual, to provide you with any information or to make any representations other than those contained or incorporated by reference in this prospectus. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are not making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information in this prospectus and the documents incorporated by reference is accurate only as of their respective dates.

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WHERE YOU CAN FIND MORE INFORMATION

We file reports, proxy statements, and other information with the SEC. Such reports, proxy statements, and other information concerning us can be read and copied at the SEC's Public Reference Room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549 or on the Internet at http://www.sec.gov. Please call the SEC at 1-800-SEC-0330 for further information on the Public Reference Room. Our common stock is listed on the NASDAQ Global Select Market, and these reports, proxy statements and other information are also available for inspection at the offices of the NASDAQ Stock Market, Inc. located at 1735 K Street, NW, Washington, D.C. 20006.

This prospectus is part of a registration statement filed with the SEC by us. The full registration statement can be obtained from the SEC as indicated above, or from us.

The SEC allows us to "incorporate by reference" the information we file with the SEC. This permits us to disclose important information to you by referring to these filed documents. Any information referred to in this way is considered part of this prospectus, and any information filed with the SEC by us after the date of this prospectus will automatically be deemed to update and supersede this information. We incorporate by reference the following documents that have been filed with the SEC (other than information in such documents that is not deemed to be filed):

- Annual Report on Form 10-K for the year ended December 31, 2015;
- Portions of the Definitive Proxy Statement on Schedule 14A for the 2016 annual meeting of stockholders incorporated by reference in the Annual Report on Form 10-K for the year ended December 31, 2015;
- Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2016, June 30, 2016 and September 30, 2016; and
- Current Reports on Form 8-K filed on March 8, 2016 (Item 8.01 only), June 13, 2016, June 14, 2016 and October 13, 2016.

We also incorporate by reference any future filings (other than information in such documents that is not deemed to be filed) made with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), until we file a post-effective amendment which indicates the termination of the offering of the securities made by this prospectus.

We will provide without charge upon written or oral request a copy of any or all of the documents that are incorporated by reference into this prospectus, other than exhibits which are specifically incorporated by reference into such documents. Requests should be directed to our Investor Relations department at Natera, Inc., 201 Industrial Road, Suite 410, San Carlos, California 94070. Our telephone number is (650) 249-9090.

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RISK FACTORS

An investment in our securities involves a high degree of risk. The prospectus supplement applicable to each offering of our securities will contain a discussion of the risks applicable to an investment in our securities. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading "Risk Factors" in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. You should also consider the risks, uncertainties and assumptions discussed under Item 1A, "Risk Factors," in our Annual Report on Form 10-K for the fiscal year ended December 31, 2015, all of which are incorporated herein by reference, and may be amended, supplemented or superseded from time to time by other reports we subsequently have filed with the SEC or may file with the SEC in the future and any prospectus supplement related to a particular offering. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference herein contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Exchange Act, which are subject to the "safe harbor" created by those sections. The forward-looking statements are contained principally in our Annual Reports on Form 10-K and in our quarterly reports on Form 10-Q and in any prospectus supplement related hereto in greater detail under the sections titled "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations," and "Business", but are also contained elsewhere in this prospectus and the documents incorporated by reference herein. Forward-looking statements include information concerning our future results of operations and financial position, strategy and plans, and our expectations for future operations. Forward-looking statements include all statements that are not historical facts and, in some cases, can be identified by terms such as "believe," "may," "will," "estimate," "continue," "anticipate," "design," "intend," "expect," "could," "plan," "potential," "predict," "seek," "should," "would" or the negative version of these words and similar expressions.

Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including those described in "Risk Factors" and elsewhere in prospectus and the documents incorporated by reference herein. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Also, forward-looking statements represent our beliefs and assumptions only as of the date of the document containing the applicable statement. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. You should read this prospectus and the documents incorporated by reference herein completely and with the understanding that our actual future results may be materially different from what we expect.

These forward-looking statements include, but are not limited to, statements concerning the following:

- our expectation that, for the foreseeable future, a significant portion of our revenues will be derived from sales of Panorama;
- our ability to increase demand for Panorama, expand geographically, and obtain favorable coverage and reimbursement determinations from third-party payers;

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- our reliance on our partners to market and offer Panorama in the United States and in international markets;
- our expectation that Panorama will be adopted for broader use in average-risk pregnancies and for the screening of microdeletions and that third-party payer reimbursement will be available for these applications;
- the scope of protection we establish and maintain for, and developments or disputes concerning our intellectual property or other proprietary rights;
- our ability to successfully develop additional revenue opportunities and expand our product offerings to include new tests, including the field of cancer diagnostic tests;
- competition in the markets we serve;
- our expectations of the reliability, accuracy, and performance of Panorama, as well as expectations of the benefits to patients, providers, and payers of Panorama;
- our reliance on collaborators such as medical institutions, contract laboratories, laboratory partners, and other third parties;
- our ability to operate our laboratory facility and meet expected demand;
- our reliance on a limited number of suppliers, including sole source suppliers, which may impact the availability of replacement laboratory instruments and materials;
- our expectations of the rate of adoption of Panorama and of any of our future tests by laboratories, clinics, clinicians, payers, and patients;
- our ability to publish clinical data in peer-reviewed medical publications regarding Panorama and any of our future tests;
- our ability to successfully implement our cloud-based distribution model;
- our estimates regarding our costs and risks associated with our international operations and international expansion;
- our ability to retain and recruit key personnel;
- our reliance on our direct sales efforts;
- our expectations regarding acquisitions and strategic operations;
- our ability to fund our working capital requirements;
- our compliance with federal, state, and foreign regulatory requirements;
- the factors that may impact our financial results; and
- anticipated trends and challenges in our business and the markets in which we operate.

Any forward-looking statement made by us in this prospectus and the documents incorporated by reference herein speaks only as of the date on which it is made. Except as required by law, we disclaim any obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

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NATERA, INC.

We are a rapidly growing diagnostics company with proprietary molecular and bioinformatics technology that we are deploying to change the management of genetic disease worldwide. Our novel molecular assays reliably measure many informative regions across the genome from samples as small as a single cell. Our statistical algorithms combine these measurements with data available from the broader scientific community to screen for a wide range of serious conditions with best in class accuracy and coverage. Our technology has been proven clinically and commercially in the prenatal testing space. We believe this success can be translated into the liquid biopsy space, and we are developing products for a number of oncology applications. In addition to our direct sales force in the United States, we have a global network of approximately 70 laboratory and distribution partners, including many of the largest international laboratories. We are enabling even wider adoption of our technology by introducing a global cloud-based distribution model. We have launched seven molecular diagnostic tests since 2009, and we intend to launch new products in prenatal testing and oncology in the future.

Our principal executive offices are located at 201 Industrial Road, Suite 410, San Carlos, California 94070, and our telephone number is (650) 249-9090. Our website address is www.natera.com. We do not incorporate the information on, or accessible through, our website into this prospectus, and you should not consider any information on, or accessible through, our website as part of this prospectus.

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USE OF PROCEEDS

Unless otherwise set forth in a prospectus supplement with respect to the proceeds from the sale of the particular securities to which such prospectus supplement relates, we intend to use the net proceeds from the sale of the offered securities for working capital and general corporate purposes and for continued investments in research and development for our core technology and development of our product offerings. In addition, we may use a portion of such net proceeds for acquisitions of complementary businesses, technologies or other assets, or to fund the repayment, refinancing or redemption of outstanding debt. However, we have no current understandings, agreements or commitments for any material acquisitions at this time, and we have not allocated specific amounts of the net proceeds to be received by us from any offering for any of these purposes. If we decide to use the net proceeds from a particular offering of securities for a particular purpose, we will describe that purpose, as well as any other required disclosures, in the related prospectus supplement.

RATIO OF EARNINGS TO FIXED CHARGES AND PREFERRED STOCK DIVIDENDS

Anytime preferred stock or debt securities are offered pursuant to this prospectus, our historical ratio of earnings to fixed charges and ratio of earnings to fixed charges and preferred stock dividends will each be specified in, or incorporated by reference in, the applicable prospectus supplement.

DESCRIPTION OF SECURITIES

This prospectus contains a summary of our common stock, preferred stock, depositary shares, debt securities, warrants and units. These summaries are not meant to be a complete description of each security. The particular terms of any security to be issued pursuant hereto will be set forth in a related prospectus supplement. This prospectus and the accompanying prospectus supplement will contain the material terms and conditions for each security.

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DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock, certain provisions of our amended and restated certificate of incorporation, or our certificate of incorporation, and our amended and restated bylaws, or our bylaws, and certain provisions of Delaware law is a summary and is qualified in its entirety by reference to our certificate of incorporation, bylaws and the Delaware General Corporation Law (the "DGCL"). Copies of our certificate of incorporation and our bylaws have been filed with the SEC and are filed as exhibits to the registration statement of which this prospectus forms a part.

Our authorized capital stock consists of 750,000,000 shares of common stock, $0.0001 par value, and 50,000,000 shares of preferred stock, $0.0001 par value. As of September 30, 2016, there were 52,130,615 shares of common stock outstanding and no shares of preferred stock outstanding.

Common Stock

Each holder of common stock is entitled to one vote per share on all matters submitted to a vote of stockholders. We have not provided for cumulative voting in the election of directors. Subject to preferences that may apply to shares of preferred stock outstanding at the time, the holders of outstanding shares of our common stock are entitled to receive dividends out of assets legally available at the times and in the amounts that our board of directors may determine from time to time. Upon our liquidation, dissolution or winding-up, the holders of common stock are entitled to share ratably in all assets remaining after payment of all liabilities and the liquidation preferences of any outstanding preferred stock. Holders of common stock have no preemptive or conversion rights or other subscription rights. There are no redemption or sinking fund provisions applicable to our common stock.

Preferred Stock

Our board of directors has the authority, without further action by our stockholders, to issue from time to time up to 50,000,000 shares of preferred stock in one or more series, and to establish the number of shares to be included in each series and fix the powers, preferences and rights of the shares of each wholly unissued series and any of its qualifications, limitations or restrictions. Our board of directors will also be able to increase or decrease the number of shares of any series, but not below the number of shares of that series then outstanding, without any further vote or action by the stockholders.

The particular terms of any series of preferred stock will be described in the prospectus supplement relating to that series of preferred stock. Those terms may include:

- the title and stated value;
- the number of shares we are offering;
- the liquidation preference per share;
- the purchase price;
- the dividend rate, period and payment date and method of calculation for dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;

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- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price, or how it will be calculated, and the conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price, or how it will be calculated, and the exchange period;
- voting rights, if any, of the preferred stock;
- preemption rights, if any;
- restrictions on transfer, sale or other assignment, if any;
- whether interests in the preferred stock will be represented by depositary shares;
- a discussion of any material or special United States federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;
- any limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the preferred stock.

The DGCL provides that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of that preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

The issuance of preferred stock could adversely affect the voting power, conversion or other rights of holders of common stock. Preferred stock could be issued quickly with terms calculated to delay or prevent a change in control of our company or make removal of management more difficult. Additionally, the issuance of preferred stock may have the effect of decreasing the market price of our common stock.

Anti-Takeover Effects of Provisions of Delaware Law and Our Certificate of Incorporation and Bylaws

Certain provisions of Delaware law, our amended and restated certificate of incorporation and our amended and restated bylaws could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage certain types of coercive takeover practices and inadequate takeover bids. These provisions are also designed, in part, to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with an unfriendly or unsolicited acquirer outweigh the disadvantages of discouraging such proposals, including proposals that are priced above the then-current market value of our common stock, because, among other reasons, the negotiation of such proposals could result in an improvement of their terms.

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Certificate of Incorporation and Bylaws

Our amended and restated certificate of incorporation and amended and restated bylaws include provisions that:

- authorize our board of directors to issue, without further action by the stockholders, up to 50,000,000 shares of undesignated preferred stock;
- require that any action to be taken by our stockholders be effected at a duly called annual or special meeting and not by written consent;
- specify that special meetings of our stockholders can be called only by our board of directors, our chairman of the board, or our chief executive officer;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- establish that our board of directors is divided into three classes, Class I, Class II and Class III, with each class serving staggered terms;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may, except as otherwise required by law, be filled only by a majority of directors then in office, even if less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors; and
- require a super-majority of votes to amend certain of the above-mentioned provisions.

Delaware Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law regulating corporate takeovers. Section 203 prohibits a Delaware corporation, under certain circumstances, from engaging in a business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, unless:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon the closing of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned by (i) persons who are directors and also officers and (ii) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders by at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

In general, Section 203 defines business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;

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- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loss, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person who, together with the entity's or person's affiliates and associates, beneficially owns, or within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporations.

A Delaware corporation may "opt out" of these provisions with an express provision in its original certificate of incorporation or an express provision in its amended and restated certificate of incorporation or amended and restated bylaws resulting from a stockholders' amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Choice of Forum

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law or any action asserting a claim against us that is governed by the internal affairs doctrine. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that a court could find these types of provisions to be inapplicable or unenforceable.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent's address is 250 Royall Street, Canton, Massachusetts 02021, and the telephone number is (800) 662-7232.

Listing

Our common stock is listed on the NASDAQ Global Select Market under the symbol "NTRA".

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DESCRIPTION OF DEPOSITARY SHARES

The depositary shares will be issued under deposit agreements to be entered into between us and a bank or trust company, as depositary, all to be set forth in the applicable prospectus supplement relating to any or all depositary shares in respect of which this prospectus is being delivered. We will file a copy of the deposit agreement and the depositary receipt with the SEC each time we issue a series of depositary shares, and these depositary receipts and deposit agreement will be incorporated by reference into the registration statement of which this prospectus forms a part.

General

If we elect to offer fractional interests in shares of preferred stock, we will provide for the issuance by a depositary to the public of receipts for depositary shares. Each depositary share will represent fractional interests of preferred stock. We will deposit the shares of preferred stock underlying the depositary shares under a deposit agreement between us and a bank or trust company selected by us. The bank or trust company must have its principal office in the United States and a combined capital and surplus of at least $50 million. The depositary receipts will evidence the depositary shares issued under the deposit agreement.

The deposit agreement will contain terms applicable to the holders of depositary shares in addition to the terms stated in the depositary receipts. Each owner of depositary shares will be entitled to all the rights and preferences of the preferred stock underlying the depositary shares in proportion to the applicable fractional interest in the underlying shares of preferred stock. The depositary will issue the depositary receipts to individuals purchasing the fractional interests in shares of the related preferred stock according to the terms of the offering described in a prospectus supplement.

Dividends and Other Distributions

The depositary will distribute all cash dividends or other cash distributions received for the preferred stock to the entitled record holders of depositary shares in proportion to the number of depositary shares that the holder owns on the relevant record date. The depositary will distribute only an amount that can be distributed without attributing to any holder of depositary shares a fraction of one cent. The depositary will add the undistributed balance to and treat it as part of the next sum received by the depositary for distribution to holders of depositary shares.

If there is a non-cash distribution, the depositary will distribute property received by it to the entitled record holders of depositary shares, in proportion, insofar as possible, to the number of depositary shares owned by the holders, unless the depositary determines, after consultation with us, that it is not feasible to make such distribution. If this occurs, the depositary may, with our approval, sell such property and distribute the net proceeds from the sale to the holders. The deposit agreement also will contain provisions relating to how any subscription or similar rights that we may offer to holders of the preferred stock will be available to the holders of the depositary shares.

Conversion, Exchange and Redemption

If any series of preferred stock underlying the depositary shares may be converted or exchanged, each record holder of depositary receipts will have the right or obligation to convert or exchange the depositary shares represented by the depositary receipts.

Whenever we redeem shares of preferred stock held by the depositary, the depositary will redeem, at the same time, the number of depositary shares representing the preferred stock. The depositary will redeem the depositary shares from the proceeds it receives from the corresponding redemption, in whole or in part, of the applicable series of preferred stock. The depositary will mail a notice of redemption to the record holders of the depositary shares that are to be redeemed between 30 and

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60 days before the date fixed for redemption. The redemption price per depositary share will be equal to the applicable fraction of the redemption price per share on the applicable series of preferred stock. If less than all the depositary shares are to be redeemed, the depositary will select which shares to be redeemed by lot, proportionate allocation or another method.

After the date fixed for redemption, the depositary shares called for redemption will no longer be outstanding. When the depositary shares are no longer outstanding, all rights of the holders will end, except the right to receive money, securities or other property payable upon redemption.

Voting

When the depositary receives notice of a meeting at which the holders of the preferred stock are entitled to vote, the depositary will mail the particulars of the meeting to the record holders of the depositary shares. Each record holder of depositary shares on the record date may instruct the depositary on how to vote the shares of preferred stock underlying the holder's depositary shares. The depositary will try, if practical, to vote the number of shares of preferred stock underlying the depositary shares according to the instructions. The depositary will abstain from voting shares of the preferred stock to the extent it does not receive specific instructions from the holders of depositary shares representing such preferred stock. We will agree to take all reasonable action requested by the depositary to enable it to vote as instructed.

Record Date

Whenever (1) any cash dividend or other cash distribution shall become payable, any distribution other than cash shall be made, or any rights, preferences or privileges shall be offered with respect to the preferred stock, or (2) the depositary shall receive notice of any meeting at which holders of preferred stock are entitled to vote or of which holders of preferred stock are entitled to notice, or of the mandatory conversion of or any election on our part to call for the redemption of any preferred stock, the depositary shall in each such instance fix a record date (which shall be the same as the record date for the preferred stock) for the determination of the holders of depositary receipts (x) who shall be entitled to receive such dividend, distribution, rights, preferences or privileges or the net proceeds of the sale thereof or (y) who shall be entitled to give instructions for the exercise of voting rights at any such meeting or to receive notice of such meeting or of such redemption or conversion, subject to the provisions of the deposit agreement.

Amendments

We and the depositary may agree to amend the deposit agreement and the depositary receipt evidencing the depositary shares. Any amendment that (a) imposes or increases certain fees, taxes or other charges payable by the holders of the depositary shares as described in the deposit agreement or (b) otherwise prejudices any substantial existing right of holders of depositary shares, will not take effect until 30 days after the depositary has mailed notice of the amendment to the record holders of depositary shares. Any holder of depositary shares that continues to hold its shares at the end of the 30-day period will be deemed to have agreed to the amendment.

Termination

We may direct the depositary to terminate the deposit agreement by mailing a notice of termination to holders of depositary shares at least 30 days prior to termination. In addition, a deposit agreement will automatically terminate if:

- the depositary has redeemed all related outstanding depositary shares, or

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- we have liquidated, terminated or wound up our business and the depositary has distributed the preferred stock of the relevant series to the holders of the related depositary shares.

The depositary may likewise terminate the deposit agreement if at any time 60 days shall have expired after the depositary shall have delivered to us a written notice of its election to resign and a successor depositary shall not have been appointed and accepted its appointment. If any depositary receipts remain outstanding after the date of termination, the depositary thereafter will discontinue the transfer of depositary receipts, will suspend the distribution of dividends to the holders thereof, and will not give any further notices (other than notice of such termination) or perform any further acts under the deposit agreement except as provided below and except that the depositary will continue (1) to collect dividends on the preferred stock and any other distributions with respect thereto and (2) to deliver the preferred stock together with such dividends and distributions and the net proceeds of any sales of rights, preferences, privileges or other property, without liability for interest thereon, in exchange for depositary receipts surrendered. At any time after the expiration of two years from the date of termination, the depositary may sell the preferred stock then held by it at public or private sales, at such place or places and upon such terms as it deems proper and may thereafter hold the net proceeds of any such sale, together with any money and other property then held by it, without liability for interest thereon, for the pro rata benefit of the holders of depositary receipts which have not been surrendered.

Payment of Fees and Expenses

We will pay all fees, charges and expenses of the depositary, including the initial deposit of the preferred stock and any redemption of the preferred stock. Holders of depositary shares will pay transfer and other taxes and governmental charges and any other charges as are stated in the deposit agreement for their accounts.

Resignation and Removal of Depositary

At any time, the depositary may resign by delivering notice to us, and we may remove the depositary. Resignations or removals will take effect upon the appointment of a successor depositary and its acceptance of the appointment. The successor depositary must be appointed within 60 days after delivery of the notice of resignation or removal and must be a bank or trust company having its principal office in the United States and having a combined capital and surplus of at least $50 million.

Reports

The depositary will forward to the holders of depositary shares all reports and communications from us that are delivered to the depositary and that we are required by law, the rules of an applicable securities exchange or our amended and restated certificate of incorporation to furnish to the holders of the preferred stock. Neither we nor the depositary will be liable if the depositary is prevented or delayed by law or any circumstances beyond its control in performing its obligations under the deposit agreement. The deposit agreement limits our obligations and the depositary's obligations to performance in good faith of the duties stated in the deposit agreement. Neither we nor the depositary will be obligated to prosecute or defend any legal proceeding connected with any depositary shares or preferred stock unless the holders of depositary shares requesting us to do so furnish us with satisfactory indemnity. In performing our obligations, we and the depositary may rely upon the written advice of our counsel or accountants, on any information that competent people provide to us and on documents that we believe are genuine.

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DESCRIPTION OF DEBT SECURITIES

We have summarized below general terms and conditions of the debt securities that we will offer and sell pursuant to this prospectus. When we offer to sell a particular series of debt securities, we will describe the specific terms and conditions of the series in a prospectus supplement to this prospectus. We will also indicate in the applicable prospectus supplement whether the general terms and conditions described in this prospectus apply to the series of debt securities. The terms and conditions of the debt securities of a series may be different in one or more respects from the terms and conditions described below. If so, those differences will be described in the applicable prospectus supplement.

We will issue the debt securities in one or more series under an indenture between us and a trustee to be selected by us. The following description of provisions of the indenture does not purport to be complete and is subject to, and qualified in its entirety by reference to, the indenture, which has been filed with the SEC as an exhibit to the registration statement of which this prospectus forms a part. A form of each debt security, any future supplemental indenture or similar document also will be so filed. You should read the indenture and any supplemental indenture or similar document because they, and not this description, define your rights as holder of our debt securities. All capitalized terms have the meanings specified in the indenture.

For purposes of this section of this prospectus, references to "we," "us" and "our" are to Natera, Inc. and not to any of its subsidiaries.

General

We may issue, from time to time, debt securities, in one or more series, that will consist of either senior debt ("Senior Debt Securities"), senior subordinated debt ("Senior Subordinated Debt Securities"), subordinated debt ("Subordinated Debt Securities") or junior subordinated debt ("Junior Subordinated Debt Securities" and, together with the Senior Subordinated Debt Securities and the Subordinated Debt Securities, the "Subordinated Securities"). Debt securities, whether senior, senior subordinated, subordinated or junior subordinated, may be issued as convertible debt securities or exchangeable debt securities.

The indenture does not limit the amount of debt securities that we may issue. We may, without the consent of the holders of the debt securities of any series, issue additional debt securities ranking equally with, and otherwise similar in all respects to, the debt securities of the series (except for any differences in the issue price and, if applicable, the initial interest accrual date and interest payment date) so that those additional debt securities will be consolidated and form a single series with the debt securities of the series previously offered and sold; provided that if the additional debt securities are not fungible with the debt securities of the series previously offered or sold for U.S. federal income tax purposes, the additional debt securities will have a separate CUSIP or other identifying number.

The indenture provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit designated by us. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to afford holders of any debt securities protection with respect to our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as "discount securities," which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may, for U.S. federal income tax purposes, be treated as if they were issued with "original issue discount," because of interest payment and other characteristics. Special U.S. federal income tax considerations applicable to debt securities issued with original issue discount will be described in more detail in any applicable prospectus supplement.

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Provisions of the Indenture

The applicable prospectus supplement for a series of debt securities that we issue will describe, among other things, the following terms of the offered debt securities:

- the title;
- the price or prices at which the debt securities will be issued;
- any limit on the aggregate principal amount of debt securities of such series;
- the currency or currencies of payment of principal or interest;
- the date or dates on which principal is payable;
- interest rates, and the date or dates from which interest, if any, will accrue, and the date or dates when interest is payable;
- the right, if any, to extend the interest payment periods and the duration of the extensions;
- the record date or record dates for determining to whom interest is payable;
- the place or places where and the manner in which principal, premium or interest will be payable and the place or places where the debt securities may be presented for transfer and, if applicable, conversion or exchange;
- our rights or obligations to redeem or purchase the debt securities, including sinking fund or partial redemption payments;
- the terms, if any, pursuant to which any debt securities will be subordinate to any of our other debt;
- the denominations in which the debt securities will be issued;
- if other than the entire principal amount of the debt securities when issued, the portion of the principal amount payable upon acceleration of maturity as a result of an Event of Default;
- if the amount of payments of principal or interest is to be determined by reference to an index or formula, or based on a coin or currency other than that in which the debt securities are stated to be payable, the manner in which these amounts are determined and the calculation agent, if any, with respect thereto;
- the terms applicable to any debt securities issued at a discount from their stated principal amount;
- any provisions for the remarketing of the debt securities;
- any additional Events of Default applicable to any debt securities;
- if applicable, covenants affording holders of debt protection with respect to our operations, financial condition or transactions involving us;
- conversion or exchange provisions, if any, including conversion or exchange prices or rates and adjustments thereto; and
- any other specific terms of any debt securities.

The applicable prospectus supplement will set forth certain U.S. federal income tax considerations for holders of any debt securities and the securities exchange or quotation system on which any debt securities are listed or quoted, if any.

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Debt securities issued by us will be structurally subordinated to all indebtedness and other liabilities of our subsidiaries, except to the extent any such subsidiary guarantees or is otherwise obligated to make payment on such debt securities.

Senior Debt Securities

Payment of the principal of, and premium, if any, and interest on, Senior Debt Securities will rank on a parity with all of our other unsecured and unsubordinated debt.

Senior Subordinated Debt Securities

Payment of the principal of, and premium, if any, and interest on, Senior Subordinated Debt Securities will be junior in right of payment to the prior payment in full of all of our unsubordinated debt. We will set forth in the applicable prospectus supplement relating to any Senior Subordinated Debt Securities the subordination terms of such securities as well as the aggregate amount of outstanding debt, as of the most recent practicable date, that by its terms would be senior to the Senior Subordinated Debt Securities. We will also set forth in such prospectus supplement limitations, if any, on issuance of additional debt ranking senior to the Senior Subordinated Debt Securities.

Subordinated Debt Securities

Payment of the principal of, and premium, if any, and interest on, Subordinated Debt Securities will be subordinated and junior in right of payment to the prior payment in full of all of our unsubordinated and senior subordinated debt. We will set forth in the applicable prospectus supplement relating to any Subordinated Debt Securities the subordination terms of such securities as well as the aggregate amount of outstanding indebtedness, as of the most recent practicable date, that by its terms would be senior to the Subordinated Debt Securities. We will also set forth in such prospectus supplement limitations, if any, on issuance of additional debt ranking senior to the Subordinated Debt Securities.

Junior Subordinated Debt Securities

Payment of the principal of, and premium, if any, and interest on, Junior Subordinated Debt Securities will be subordinated and junior in right of payment to the prior payment in full of all of our unsubordinated, senior subordinated and subordinated debt. We will set forth in the applicable prospectus supplement relating to any Junior Subordinated Debt Securities the subordination terms of such securities as well as the aggregate amount of outstanding debt, as of the most recent practicable date, that by its terms would be senior to the Junior Subordinated Debt Securities. We will also set forth in such prospectus supplement limitations, if any, on issuance of additional debt ranking senior to the Junior Subordinated Debt Securities.

Conversion or Exchange Rights

Debt securities may be convertible into or exchangeable for other securities or property of us. The terms and conditions of conversion or exchange will be set forth in the applicable prospectus supplement. The terms will include, among others, the following:

- the conversion or exchange price;
- the conversion or exchange period;
- provisions regarding the ability of us or the holder to convert or exchange the debt securities;
- events requiring adjustment to the conversion or exchange price; and

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- provisions affecting conversion or exchange in the event of our redemption of the debt securities.

Consolidation, Merger or Sale

We cannot consolidate or merge with or into, or transfer or lease our properties and assets substantially as an entirety to, any person, and we shall not permit any other person to consolidate with or merge into us, unless:

- (a) we will be the continuing corporation or (b) the successor corporation or person formed by such consolidation or into which we are merged or to which our properties and assets substantially as an entirety are transferred or leased is a person organized or formed under the laws of the United States, any state of the United States or the District of Columbia and, if such entity is not a corporation, a co- obligor of the debt securities is a corporation organized or existing under any such laws, and such successor corporation or person, including such co-obligor, if any, expressly assumes our obligations under the debt securities and the indenture; and

- immediately after giving effect to such transaction, no Event of Default or event, which after notice or lapse of time or both would become an Event of Default, shall have occurred and be continuing.

Subject to certain exceptions, when the person to whom our assets are transferred or leased has assumed our obligations under the debt securities and the indenture, we shall be discharged from all our obligations under the debt securities and the indenture.

This covenant would not apply to any recapitalization transaction, a change of control of us or a highly leveraged transaction, unless the transaction or change of control were structured to include a merger or consolidation or transfer or lease of our properties and assets substantially as an entirety.

Events of Default

Unless otherwise indicated, the term "Event of Default," when used in the indenture with respect to the debt securities of any series, means any of the following:

- failure to pay interest for 30 days after the date payment on any debt security of such series is due and payable; provided that an extension of an interest payment period by us in accordance with the terms of the debt securities shall not constitute a failure to pay interest;

- failure to pay principal or premium, if any, on any debt security of such series when due, either at maturity, upon any redemption, by declaration or otherwise;

- failure to perform any other covenant in the indenture or the debt securities of such series for 90 days after written notice that performance was required, which notice must be sent by either the trustee or holders of not less than 25% of the principal amount of the outstanding debt securities of such series;

- certain events of bankruptcy, insolvency or reorganization of us; or

- any other Event of Default provided in the applicable resolution of our board of directors or the officers' certificate or supplemental indenture under which we issue such series of debt securities.

An Event of Default for a particular series of debt securities does not necessarily constitute an Event of Default for any other series of debt securities issued under the indenture.

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If an Event of Default (other than an Event of Default relating to events of bankruptcy, insolvency or reorganization of us) involving any series of debt securities has occurred and is continuing, the trustee or the holders of not less than 25% in aggregate principal amount of the debt securities of each affected series may declare the entire principal amount of all the debt securities of such affected series, and the interest accrued thereon, if any, to be due and payable immediately. The holders of not less than a majority in aggregate principal amount of the debt securities of an affected series may, after satisfying conditions, rescind and annul any of the above-described declarations and consequences involving such series.

If an Event of Default relating to events of bankruptcy, insolvency or reorganization of us occurs and is continuing, then the entire principal amount of all of the debt securities outstanding, and the interest accrued thereon, if any, will automatically become due and payable immediately, without any declaration or other act by the trustee or any holder.

The indenture imposes limitations on suits brought by holders of debt securities against us with respect to an Event of Default. Except as provided below, no holder of debt securities of any series may institute any action against us under the indenture unless:

- an Event of Default has occurred and is continuing and such holder has previously given to the trustee written notice of such continuing Event of Default;
- the holders of at least 25% in principal amount of the outstanding debt securities of the affected series have requested that the trustee institute the action in respect of such Event of Default;
- the requesting holders have offered the trustee security or indemnity reasonably satisfactory to it for expenses and liabilities that may be incurred by bringing the action;
- the trustee has not instituted the action within 60 days of the request; and
- the trustee has not received inconsistent direction by the holders of a majority in principal amount of the outstanding debt securities of the affected series.

Notwithstanding the foregoing, each holder of debt securities of any series has the right, which is absolute and unconditional, to receive payment of the principal of, and premium and interest, if any, on, such debt securities when due and to institute suit for the enforcement of any such payment, and such rights may not be impaired without the consent of that holder of debt securities.

We will be required to file annually with the trustee a certificate, signed by one of our officers, stating whether or not the officer knows of any default by us in the performance, observance or fulfillment of any condition or covenant of the indenture.

Registered Global Securities

We may issue the debt securities of a series in whole or in part in the form of one or more fully registered global securities that we will deposit with a depositary or with a nominee for a depositary identified in the applicable prospectus supplement and registered in the name of such depositary or nominee. In such case, we will issue one or more registered global securities denominated in an amount equal to the aggregate principal amount of all of the debt securities of the series to be issued and represented by such registered global security or securities.

Unless and until it is exchanged in whole or in part for debt securities in definitive registered form, a registered global security may not be transferred except as a whole:

- by the depositary for such registered global security to its nominee,
- by a nominee of the depositary to the depositary or another nominee of the depositary, or
- by the depositary or its nominee to a successor of the depositary or a nominee of the successor.

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The prospectus supplement relating to a series of debt securities will describe the specific terms of the depositary arrangement with respect to any portion of such series represented by a registered global security. We anticipate that the following provisions will apply to all depositary arrangements for debt securities:

- ownership of beneficial interests in a registered global security will be limited to persons that have accounts with the depositary for the registered global security, those persons being referred to as "participants," or persons that may hold interests through participants;
- upon the issuance of a registered global security, the depositary for the registered global security will credit, on its book-entry registration and transfer system, the participants' accounts with the respective principal amounts of the debt securities represented by the registered global security beneficially owned by the participants;
- any dealers, underwriters, or agents participating in the distribution of the debt securities will designate the accounts to be credited; and
- ownership of any beneficial interest in the registered global security will be shown on, and the transfer of any ownership interest will be effected only through, records maintained by the depositary for the registered global security (with respect to interests of participants) and on the records of participants (with respect to interests of persons holding through participants).

The laws of some states may require that certain purchasers of securities take physical delivery of the securities in definitive form. These laws may limit the ability of those persons to own, transfer or pledge beneficial interests in registered global securities.

So long as the depositary for a registered global security, or its nominee, is the registered owner of the registered global security, the depositary or the nominee, as the case may be, will be considered the sole owner or holder of the debt securities represented by the registered global security for all purposes under the indenture. Except as set forth below, owners of beneficial interests in a registered global security:

- will not be entitled to have the debt securities represented by a registered global security registered in their names;
- will not receive or be entitled to receive physical delivery of the debt securities in the definitive form; and
- will not be considered the owners or holders of the debt securities under the indenture.

Accordingly, each person owning a beneficial interest in a registered global security must rely on the procedures of the depositary for the registered global security and, if the person is not a participant, on the procedures of a participant through which the person owns its interest, to exercise any rights of a holder under the indenture.

We understand that under existing industry practices, if we request any action of holders or if an owner of a beneficial interest in a registered global security desires to give or take any action that a holder is entitled to give or take under the indenture, the depositary for the registered global security would authorize the participants holding the relevant beneficial interests to give or take the action, and those participants would authorize beneficial owners owning through those participants to give or take the action or would otherwise act upon the instructions of beneficial owners holding through them.

We will make payments of principal and premium, if any, and interest, if any, on debt securities represented by a registered global security registered in the name of a depositary or its nominee to the depositary or its nominee, as the case may be, as the registered owners of the registered global security. None of us, the trustee or any other agent of us or the trustee will be responsible or liable for any aspect of the records relating to, or payments made on account of, beneficial ownership interests in the

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registered global security or for maintaining, supervising or reviewing any records relating to the beneficial ownership interests.

We expect that the depositary for any debt securities represented by a registered global security, upon receipt of any payments of principal and premium, if any, and interest, if any, in respect of the registered global security, will immediately credit participants' accounts with payments in amounts proportionate to their respective beneficial interests in the registered global security as shown on the records of the depositary. We also expect that standing customer instructions and customary practices will govern payments by participants to owners of beneficial interests in the registered global security held through the participants, as is now the case with the securities held for the accounts of customers in bearer form or registered in "street name." We also expect that any of these payments will be the responsibility of the participants.

If the depositary for any debt securities represented by a registered global security is at any time unwilling or unable to continue as depositary or ceases to be a clearing agency registered under the Exchange Act, we will appoint an eligible successor depositary. If we fail to appoint an eligible successor depositary within 90 days, we will issue the debt securities in definitive form in exchange for the registered global security. In addition, we may at any time and in our sole discretion decide not to have any of the debt securities of a series represented by one or more registered global securities. In such event, we will issue debt securities of that series in a definitive form in exchange for all of the registered global securities representing the debt securities. The trustee will register any debt securities issued in definitive form in exchange for a registered global security in such name or names as the depositary, based upon instructions from its participants, shall instruct the trustee.

Discharge, Defeasance and Covenant Defeasance

We can discharge or defease our obligations under the indenture as set forth below. Unless otherwise set forth in the applicable prospectus supplement, the subordination provisions applicable to any Subordinated Securities will be expressly made subject to the discharge and defeasance provisions of the indenture.

We may discharge our obligations to holders of any series of debt securities that have not already been delivered to the trustee for cancellation and that have either become due and payable or are by their terms to become due and payable within one year (or to be called for redemption within one year). We may effect a discharge by irrevocably depositing with the trustee cash or U.S. government obligations, as trust funds, in an amount certified to be sufficient to pay when due, whether at maturity, upon redemption or otherwise, the principal of, and premium, if any, and interest on, the debt securities and any mandatory sinking fund payments.

Unless otherwise provided in the applicable prospectus supplement, we may also discharge any and all of our obligations to holders of any series of debt securities at any time ("legal defeasance"). We also may be released from the obligations imposed by any covenants of any outstanding series of debt securities and provisions of the indenture, and we may omit to comply with those covenants without creating an Event of Default ("covenant defeasance"). We may effect legal defeasance and covenant defeasance only if, among other things:

- we irrevocably deposit with the trustee cash or U.S. government obligations, as trust funds, in an amount certified to be sufficient to pay when due (whether at maturity, upon redemption, or otherwise) the principal of, and premium, if any, and interest on all outstanding debt securities of the series; and

- we deliver to the trustee an opinion of counsel from a nationally recognized law firm to the effect that the beneficial owners of the series of debt securities will not recognize income, gain or loss for U.S. federal income tax purposes as a result of the legal defeasance or covenant

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defeasance, as applicable, and that legal defeasance or covenant defeasance, as applicable, will not otherwise alter the beneficial owners' U.S. federal income tax treatment of principal, premium, if any, and interest payments on the series of debt securities, which opinion, in the case of legal defeasance, must be based on a ruling of the Internal Revenue Service, or a change in U.S. federal income tax law.

Although we may discharge or defease our obligations under the indenture as described in the two preceding paragraphs, we may not avoid, among other things, our duty to register the transfer or exchange of any series of debt securities, to replace any temporary, mutilated, destroyed, lost or stolen series of debt securities or to maintain an office or agency in respect of any series of debt securities.

We may exercise our legal defeasance option notwithstanding our prior exercise of our covenant defeasance option.

Modifications of the Indenture

The indenture provides that we and the trustee may enter into supplemental indentures without the consent of the holders of debt securities to:

- secure any debt securities;
- evidence the assumption by another person of our obligations, as permitted by the indenture;
- add covenants for the protection of the holders of debt securities of all or any series or to surrender any right or power conferred upon us;
- add any additional events of default for the benefit of holders of the debt securities of all or any series;
- add one or more guarantees for the benefit of holders of the debt securities;
- provide for the issuance of additional debt securities of any series;
- comply with the rules of any applicable securities depository;
- provide for uncertificated debt securities in addition to or in place of certificated debt securities;
- add to, change or eliminate any of the provisions of the indenture in respect of one or more series of debt securities; provided that any such addition, change or elimination (a) shall neither (1) apply to any debt security of any series created prior to the execution of such supplemental indenture and entitled to the benefit of such provision nor (2) modify the rights of the holder of any such debt security with respect to such provision or (b) shall become effective only when there is no debt security described in clause (a)(1) outstanding;
- supplement any of the provisions of the indenture to such extent as shall be necessary to permit or facilitate the defeasance and discharge of any series of debt securities pursuant to the indenture; provided that any such action shall not adversely affect the interests of the holders of debt securities of such series or any other series of debt securities in any material respect;
- comply with the rules or regulations of any securities exchange or automated quotation system on which any of the debt securities may be listed or traded;
- add to, change or eliminate any of the provisions of the indenture as shall be necessary or desirable in accordance with any amendments to the Trust Indenture Act of 1939, as amended, provided that such action does not adversely affect the rights or interests of any holder of debt securities in any material respect;

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- cure or correct any ambiguity, defect, omission or inconsistency in the indenture; provided that such action does not adversely affect the interests of the holders of debt securities of any series in any material respect;
- establish the forms or terms of debt securities of any series;
- evidence and provide for the acceptance of appointment by a successor trustee; and
- add to, change or eliminate any other provision of the indenture; provided that such addition, change or elimination does not adversely affect the interests of the holders of debt securities of any series in any material respect.

The indenture also provides that we and the trustee may, with the consent of the holders of not less than a majority in aggregate principal amount of the outstanding debt securities of all series of Senior Debt Securities or Subordinated Securities, as the case may be, then outstanding and affected thereby (voting as one class), add any provisions to, or change in any manner, eliminate or modify in any way the provisions of, the indenture or modify in any manner the rights of the holders of the debt securities. We and the trustee may not, however, without the consent of the holder of each outstanding debt security affected thereby:

- extend the final maturity of any debt security;
- reduce the principal amount of, or premium, if any, on any debt security;
- reduce the rate or extend the time of payment of interest on any debt security;
- reduce any amount payable on redemption of any debt security;
- change the currency in which the principal (other than as may be provided otherwise with respect to a series), premium, if any, or interest is payable on any debt security;
- reduce the amount of the principal of any debt security issued with an original issue discount that is payable upon acceleration or provable in bankruptcy;
- modify any of the subordination provisions or the definition of senior indebtedness applicable to any Subordinated Securities in a manner adverse to the holders of those securities;
- alter provisions of the indenture relating to the debt securities not denominated in U.S. dollars;
- impair the right to institute suit for the enforcement of any payment on any debt security when due; or
- reduce the percentage of holders of debt securities of any series whose consent is required for any modification of the indenture.

Concerning the Trustee

The indenture provides that there may be more than one trustee under the indenture, each with respect to one or more series of debt securities. If there are different trustees for different series of debt securities, each trustee will be a trustee of a trust under the indenture separate and apart from the trust administered by any other trustee under the indenture. Except as otherwise indicated in this prospectus or any accompanying prospectus supplement, any action permitted to be taken by a trustee may be taken by such trustee only with respect to the one or more series of debt securities for which it is the trustee under the indenture. Any trustee under the indenture may resign or be removed with respect to one or more series of debt securities. All payments of principal of, and premium, if any, and interest on, and all registration, transfer, exchange, authentication and delivery (including authentication and delivery on original issuance of the debt securities) of, the debt securities of a series will be effected by the trustee with respect to such series at an office designated by the trustee.

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The indenture contains limitations on the right of the trustee, should it become a creditor of us, to obtain payment of claims in some cases or to realize on certain property received in respect of any such claim as security or otherwise. The trustee may engage in other transactions. If it acquires any conflicting interest relating to any duties with respect to the debt securities, however, it must eliminate the conflict or resign as trustee.

The holders of a majority in aggregate principal amount of any series of debt securities then outstanding will have the right to direct the time, method and place of conducting any proceeding for exercising any remedy available to the trustee with respect to such series of debt securities, provided that the direction would not conflict with any rule of law or with the indenture, would not be unduly prejudicial to the rights of another holder of the debt securities, and would not involve any trustee in personal liability. The indenture provides that in case an Event of Default shall occur and be known to any trustee and not be cured, the trustee must use the same degree of care as a prudent person would use in the conduct of his or her own affairs in the exercise of the trustee's power. Subject to these provisions, the trustee will be under no obligation to exercise any of its rights or powers under the indenture at the request of any of the holders of the debt securities, unless they shall have offered to the trustee security and indemnity satisfactory to the trustee.

No Individual Liability of Incorporators, Stockholders, Officers or Directors

The indenture provides that no incorporator and no past, present or future stockholder, officer or director of us or any successor corporation in their capacity as such shall have any individual liability for any of our obligations, covenants or agreements under the debt securities or the indenture.

Governing Law

The indenture and the debt securities will be governed by, and construed in accordance with, the laws of the State of New York.

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DESCRIPTION OF WARRANTS

General

We may issue debt warrants for the purchase of debt securities or stock warrants for the purchase of preferred stock or common stock.

The warrants will be issued under warrant agreements to be entered into between us and the purchasers or between us and a bank or trust company, as warrant agent, all to be set forth in the applicable prospectus supplement relating to any or all warrants in respect of which this prospectus is being delivered. We will file a copy of the warrant and warrant agreement with the SEC each time we issue a series of warrants, and these warrants and warrant agreements will be incorporated by reference into the registration statement of which this prospectus forms a part.

The following description sets forth certain general terms and provisions of the warrants to which any prospectus supplement may relate. The particular terms of the warrants to which any prospectus supplement may relate and the extent, if any, to which such general provisions may apply to the warrants so offered will be described in the applicable prospectus supplement. The following summary of certain provisions of the warrants, warrant agreements and warrant certificates does not purport to be complete and is subject to, and is qualified in its entirety by express reference to, all the provisions of the warrant agreements and warrant certificates, including the definitions therein of certain terms.

Debt Warrants

General. Reference is made to the applicable prospectus supplement for the terms of debt warrants in respect of which this prospectus is being delivered, the debt securities warrant agreement relating to such debt warrants and the debt warrant certificates representing such debt warrants, including the following:

- the designation, aggregate principal amount and terms of the debt securities purchasable upon exercise of such debt warrants and the procedures and conditions relating to the exercise of such debt warrants;
- the designation and terms of any related debt securities with which such debt warrants are issued and the number of such debt warrants issued with each such debt security;
- the date, if any, on and after which such debt warrants and any related offered securities will be separately transferable;
- the principal amount of debt securities purchasable upon exercise of each debt warrant and the price at which such principal amount of debt securities may be purchased upon such exercise;
- the date on which the right to exercise such debt warrants shall commence and the date on which such right shall expire;
- a discussion of the material U.S. federal income tax considerations applicable to the ownership or exercise of debt warrants;
- whether the debt warrants represented by the debt warrant certificates will be issued in registered or bearer form, and, if registered, where they may be transferred and registered;
- call provisions of such debt warrants, if any; and
- any other terms of the debt warrants.

The debt warrant certificates will be exchangeable for new debt warrant certificates of different denominations and debt warrants may be exercised at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement. Prior to the exercise of their debt

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warrants, holders of debt warrants will not have any of the rights of holders of the debt securities purchasable upon such exercise and will not be entitled to any payments of principal and premium, if any, and interest, if any, on the debt securities purchasable upon such exercise.

Exercise of Debt Warrants. Each debt warrant will entitle the holder to purchase for cash such principal amount of debt securities at such exercise price as shall in each case be set forth in, or be determinable as set forth in, the applicable prospectus supplement relating to the debt warrants offered thereby. Unless otherwise specified in the applicable prospectus supplement, debt warrants may be exercised at any time up to 5:00 p.m., New York City time, on the expiration date set forth in the applicable prospectus supplement. After 5:00 p.m., New York City time, on the expiration date, unexercised debt warrants will become void.

Debt warrants may be exercised as set forth in the applicable prospectus supplement relating to the debt warrants. Upon receipt of payment and the debt warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will, as soon as practicable, forward the debt securities purchasable upon such exercise. If less than all of the debt warrants represented by such debt warrant certificate are exercised, a new debt warrant certificate will be issued for the remaining amount of debt warrants.

Stock Warrants

General. Reference is made to the applicable prospectus supplement for the terms of stock warrants in respect of which this prospectus is being delivered, the stock warrant agreement relating to such stock warrants and the stock warrant certificates representing such stock warrants, including the following:

- the type and number of shares of preferred stock or common stock purchasable upon exercise of such stock warrants and the procedures and conditions relating to the exercise of such stock warrants;
- the date, if any, on and after which such stock warrants and related offered securities will be separately tradeable;
- the offering price of such stock warrants, if any;
- the initial price at which such shares may be purchased upon exercise of stock warrants and any provision with respect to the adjustment thereof;
- the date on which the right to exercise such stock warrants shall commence and the date on which such right shall expire;
- a discussion of the material U.S. federal income tax considerations applicable to the ownership or exercise of stock warrants;
- call provisions of such stock warrants, if any;
- anti-dilution provisions of the stock warrants, if any;
- any other terms of the stock warrants; and
- information relating to any preferred stock purchasable upon exercise of such stock warrants.

The stock warrant certificates will be exchangeable for new stock warrant certificates of different denominations and stock warrants may be exercised at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement. Prior to the exercise of their stock warrants, holders of stock warrants will not have any of the rights of holders of shares of capital

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stock purchasable upon such exercise, and will not be entitled to any dividend payments on such capital stock purchasable upon such exercise.

Exercise of Stock Warrants. Each stock warrant will entitle the holder to purchase for cash such number of shares of preferred stock or common stock, as the case may be, at such exercise price as shall in each case be set forth in, or be determinable as set forth in, the applicable prospectus supplement relating to the stock warrants offered thereby. Unless otherwise specified in the applicable prospectus supplement, stock warrants may be exercised at any time up to 5:00 p.m., New York City time, on the expiration date set forth in the applicable prospectus supplement. After 5:00 p.m., New York City time, on the expiration date, unexercised stock warrants will become void.

Stock warrants may be exercised as set forth in the applicable prospectus supplement relating thereto. Upon receipt of payment and the stock warrant certificates properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will, as soon as practicable, forward a certificate representing the number of shares of capital stock purchasable upon such exercise. If less than all of the stock warrants represented by such stock warrant certificate are exercised, a new stock warrant certificate will be issued for the remaining amount of stock warrants.

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DESCRIPTION OF UNITS

We may issue units consisting of any combination of the other types of securities offered under this prospectus in one or more series. We may evidence each series of units by unit certificates that we will issue under a separate agreement. We may enter into unit agreements with a unit agent. Each unit agent will be a bank or trust company that we select. We will indicate the name and address of the unit agent in the applicable prospectus supplement relating to a particular series of units.

The following description, together with the additional information included in any applicable prospectus supplement, summarizes the general features of the units that we may offer under this prospectus. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreements that contain the terms of the units. Specific unit agreements will contain additional important terms and provisions and we will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of each unit agreement relating to units offered under this prospectus.

If we offer any units, certain terms of that series of units will be described in the applicable prospectus supplement, including, without limitation, the following, as applicable:

- the title of the series of units;
- identification and description of the separate constituent securities comprising the units;
- the price or prices at which the units will be issued;
- the date, if any, on and after which the constituent securities comprising the units will be separately transferable;
- a discussion of certain United States federal income tax considerations applicable to the units; and
- any other terms of the units and their constituent securities.

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PLAN OF DISTRIBUTION

We may sell common stock, preferred stock, depositary shares, debt securities, warrants or units in one or more of the following ways from time to time:

- to or through underwriters, dealers or agents;
- directly to one or more purchasers, including our affiliates; or
- through a combination of any of these methods of sale.

The prospectus supplements relating to an offering of offered securities will set forth the terms of such offering, including:

- the name or names of any underwriters, dealers or agents;
- the purchase price of the offered securities and the proceeds to us from the sale;
- any underwriting discounts and commissions or agency fees and other items constituting underwriters' or agents' compensation;
- any initial public offering price, any discounts or concessions allowed or reallowed or paid to dealers; and
- any securities exchanges on which such offered securities may be listed.

Any initial public offering prices, discounts or concessions allowed or reallowed or paid to dealers may be changed from time to time.

If underwriters are used in the sale, the underwriters will acquire the offered securities for their own account and may resell them from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. The offered securities may be offered either to the public through underwriting syndicates represented by one or more managing underwriters or by one or more underwriters without a syndicate. Unless otherwise set forth in a prospectus supplement, the obligations of the underwriters to purchase any series of securities will be subject to certain conditions precedent, and the underwriters will be obligated to purchase all of such series of securities if any are purchased.

In connection with underwritten offerings of the offered securities and in accordance with applicable law and industry practice, underwriters may over-allot or effect transactions that stabilize, maintain or otherwise affect the market price of the offered securities at levels above those that might otherwise prevail in the open market, including by entering stabilizing bids, effecting syndicate covering transactions or imposing penalty bids, each of which is described below.

- A stabilizing bid means the placing of any bid, or the effecting of any purchase, for the purpose of pegging, fixing or maintaining the price of a security.
- A syndicate covering transaction means the placing of any bid on behalf of the underwriting syndicate or the effecting of any purchase to reduce a short position created in connection with the offering.
- A penalty bid means an arrangement that permits the managing underwriter to reclaim a selling concession from a syndicate member in connection with the offering when offered securities originally sold by the syndicate member are purchased in syndicate covering transactions.

These transactions may be effected on the NASDAQ, in the over-the-counter market, or otherwise. Underwriters are not required to engage in any of these activities, or to continue such activities if commenced.

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If a dealer is used in the sale, we will sell such offered securities to the dealer, as principal. The dealer may then resell the offered securities to the public at varying prices to be determined by that dealer at the time for resale. The names of the dealers and the terms of the transaction will be set forth in the prospectus supplement relating to that transaction.

Offered securities may be sold directly by us to one or more institutional purchasers, or through agents designated by us from time to time, at a fixed price or prices, which may be changed, or at varying prices determined at the time of sale. Any agent involved in the offer or sale of the offered securities in respect of which this prospectus is delivered will be named, and any commissions payable by us to such agent will be set forth, in the prospectus supplement relating to that offering. Unless otherwise indicated in such prospectus supplement, any such agent will be acting on a best efforts basis for the period of its appointment.

Underwriters, dealers and agents may be entitled under agreements entered into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments that the underwriters, dealers or agents may be required to make in respect thereof. Underwriters, dealers and agents may be customers of, engage in transactions with, or perform services for us and our affiliates in the ordinary course of business.

Other than our common stock, which is listed on the NASDAQ Global Select Market, each of the securities issued hereunder will be a new issue of securities, will have no prior trading market, and may or may not be listed on a national securities exchange. Any common stock sold pursuant to a prospectus supplement will be listed on the NASDAQ Global Select Market, subject to official notice of issuance. Any underwriters to whom we sell securities for public offering and sale may make a market in the securities, but such underwriters will not be obligated to do so and may discontinue any market making at any time without notice. We cannot assure you that there will be a market for the offered securities.

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LEGAL MATTERS

The validity of the securities being offered hereby is being passed upon for us by Gunderson Dettmer Stough Villeneuve Franklin & Hachigian, LLP, Redwood City, California and Skadden, Arps, Slate, Meagher & Flom LLP, Palo Alto, California. As of the date of this prospectus, an investment fund associated with Gunderson Dettmer Stough Villeneuve Franklin & Hachigian, LLP beneficially owned less than 0.1% of the outstanding shares of our common stock. Any underwriters will also be advised about the validity of the securities and other legal matters by their own counsel, which will be named in the applicable prospectus supplement.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2015 as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

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4,500,000 Shares

COMMON STOCK

PROSPECTUS SUPPLEMENT

July 12, 2018

J.P. Morgan **Morgan Stanley** **Cowen**

EXHIBIT 6

News Release

Natera Announces Publication of Kidney Transplant Validation Study, Demonstrating Superior Data in Detection of Clinical and Subclinical Rejection

Represents Successful Achievement of All 2018 Commercialization Milestones, on Path to 2019 Launch

SAN CARLOS, Calif., Jan. 7, 2019 /PRNewswire/ -- Natera, Inc. (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=3123807725&u=http%3A%2F%2Fwww.natera.com%2F&a=Natera%2C+Inc.) (NASDAQ: NTRA), a leader in cell-free DNA, today announced clinical validation study results published in the *Journal of Clinical Medicine*,[1] demonstrating the highly accurate performance of its donor-derived cell-free DNA (dd-cfDNA) test for active allograft rejection in kidney transplant recipients, including higher sensitivity and nearly 18% higher area under the curve (AUC) than the competitive dd-cfDNA assay.[1,2] The study also reports the first accurate detection of T-cell mediated rejection (TCMR) and subclinical rejection. This marks the successful completion of all 2018 commercialization milestones, and is in line with the company's plan to secure Medicare coverage and commercially launch its test in 2019.

The blinded study, conducted in collaboration with the University of California, San Francisco (UCSF), leveraged Natera's massively-multiplexed PCR (mmPCR) technology to measure dd-cfDNA levels in plasma collected on the same day as a kidney biopsy from 193 unique kidney transplant recipients. The primary analysis focused on 217 plasma samples from 178 unique kidney transplant patients, including 38 cases of histologically-confirmed active rejection (AR), making it the

largest published study of its kind, with approximately two times more patients and 40 percent more affected cases of AR than the next largest study.[2] Another strength of the study is its broad ethnic diversity, which is important because kidney transplant assessment and biomarker performance are known to vary by ethnicity.

In the study, Natera's assay detected AR with 89% sensitivity and 0.87 AUC. This test performance compared favorably to the current standard of care, eGFR (estimated glomerular filtration rate), which is a clinically accepted but inaccurate biomarker for AR. The study results also showed higher sensitivity (89% vs. 59%) and higher AUC (0.87 vs. 0.74) than the competitive dd-cfDNA assay.[2] This superior data may be due to differences in the analytical performance and underlying technology behind the assays.

The new study also had two novel, clinically significant findings:

- **TCMR detection:** Test performance was independent of rejection type, including antibody-mediated rejection (ABMR, 16 cases), T-cell mediated rejection (TCMR, 10 cases), and combinations of the two (ABMR/TCMR, 12 cases). By contrast, previous dd-cfDNA studies reported a poor ability to detect TCMR, which represents approximately one third of all AR diagnoses, and more than half of the AR cases in certain patient subgroups.[3]
- **Subclinical AR detection:** Test performance was also independent of clinical presentation, demonstrating high accuracy in detecting both clinical and subclinical AR. The study was unique in that 13 of the 38 AR cases were diagnosed using protocol (or surveillance) biopsies, in contrast to the other 25 cases diagnosed using for-cause (or clinically-indicated) biopsies. The 13 cases are considered "subclinical AR," because the patients otherwise had stable renal function based on serum creatinine, showing no clinical signs of rejection. In the study, Natera's assay detected the subclinical AR cases with 92% sensitivity and 75% specificity. No other dd-cfDNA assay has been validated to detect subclinical AR, which occurs in 20-25% of patients in the first two years post-transplant,[4] and which is considered a major driver of graft failure.

According to Paul Billings, M.D., Ph.D., Natera's Chief Medical Officer and Senior Vice President of Medical Affairs, Natera's dd-cfDNA-based assay is designed to help physicians detect active rejection events earlier, avoid unnecessary biopsies, and better optimize immunosuppression levels. "This published study adds to the mounting body of evidence showing the validity of dd-cfDNA in detecting active allograft rejection," Billings said.

"With this publication, we have achieved all of the company's 2018 milestones related to our transplant business, including the attainment of a Z-code, completion of analytical and clinical validation studies, and completion of the CLIA validation," said Steve Chapman, Natera's CEO. "This is in line with Natera's history of successful execution with regard to commercializing novel clinical assays."

There are more than 190,000 people living with a kidney transplant in the U.S.[5] and roughly 20,000 new kidney transplant surgeries performed each year.[6] It is estimated that 20-30 percent of organ transplants fail within five years and approximately 50 percent fail within 10 years.[7,8] The current tools for diagnosing organ transplant rejection are either invasive (biopsies) or inaccurate (serum creatinine), creating a strong unmet need for better diagnostic tools to improve patient management and outcomes.

About Natera's dd-cfDNA Organ Transplant Assay

Natera's organ transplant rejection assay is designed to detect active allograft rejection in patients who have undergone renal (kidney) transplantation. The assay works by measuring the fraction of donor-derived cell-free DNA (dd-cfDNA) in the recipient's blood, which can spike relative to background cfDNA when the transplanted organ is injured due to immune rejection. The assay leverages Natera's core single nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) technology, to more accurately measure dd-cfDNA levels without the need for donor genotyping, and it has been clinically validated for test performance independent of donor type, rejection type, and clinical presentation.

About Natera

Natera (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=2651265320&u=http%3A%2F%2Fwww.natera.com%2F&a=Natera) is a global leader in cell-free DNA testing. The

mission of the company is to transform the management of diseases worldwide. Natera operates an ISO 13485-certified and CAP-accredited laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) in San Carlos, Calif. It offers a host of proprietary genetic testing services to inform physicians who care for pregnant women, researchers in cancer including bio pharmaceutical companies, and genetic laboratories through its cloud-based software platform. For more information, visit natera.com (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=3905460127&u=http%3A%2F%2Fwww.natera.com%2F&a=natera.com). Follow Natera on LinkedIn (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=1342219293&u=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Fnatera%2F&a=LinkedIn) and (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=1788793007&u=https%3A%2F%2Ftwitter.com%2FNateraGenetics&a=%C2%A0)Twitter (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=3981149194&u=https%3A%2F%2Ftwitter.com%2FNateraGenetics&a=Twitter).

Forward-Looking Statements

All statements other than statements of historical facts contained in this press release are forward-looking statements and are not a representation that Natera's plans, estimates, or expectations will be achieved. These forward-looking statements represent Natera's expectations as of the date of this press release, and Natera disclaims any obligation to update the forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual results to differ materially, including with respect to our efforts to develop and commercialize new product offerings, our ability to successfully increase demand for and grow revenues for our product offerings, whether the results of clinical studies will support the use of our product offerings, our expectations of the reliability, accuracy and performance of our tests, or of the benefits of our tests and product offerings to patients, providers and payers. Additional risks and uncertainties are discussed in greater detail in "Risk Factors" in Natera's recent filings on Forms 10-K and 10-Q and in other filings Natera makes with the SEC from time to time. These documents are available at www.natera.com/investors (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=3621891654&u=http%3A%2F%2Fwww.natera.com%2Finvestors&a=www.natera.com%2Finvestors) and (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=2760063341&u=https%3A%2F%2Fwww.sec.gov%2F&a=%C2%A0)www.sec.gov (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=1223606294&u=http%3A%2F%2Fwww.sec.gov%2F&a=www.sec.gov). (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=1826827854&u=https%3A%2F%2Fwww.sec.gov%2F&a=.)

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References

1. Sigdel TK, Archila FA, Constantin T, et al. Optimizing Detection of Kidney Transplant Injury by Assessment of Donor-Derived Cell-Free DNA via Massively Multiplex PCR. *J. Clin. Med*. 2019, *8*, 19.
2. Bloom RD, Bromberg JS, Poggio ED, et al. Cell-free DNA and active rejection in kidney allografts. *J Am Soc Nephrol*. 2017 Jul;28(7):2221-2232. doi: 10.1681/ASN.2016091034. Epub 2017 Mar 9.
3. Wehmeier C, Amico P, Minkowski, PH, et al. Acute Rejection Phenotypes in the Current Era of Immunosuppression: A Single-Center Analysis. Transplantation Direct 2017;3: e136; doi: 10.1097/TXD.0000000000000650. Published online 9 February, 2017.
4. Choi BS, Shin MJ, Shin SJ, et al. Clinical significance of an early protocol biopsy in living-donor renal transplantation: Ten-year experience at a single center. *Am J Transplant* 2006; 5: 1354-1360
5. Kidney Disease Statistics for the United States. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=3131343829&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2311473-1%26h%3D473521873%26u%3Dhttps%253A%252F%252Fwww.niddk.nih.gov%252Fhealth-

information%252Fhealth-statistics%252Fkidney-disease%26a%3Dhttps%253A%252F%252Fwww.niddk.nih.gov%252Fhealth-information%252Fhealth-statistics%252Fkidney-disease&a=https%3A%2F%2Fwww.niddk.nih.gov%2Fhealth-information%2Fhealth-statistics%2Fkidney-disease). Published Dec. 1, 2016.

6. Organ Donation Statistics. U.S. Department of Health and Human Services. U.S. Government Information on Organ Donation and Transplantation. https://www.organdonor.gov/statistics-stories/statistics.html (https://c212.net/c/link/?t=0&l=en&o=2339767-1&h=3287202203&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2311473-1%26h%3D3614975809%26u%3Dhttps%253A%252F%252Fwww.organdonor.gov%252Fstatistics-stories%252Fstatistics.html%26a%3Dhttps%253A%252F%252Fwww.organdonor.gov%252Fstatistics-stories%252Fstatistics.html&a=https%3A%2F%2Fwww.organdonor.gov%2Fstatistics-stories%2Fstatistics.html). Published March 31, 2016.
7. Stegall MD, Gaston RS, Cosio FG, Matas A. Through a glass darkly: seeking clarity in preventing late kidney transplant failure. *J Am Soc Nephrol*. 2015; 26(1):20-9.
8. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant*. 2011; 11(3):450-62.

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SOURCE Natera

EXHIBIT 7


Natera Company Presentation
J.P. Morgan Healthcare Conference
January 9, 2019
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https://jpmorgan.metameetings.net/events/healthcare19/sessions/24088-natera/webcast

Implemented planned succession strategy

Matthew Rabinowitz moving to Executive Chairman

- Will remain heavily involved focusing on long-term technology and strategy

Steve Chapman selected for CEO

- Extensive track record of rapid growth and commercial success

Robert "Bob" Schueren recruited as COO

- Extensive track record of driving profitability and efficiency
- Formerly CEO of IntegenX, Senior Executive at Thermo-Fisher, Agilent, Genentech

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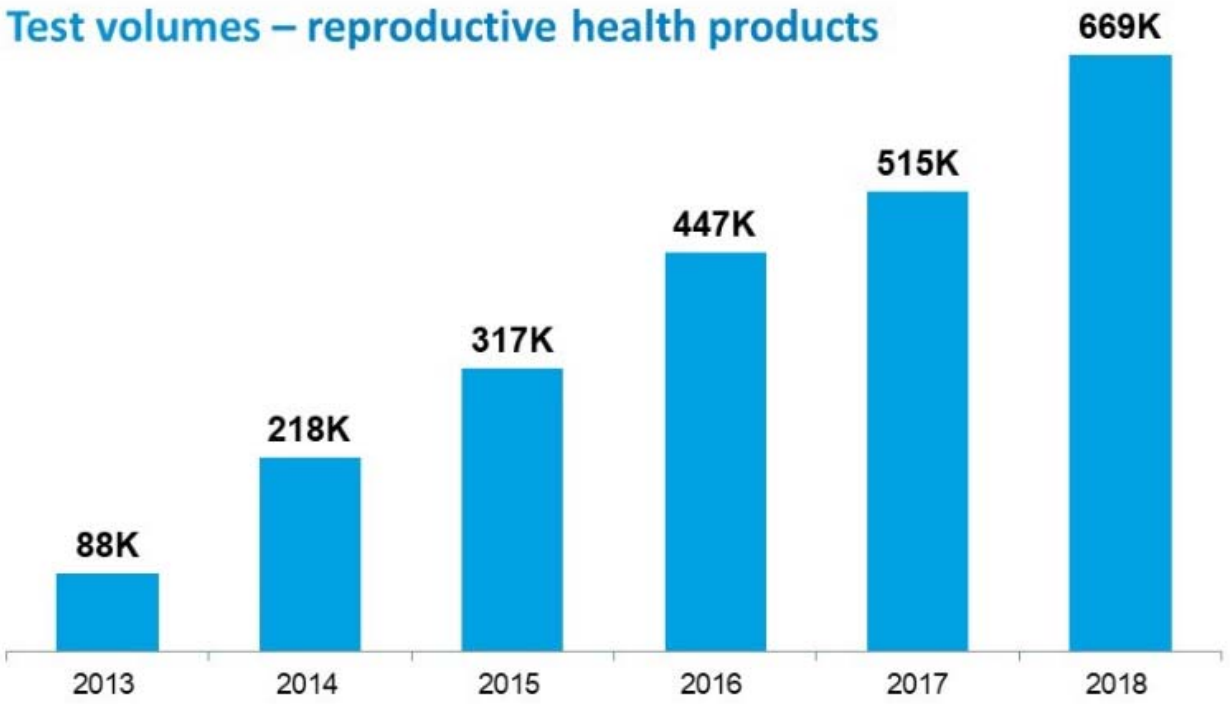
Leadership position and rapid growth in genetic testing

Test volumes – reproductive health products



- **Horizon™** Advanced carrier screening
- **Spectrum®** Preimplantation genetics
- **Panorama®** Next-generation NIPT
- **Vistara** Single-gene NIPT
- **Anora®** Miscarriage test (POC)
- **Evercord™** Newborn stem cell banking
- **Signatera™** Research use only

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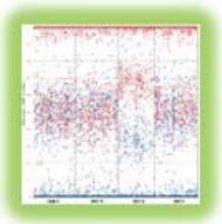
Core technology driving $18B U.S. market opportunity



NOVEL
cfDNA MOLECULAR
METHODS

PROPRIETARY
BIOINFORMATICS
IN CLOUD

Validated with NYS, CAP, CLIA, CE-Mark and published in 46 peer reviewed publications

REPRODUCTIVE
$4 Billion

ONCOLOGY
$12+ Billion

TRANSPLANT
$2 Billion

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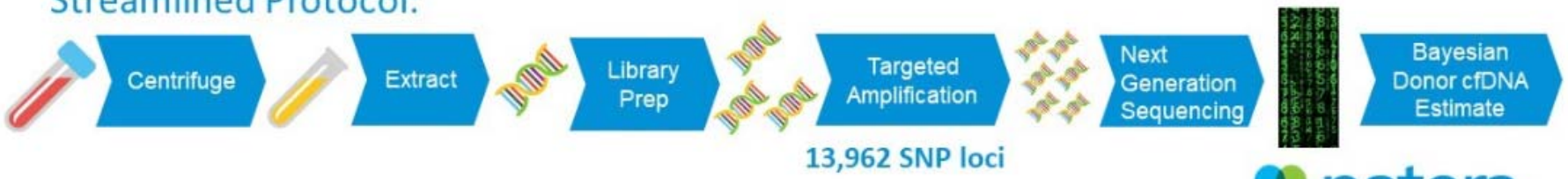
Natera mmPCR and informatics technology: Significant performance advantage in transplant*

- Optimized NIPT extraction and library prep for high yield of kidney dd-cfDNA
- Targeted mmPCR amplification > 13,000 SNPs; each primer has uniform thermodynamics and minimal cross-reactions
- Larger number of SNPs ensures minimal variance, including related donors
- Maximum likelihood Bayesian optimization to precisely estimate cfDNA with minimal variance at levels < 1%

Streamlined Protocol:



* Based on SNP-based dd-cfDNA of 217 plasma specimens from 178 unique kidney transplant recipients

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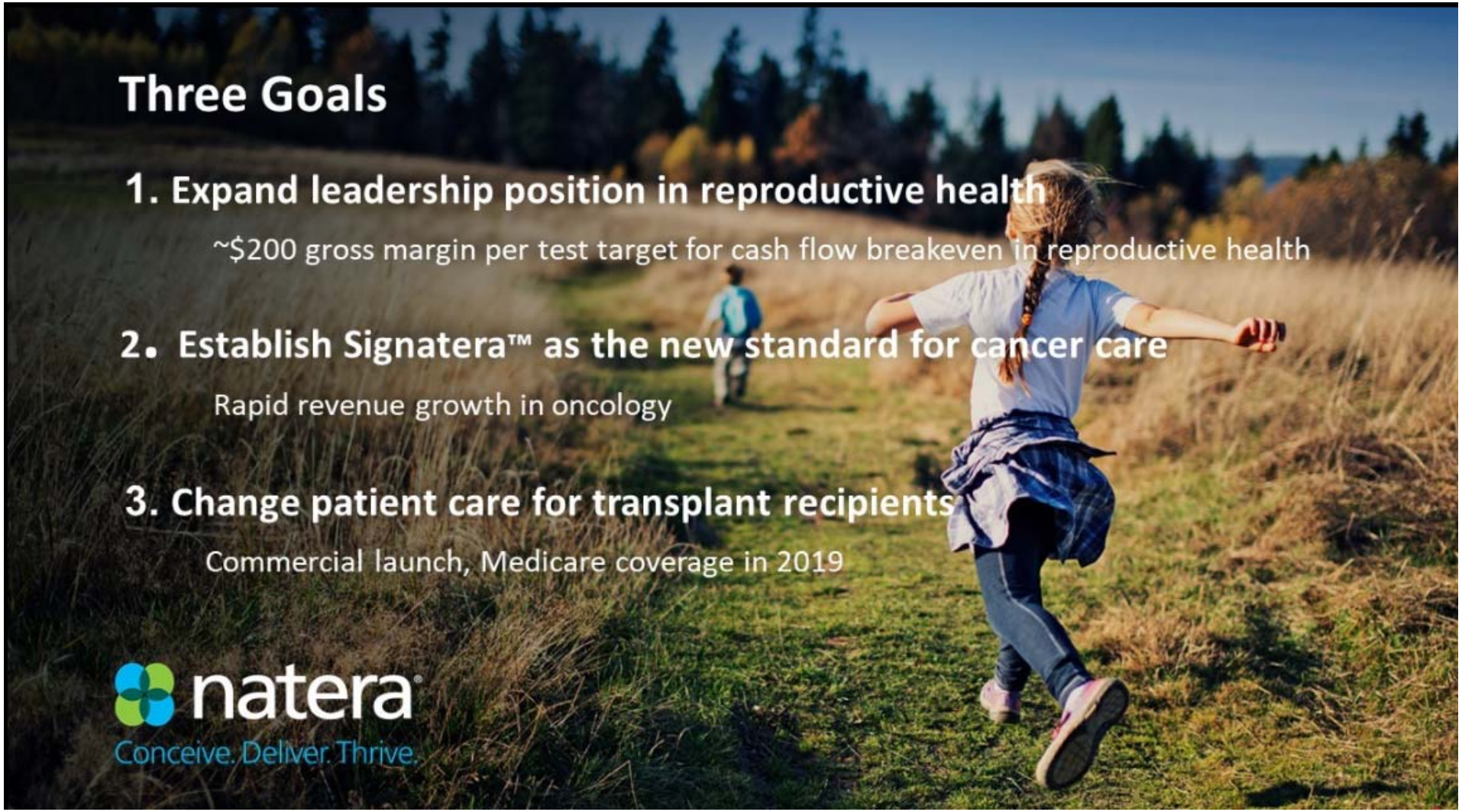
Three Goals
1. Expand leadership position in reproductive health
~$200 gross margin per test target for cash flow breakeven in reproductive health
2. Establish Signatera™ as the new standard for cancer care
Rapid revenue growth in oncology
3. Change patient care for transplant recipients
Commercial launch, Medicare coverage in 2019
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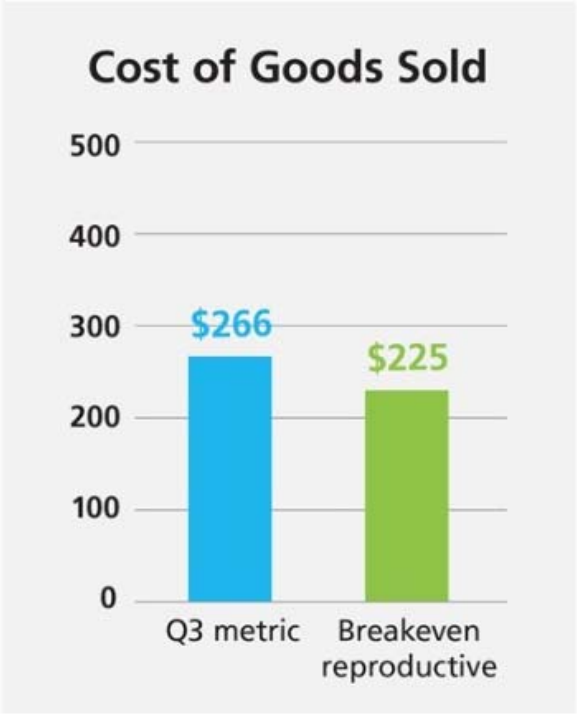
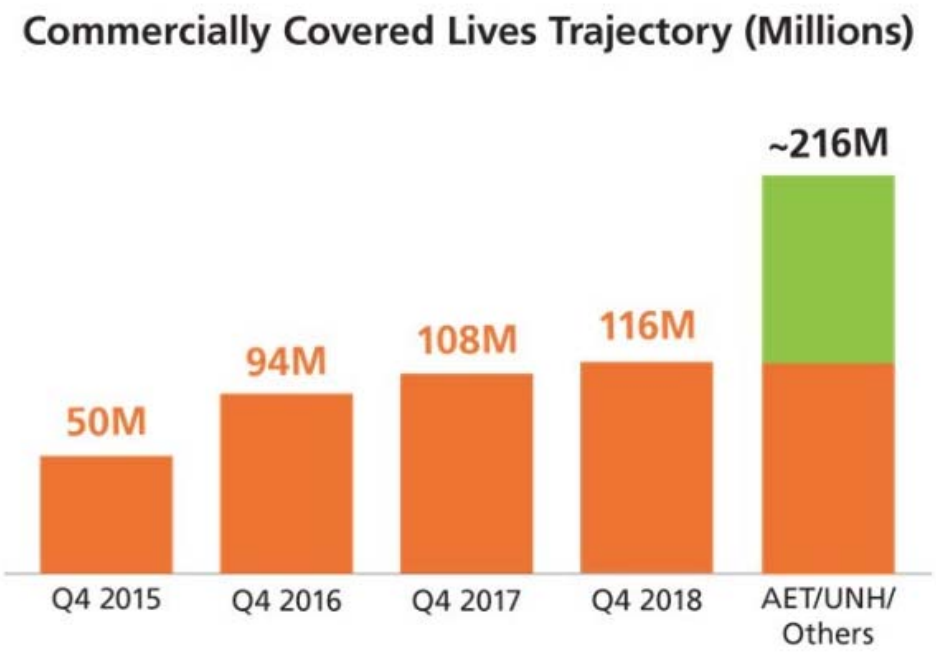
Goal 1: Expand leadership in reproductive health



$200 gross margin per test x 900,000 units = $180 million gross margin

Average risk NIPT adoption growing



 Source: Company Estimates

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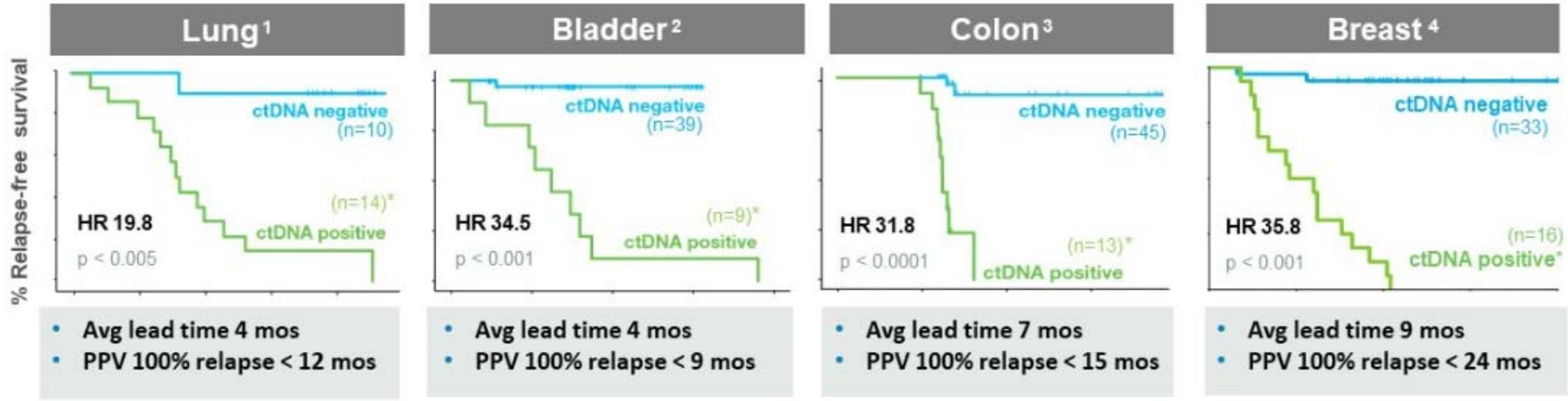
Goal 2: Establish Signatera™ as the new standard in cancer



- Avg lead time 4 mos
- PPV 100% relapse < 12 mos

- Avg lead time 4 mos
- PPV 100% relapse < 9 mos

- Avg lead time 7 mos
- PPV 100% relapse < 15 mos

- Avg lead time 9 mos
- PPV 100% relapse < 24 mos

Positive result without further treatment has always predicted relapse

1. RFS post treatment. Abbosh C, et al. Nature. 2017 Apr 26;545(7655):446-451
2. RFS post cystectomy. Birkenkamp-Demtroder K, et al. AACR; 2018. Abstract nr 3653
3. RFS post ACT treatment. Reinert T, et al. AACR; 2018 Abstract nr 1590
4. Coombes RC, et al. 2018 SABCS Abstract nr 1266

* Positive at any time point at or before clinical relapse

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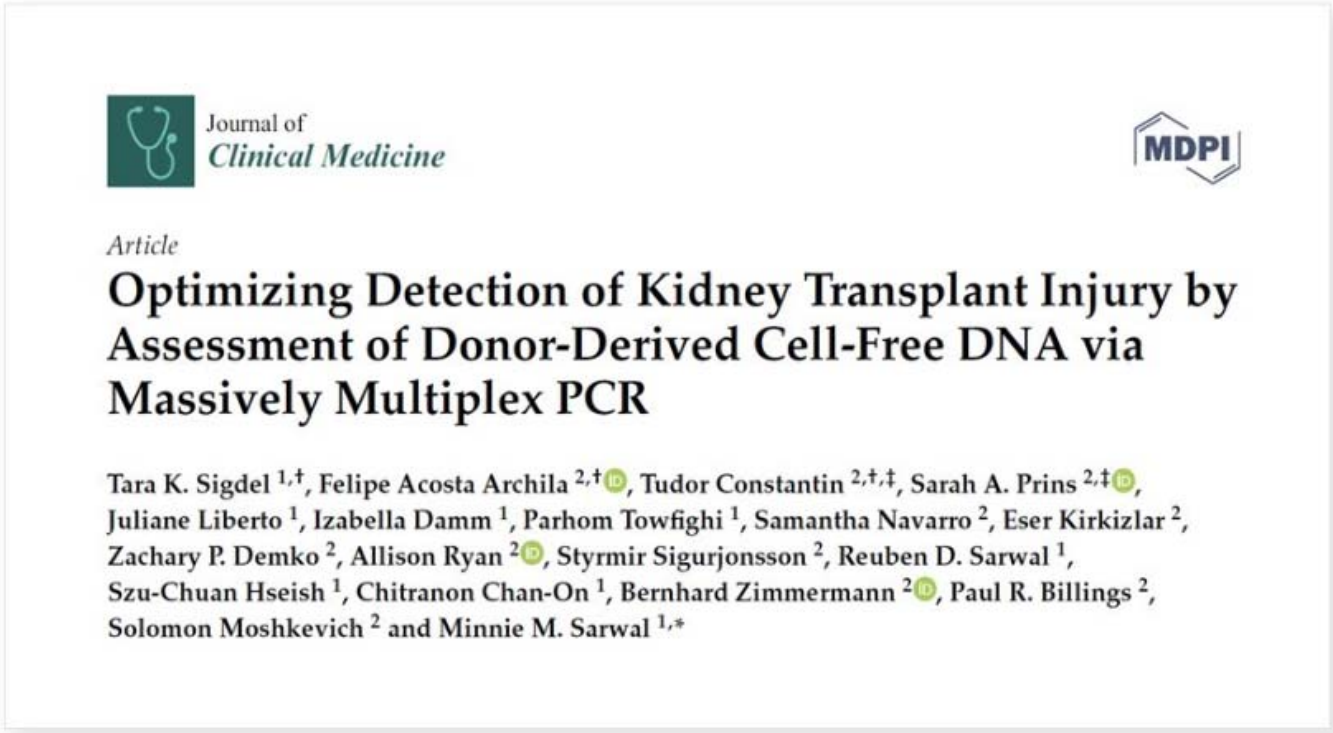
Pharma adoption continues to ramp

Key trial indications:

- **Recurrence monitoring**
- **Therapy effectiveness**
  - Neoadjuvant
  - Metastatic
- **Neoantigen tracking**
- **MRD for clinical trials**
  - Inclusion criteria
  - Surrogate endpoint

Data generated in pharma trials to drive clinical adoption

Goal 3: Change patient care for transplant recipients



Journal of *Clinical Medicine*

MDPI

Article

Optimizing Detection of Kidney Transplant Injury by Assessment of Donor-Derived Cell-Free DNA via Massively Multiplex PCR

Tara K. Sigdel [1,†], Felipe Acosta Archila [2,†], Tudor Constantin [2,†,‡], Sarah A. Prins [2,‡], Juliane Liberto [1], Izabella Damm [1], Parhom Towfighi [1], Samantha Navarro [2], Eser Kirkizlar [2], Zachary P. Demko [2], Allison Ryan [2], Styrmir Sigurjonsson [2], Reuben D. Sarwal [1], Szu-Chuan Hseish [1], Chitranon Chan-On [1], Bernhard Zimmermann [2], Paul R. Billings [2], Solomon Moshkevich [2] and Minnie M. Sarwal [1,*]

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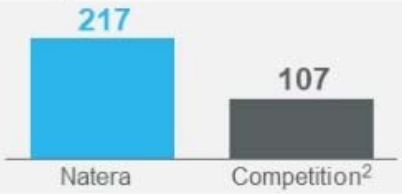
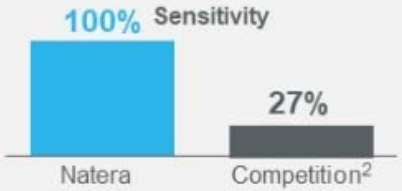
Change patient care for transplant recipients

- Largest dd-cfDNA validation study[1]

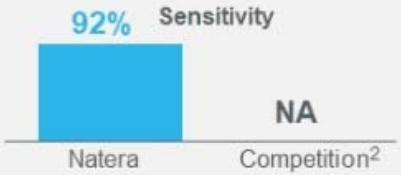


- Highest area under the curve; driven by superior clinical data[1]

- First test to perform well in T-cell mediated rejection cases[1] (about 1/3 of cases[3])



- First test to consistently detect subclinical acute rejection[1] (20-25% of cases[4])



1 Sigdel TK,, et al.. J. Clin. Med. 2019, 8, 19. 2. Bloom RD, et al. J Am Soc Nephrol. 2017 Jul;28(7):2221-2232. 3. Wehmeier C, et al. Transplantation Direct 2017;3: e136. 4. Choi BS, et al. Am J Transplant 2006; 5: 1354-1360

Transplant reimbursement pathway on track

- ✓ Completed analytical validation
- ✓ Completed clinical validation
- ✓ Successful pre-submission meeting
- ✓ Obtained Z-code
- ✓ Completed CLIA validation
- ✓ Formal LCD submission

2018 / 2019

- Draft LCD release
- Establish coding and pricing
- Launch registry study
- Final LCD published

2019

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Horizon™
Advanced carrier screening

Spectrum®
Preimplantation genetics

Panorama®
Next-generation NIPT

Vistara
Single-gene NIPT

Anora®
Miscarriage test (POC)

Evercord™
Newborn stem cell banking

Signatera™
Research use only

Constellation™
Technology licensing

EXHIBIT 8

News Release

Natera Announces Agreement with One Lambda to Co-Distribute Its Kidney Transplant Rejection Test

Agreement Enhances Commercial Presence in Organ Transplant Centers

SAN CARLOS, Calif., Feb. 1, 2019 /PRNewswire/ -- Natera, Inc. (https://c212.net/c/link/?t=0&l=en&o=2363243-1&h=441237491&u=http%3A%2F%2Fwww.natera.com%2F&a=Natera%2C+Inc.) (NASDAQ: NTRA), a leader in non-invasive genetic testing and the analysis of cell-free DNA, today announced a partnership with Thermo Fisher Scientific's One Lambda brand, a global leader in human leukocyte antigen (HLA) typing and antibody monitoring assays for transplantation, to co-distribute Natera's kidney transplant rejection test in the United States in collaboration with the company's direct sales team.

"We are excited to partner with One Lambda, a pioneer in transplant diagnostics," said Steve Chapman, CEO, Natera. "This partnership will help accelerate our entry into this new market by leveraging the commercial infrastructure of a highly respected and well-established leader in the field, along with our direct sales team."

"Natera's donor-derived cell-free DNA test complements our existing transplant offerings and enables us to provide a more advanced portfolio for monitoring kidney rejection," said Parisa Khosropour, President, Transplant Diagnostics, Thermo Fisher Scientific. "We look forward to offering our customers a test that improves upon currently available options and provides unique performance advantages in detecting T-cell mediated rejection and subclinical acute rejection, both of which may have a more positive impact on patient outcomes."

About Natera's dd-cfDNA Organ Transplant Assay

Natera's organ transplant rejection assay is designed to detect active allograft rejection in patients who have undergone kidney transplantation. The assay works by measuring the fraction of donor-derived cell-free DNA (dd-cfDNA) in the recipient's blood, which can spike relative to normal cfDNA when the transplanted organ is injured due to immune rejection. The assay leverages Natera's core single

nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) technology to accurately measure dd-cfDNA levels without the need for donor genotyping, and it has been clinically validated with test performance independent of donor type, rejection type, and clinical presentation.

In a recent study published in the *Journal of Clinical Medicine*, Natera's assay detected acute rejection (AR) with 89% sensitivity and 0.87 area under the curve (AUC).[1] This test performance compares favorably to the current standard of care, which is based on serial measurements of serum creatinine; and it compares favorably against competition, which in a 2017 study reported 59% sensitivity and 0.74 AUC.[2] The recent study also had two novel, clinically significant findings relative to previously published studies of dd-cfDNA. The Natera dd-cfDNA assay was able to accurately detect TCMR (T-cell mediated rejection), a common and treatable form of active rejection, and subclinical acute rejection.[1] No other dd-cfDNA assay has been shown to detect TCMR or validated to detect subclinical AR, which occurs in 20-25% of patients in the first two years post-transplant,[3] and which is considered a major driver of graft failure.

About One Lambda

One Lambda, a Thermo Fisher Scientific brand, is the global leader in HLA and antibody monitoring assays for transplantation. Known for its commitment to quality, service, and innovation, the company develops and distributes several lines of HLA typing and antibody monitoring tests utilizing serological, molecular, flow, solid phase & NGS technologies. In addition, One Lambda also provides laboratory instrumentation and computer software that are used to simplify and automate testing procedures and final test evaluations. For more information, please visit www.onelambda.com (https://c212.net/c/link/?t=0&l=en&o=2363243-1&h=1743076005&u=http%3A%2F%2Fwww.onelambda.com%2F&a=www.onelambda.com).

About Natera

Natera (https://c212.net/c/link/?t=0&l=en&o=2363243-1&h=1048191798&u=http%3A%2F%2Fwww.natera.com%2F&a=Natera) is a global leader in cell-free DNA testing. The mission of the company is to transform the management of diseases worldwide. Natera operates an ISO 13485-certified and CAP-accredited laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) in San Carlos, Calif. It offers a host of proprietary genetic testing services to inform physicians who care for pregnant women, researchers in cancer including biopharmaceutical companies, and genetic laboratories through its cloud-based software platform. Follow Natera on LinkedIn (https://c212.net/c/link/?t=0&l=en&o=2363243-1&h=4034764291&u=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Fnatera%2F&a=LinkedIn) and Twitter (https://c212.net/c/link/?t=0&l=en&o=2363243-1&h=1295433236&u=https%3A%2F%2Ftwitter.com%2FNateraGenetics&a=Twitter).

Natera Forward-Looking Statements

All statements other than statements of historical facts contained in this press release are forward-looking statements and are not a representation that Natera's plans, estimates, or expectations will be achieved. These forward-looking statements represent Natera's expectations as of the date of this press release, and Natera disclaims any obligation to update the forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual results to differ materially, including with respect to our efforts to develop and commercialize new product offerings, our ability to successfully increase demand for and grow revenues for our product offerings, whether the results of clinical studies will support the use of our product offerings, our

expectations of the reliability, accuracy and performance of our screening tests, or of the benefits of our screening tests and product offerings to patients, providers and payers. Additional risks and uncertainties are discussed in greater detail in "Risk Factors" in Natera's recent filings on Forms 10-K and 10-Q and in other filings Natera makes with the SEC from time to time. These documents are available at www.natera.com/investors (https://c212.net/c/link/?t=0&l=en&o=2363243-1&h=2006750296&u=http%3A%2F%2Fwww.natera.com%2Finvestors&a=www.natera.com%2Finvestors) and www.sec.gov (https://c212.net/c/link/?t=0&l=en&o=2363243-1&h=3902011912&u=http%3A%2F%2Fwww.sec.gov%2F&a=www.sec.gov).

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Media: Andrea Sampson, Sullivan & Sampson, 714-374-6174, asampson@sullivanpr.com (mailto:asampson@sullivanpr.com)

References

1. Sigdel TK, Archila FA, Constantin T, et al. Optimizing detection of kidney transplant injury by assessment of donor-derived cell-free DNA via massively multiplex PCR. *J Clin Med*. 2019;8 (1):19.
2. Bloom RD, Bromberg JS, Poggio ED, et al. Cell-free DNA and active rejection in kidney allografts. *J Am Soc Nephrol*. 2017;28(7):2221-2232. doi: 10.1681/ASN.2016091034.
3. Choi BS, Shin MJ, Shin SJ, et al. Clinical significance of an early protocol biopsy in living-donor renal transplantation: ten-year experience at a single center. *Am J Transplant*. 2005;6:1354-1360.

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SOURCE Natera, Inc.

EXHIBIT 9

News Release

Natera Announces Publication of Analytical Validation Study Demonstrating Superior Precision of Its Kidney Transplant Rejection Assay

Core Technology Delivers Superior Analytical Performance, Underpins Outstanding Clinical Performance

SAN CARLOS, Calif., Feb. 22, 2019 /PRNewswire/ -- Natera, Inc. (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=3147252355&u=http%3A%2F%2Fwww.natera.com%2F&a=Natera%2C+Inc.) (NASDAQ: NTRA), a leader in cell-free DNA, today announced analytical validation study results to be published online in the journal *Transplantation* demonstrating the superior performance of its donor-derived cell-free DNA (dd-cfDNA) test for detecting active rejection in kidney transplant recipients.[1] The study showed superior assay precision with coefficient of variation up to five times better than previously published studies.[1,2]

Natera's analytical validation was based on the analysis of 1,064 replicate samples from both related and non-related donor-recipient pairs. Conducted according to rigorous guidelines from the Clinical & Laboratory Standards Institute, the validation study measured key properties of the assay, including lower limit of detection, linearity, and precision. The assay's precision was particularly strong, showing a coefficient of variation up to five times better than that of a competitive dd-cfDNA assay (1.85% vs. 9.2% within run; 1.99% vs. 4.5% across runs) in repeatability and reproducibility studies.[1,2]

Previously published analytical studies using other dd-cfDNA assays did not include related donor-recipient cases (such as parents or siblings), which is notable given the technical challenge of differentiating DNA patterns from close relatives. It has been estimated that 52 percent of live kidney donations originate from biologically related donors.[3] Natera has leveraged its deep experience using single-nucleotide polymorphism (SNP)-based methods to analyze fetal DNA in maternal blood to achieve high accuracy in these cases.

"We believe the excellent analytical performance can be attributed to the test's underlying core technology, based on Natera's unique SNP-based mmPCR method, which has been a key differentiator in the analysis of cell-free DNA in the prenatal setting, in oncology, and now in organ transplantation," said Allison Ryan, Ph.D., Natera's Vice-President of Data Science. "We achieved high precision by targeting more than 13,000 SNPs, selected to be informative regardless of ethnicity, optimizing the DNA extraction and library preparation to maximize performance, and by developing a unique bioinformatics method that is highly accurate, even in more challenging related donor-recipient cases."

The excellent analytical performance of Natera's dd-cfDNA assay underpins its superior clinical performance in detecting active allograft rejection (AR). In its recently published clinical validation study,[4] Natera reported higher sensitivity (89% vs. 59%) and higher area under the curve (0.87 vs. 0.74) than the competing dd-cfDNA assay.[4,5] In that study, Natera also outperformed the competing assay in detecting T-cell mediated rejection (TCMR), which represents approximately one-third of all AR diagnoses.[6] In addition, it was the first assay to report high accuracy in detecting subclinical rejection, which occurs in 20-25 percent of patients in the first two years post-transplant[7] and is considered a major driver of graft failure.

"The growing body of evidence from our analytical and clinical validation studies supports our belief that Natera's non-invasive test will be a valuable tool for the management of kidney transplant recipients," said Paul Billings, M.D., Ph.D., Natera's Chief Medical Officer and Senior Vice President of Medical Affairs. "Our ultimate goal is to help physicians detect rejection earlier so that patients' immunosuppression levels can be optimized before irreversible organ damage occurs."

There are more than 190,000 people living with a kidney transplant in the U.S.[8] and roughly 20,000 new kidney transplant surgeries are performed each year.[9] It is estimated that 20-30 percent of organ transplants fail within five years and approximately 50 percent fail within 10 years.[10,11] The current tools for diagnosing organ transplant rejection are either invasive (biopsies) or inaccurate (serum creatinine), creating a strong unmet need for better diagnostic tools to improve patient management and outcomes.

The study, titled Analytical Validation of a Single-Nucleotide Polymorphism-Based Donor-Derived Cell-Free DNA Assay for Detecting Rejection in Kidney Transplant Patients, will be available here (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=7696022&u=https%3A%2F%2Fjournals.lww.com%2Ftransplantjournal%2Fpages%2Fdefault.aspx&a=here).

About Natera's dd-cfDNA Organ Transplant Assay

Natera's organ transplant rejection assay is designed to detect active allograft rejection in patients who have undergone renal (kidney) transplantation. The assay works by measuring the fraction of donor-derived cell-free DNA (dd-cfDNA) in the recipient's blood, which can spike relative to background recipient cfDNA when the transplanted organ is injured due to immune rejection. The assay leverages Natera's core single-nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) technology to more accurately measure dd-cfDNA levels without the need for donor genotyping. It has been clinically and analytically validated for test performance independent of donor type, rejection type, and clinical presentation.

About Natera

Natera (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=2678185542&u=http%3A%2F%2Fwww.natera.com%2F&a=Natera) is a global leader in cell-free DNA testing. The mission of the company is to change the management of disease worldwide. Natera operates an ISO 13485-certified and CAP-accredited laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) in San Carlos, Calif. It offers a host of proprietary genetic testing services to inform physicians who care for pregnant women,

researchers in cancer including bio pharmaceutical companies, and genetic laboratories through its cloud-based software platform. For more information, visit (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=2463454137&u=http%3A%2F%2Fwww.natera.com%2F&a=%C2%A0)natera.com (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=3916321009&u=http%3A%2F%2Fwww.natera.com%2F&a=natera.com). Follow Natera on (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=3636774139&u=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Fnatera%2F&a=%C2%A0)LinkedIn (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=1369858931&u=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Fnatera%2F&a=LinkedIn) and Twitter (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=2975344652&u=https%3A%2F%2Ftwitter.com%2FNateraGenetics&a=%C2%A0Twitter).

Forward-Looking Statements

All statements other than statements of historical facts contained in this press release are forward-looking statements and are not a representation that Natera's plans, estimates, or expectations will be achieved. These forward-looking statements represent Natera's expectations as of the date of this press release, and Natera disclaims any obligation to update the forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual results to differ materially, including with respect to our efforts to develop and commercialize new product offerings, our ability to successfully increase demand for and grow revenues for our product offerings, whether the results of clinical studies will support the use of our product offerings, our expectations of the reliability, accuracy and performance of our tests, or of the benefits of our tests and product offerings to patients, providers and payers. Additional risks and uncertainties are discussed in greater detail in "Risk Factors" in Natera's recent filings on Forms 10-K and 10-Q and in other filings Natera makes with the SEC from time to time. These documents are available at (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=3170498759&u=http%3A%2F%2Fwww.natera.com%2Finvestors&a=%C2%A0)www.natera.com/investors (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=3595004200&u=http%3A%2F%2Fwww.natera.com%2Finvestors&a=www.natera.com%2Finvestors) and www.sec.gov (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=2396191255&u=http%3A%2F%2Fwww.sec.gov%2F&a=%C2%A0www.sec.gov). (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=1833298208&u=https%3A%2F%2Fwww.sec.gov%2F&a=.)

The test was developed by Natera, Inc. a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA). This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Although FDA does not currently clear or approve laboratory-developed tests in the U.S., certification of the laboratory is required under CLIA to ensure the quality and validity of the tests.

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References

1. Altuğ Y, Liang N, Ram R, et al. Analytical validation of a single-nucleotide polymorphism-based donor-derived cell-free DNA assay for detecting rejection in kidney transplant patients. Transplantation, 2019
2. Grskovic M, Hiller DJ, Eubank LA, et al. Validation of a clinical-grade assay to measure donor-derived cell-free DNA in solid organ transplant recipients. *J Mol Diagn*. 2016;18(6):890-902.
3. Hart A, Smith JM, Skeans MA, et al. 2014 Annual report of the U.S. organ procurement and transplantation network and the scientific registry of transplant recipients: kidney. *Am J Transplant*. 2016;16(Suppl 2):11-46.
4. Sigdel TK, Archila FA, Constantin T, et al. Optimizing detection of kidney transplant injury by assessment of donor-derived cell-free DNA via massively multiplex PCR. *J Clin Med*. 2019;8(1):19.
5. Bloom RD, Bromberg JS, Poggio ED, et al. Cell-free DNA and active rejection in kidney allografts. *J Am Soc Nephrol*. 2017;28(7):2221-2232. doi: 10.1681/ASN.2016091034.

6. Wehmeier C, Amico P, Minkowski, PH, et al. Acute rejection phenotypes in the current era of immunosuppression: a single-center analysis. *Transplantation Direct*. 2017;3(3):e136. doi: 10.1097/TXD.0000000000000650.
7. Choi BS, Shin MJ, Shin SJ, et al. Clinical significance of an early protocol biopsy in living-donor renal transplantation: Ten-year experience at a single center. *Am J Transplant.* 2006;5:1354-1360.
8. Kidney Disease Statistics for the United States. National Institute of Diabetes and Digestive and Kidney Diseases. (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=999843739&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2311473-1%26h%3D473521873%26u%3Dhttps%253A%252F%252Fwww.niddk.nih.gov%252Fhealth-information%252Fhealth-statistics%252Fkidney-disease%26a%3Dhttps%253A%252F%252Fwww.niddk.nih.gov%252Fhealth-information%252Fhealth-statistics%252Fkidney-disease&a=%C2%A0)https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=3137488059&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2311473-1%26h%3D473521873%26u%3Dhttps%253A%252F%252Fwww.niddk.nih.gov%252Fhealth-information%252Fhealth-statistics%252Fkidney-disease%26a%3Dhttps%253A%252F%252Fwww.niddk.nih.gov%252Fhealth-information%252Fhealth-statistics%252Fkidney-disease&a=https%3A%2F%2Fwww.niddk.nih.gov%2Fhealth-information%2Fhealth-statistics%2Fkidney-disease). Published Dec. 1, 2016.
9. Organ Donation Statistics. U.S. Department of Health and Human Services. U.S. Government Information on Organ Donation and Transplantation. (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=2658069173&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2311473-1%26h%3D3614975809%26u%3Dhttps%253A%252F%252Fwww.organdonor.gov%252Fstatistics-stories%252Fstatistics.html%26a%3Dhttps%253A%252F%252Fwww.organdonor.gov%252Fstatistics-stories%252Fstatistics.html&a=%C2%A0)https://www.organdonor.gov/statistics-stories/statistics.html (https://c212.net/c/link/?t=0&l=en&o=2383031-1&h=3259530997&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2311473-1%26h%3D3614975809%26u%3Dhttps%253A%252F%252Fwww.organdonor.gov%252Fstatistics-stories%252Fstatistics.html%26a%3Dhttps%253A%252F%252Fwww.organdonor.gov%252Fstatistics-stories%252Fstatistics.html&a=https%3A%2F%2Fwww.organdonor.gov%2Fstatistics-stories%2Fstatistics.html). Published March 31, 2016.
10. Stegall MD, Gaston RS, Cosio FG, Matas A. Through a glass darkly: seeking clarity in preventing late kidney transplant failure. *J Am Soc Nephrol*. 2015;26(1):20-9.
11. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant*. 2011;11(3):450-62.

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SOURCE Natera, Inc.

EXHIBIT 10

Natera Announces Agreement with One Lambda to Co-Distribute Its Kidney Transplant Rejection Test

SAN CARLOS, Calif.,-- Natera, Inc. a leader in non-invasive genetic testing and the analysis of cell-free DNA, today announced a partnership with Thermo Fisher Scientific's One Lambda brand, a global leader in human leukocyte antigen (HLA) typing and antibody monitoring assays for transplantation, to co-distribute Natera's kidney transplant rejection test in the United States in collaboration with the company's direct sales team.

"We are excited to partner with One Lambda, a pioneer in transplant diagnostics," said Steve Chapman, CEO, Natera. "This partnership will help accelerate our entry into this new market by leveraging the commercial infrastructure of a highly respected and well-established leader in the field, along with our direct sales team."

"Natera's donor-derived cell-free DNA test complements our existing transplant offerings and enables us to provide a more advanced portfolio for monitoring kidney rejection," said Parisa Khosropour, President, Transplant Diagnostics, Thermo Fisher Scientific. "We look forward to offering our customers a test that improves upon currently available options and provides unique performance advantages in detecting T-cell mediated rejection and subclinical acute rejection, both of which may have a more positive impact on patient outcomes."

About Natera's dd-cfDNA Organ Transplant Assay

Natera's organ transplant rejection assay is designed to detect active allograft rejection in patients who have undergone kidney transplantation. The assay works by measuring the fraction of donor-derived cell-free DNA (dd-cfDNA) in the recipient's blood, which can spike relative to normal cfDNA when the transplanted organ is injured due to immune rejection. The assay leverages Natera's core single nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) technology to accurately measure dd-cfDNA levels without the need for donor genotyping, and it has been clinically validated with test performance independent of donor type, rejection type, and clinical presentation.

Personalized Transplant Care Through Precision Medicine

“In a recent study published in the Journal of Clinical Medicine, Natera’s assay detected acute rejection (AR) with 89% sensitivity and 0.87 area under the curve (AUC) [1]. This test performance compares favorably to the current standard of care, which is based on serial measurements of serum creatinine; and it compares favorably against competition, which in a 2017 study reported 59% sensitivity and 0.74 AUC.[2]

The recent study also had two novel, clinically significant findings, relative to previously published studies of dd-cfDNA. The Natera dd-cfDNA assay was able to accurately detect TCMR (T-cell mediated rejection), a common and treatable form of active rejection, and subclinical acute rejection.[1] No other dd-cfDNA assay has been shown to detect TCMR or validated to detect subclinical AR, which occurs in 20-25% of patients in the first two years post-transplant,[3] and which is considered a major driver of graft failure.”

References:

1 Sigdel TK, Archila FA, Constantin T, et al. Optimizing Detection of Kidney Transplant Injury by Assessment of Donor-Derived Cell-Free DNA via Massively Multiplex PCR. J. Clin. Med. 2019, 8(1), 19.

2 Bloom RD, Bromberg JS, Poggio ED, et al. Cell-free DNA and active rejection in kidney allografts. J Am Soc Nephrol. 2017 Jul;28(7):2221-2232. doi: 10.1681/ASN.2016091034. Epub 2017 Mar 9

3 Choi BS, Shin MJ, Shin SJ et al. Clinical significance of an early protocol biopsy in living-donor renal transplantation: Ten-year experience at a single center. Am J Transplant 2006; 5: 1354- 1360

About One Lambda

One Lambda, a Thermo Fisher Scientific brand, is the global leader in HLA and antibody monitoring assays for transplantation. Known for its commitment to quality, service, and innovation, the company develops and distributes several lines of HLA typing and antibody monitoring tests utilizing serological, molecular, flow, solid phase & NGS technologies. In addition, One Lambda also provides laboratory instrumentation and computer software that are used to simplify and automate testing procedures and final test evaluations. For more information, please visit www.onelambda.com.

About Natera

Natera is a global leader in cell-free DNA testing. The mission of the company is to transform the management of diseases worldwide. Natera operates an ISO 13485-certified and CAP-accredited laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) in San Carlos, Calif. It offers a host of proprietary genetic testing services to inform physicians who care for pregnant women, researchers in cancer including biopharmaceutical companies, and genetic laboratories through its cloud-based software platform. Follow Natera on LinkedIn and Twitter.

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natera

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EXHIBIT 11

News Release

Medicare Issues Draft Local Coverage Determination for Natera's New Prospera™ Kidney Transplant Rejection Test

Represents Major Reimbursement Milestone on Company's Path to Commercialization in 2019

SAN CARLOS, Calif., March 28, 2019 /PRNewswire/ -- Natera, Inc. (https://c212.net/c/link/?t=0&l=en&o=2417818-1&h=3666138566&u=https%3A%2F%2Fwww.natera.com%2F&a=Natera%2C+Inc.) (NASDAQ: NTRA), a global leader in cell-free DNA testing, today announced that Palmetto MolDx has issued draft local coverage determination (LCD) for use of the company's new Prospera donor-derived cell-free DNA (dd-cfDNA) test to detect active rejection in kidney transplant recipients.

This draft coverage determination represents a major reimbursement milestone on the company's path to commercialization. In its draft LCD, Medicare states, "Prospera is an effective, non-invasive method of assessing kidney allograft status with better performance than the current standard-of-care." It also states, "The evidence is sufficient to support that Prospera provides a non-invasive assessment tool to assess for the presence of active allograft rejection." Furthermore, "The evidence also supports that Prospera identifies both ABMR [antibody-mediated rejection] and TCMR [T-cell mediated rejection], and it is validated to detect subclinical AR [active rejection]."

"I am pleased with the draft coverage decision and look forward to working with Medicare to make this test accessible for those in greatest need," said Paul Billings, MD, PhD, Natera's Chief Medical Officer.

There are more than 190,000 people living with a kidney transplant in the U.S.[1] and roughly 20,000 new kidney transplant surgeries are performed each year.[2] It is estimated that 20-30 percent of organ transplants fail within five years and approximately 50 percent fail within 10 years.[3,4] Traditional tools for diagnosing organ transplant rejection are either invasive (biopsies) or inaccurate (serum creatinine), creating a strong unmet need for better diagnostic tools to help optimize immunosuppression levels, avoid unnecessary biopsies, and improve graft survival. Medicare coverage is available for kidney transplant patients, regardless of age, as either a primary or secondary insurer for a minimum of 36 months following a successful transplant.

The Prospera test detects allograft rejection noninvasively and with high accuracy, by measuring the fraction of dd-cfDNA in the patient's blood, without the need for prior donor or recipient genotyping. Recently published validation studies show Prospera's superior precision and superior clinical accuracy, relative to other commercially available dd-cfDNA assays.[5,6] Prospera is the first assay with high sensitivity to both T-cell mediated and antibody mediated rejection,[5,7] and it is the first to detect subclinical rejection, which occurs in 20-25 percent of patients in the first two years post-transplant[5,8] and is considered a major driver of graft failure. This test performance is a direct result of Natera's experience using its core SNP-based cell-free DNA technology to analyze over 1.5 million Panorama tests from pregnant women.

The draft LCD (https://c212.net/c/link/?t=0&l=en&o=2417818-1&h=3920796319&u=https%3A%2F%2Fwww.cms.gov%2Fmedicare-coverage-database%2Fdetails%2Flcd-details.aspx%3FLCDId%3D38040%26ver%3D5%26DraftContr%3DAll%26bc%3DAAAAAAgAAAAA%26&a=draft+LCD) is posted on the Centers for Medicare and Medicaid Services website and is subject to public comments and further Medicare review before it is finalized.

About the Prospera dd-cfDNA organ transplant test

The Prospera test is intended to supplement the evaluation and management of kidney (renal) injury and active rejection in patients who have undergone organ transplantation. It may be used by physicians considering the diagnosis of active rejection, helping to rule in or out this condition when evaluating the need for diagnostic testing or the results of an invasive biopsy. The test works by measuring the fraction of donor-derived cell-free DNA (dd-cfDNA) in the recipient's blood, which can spike relative to background recipient cfDNA when the transplanted organ is injured due to immune rejection. The test leverages Natera's core single-nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) technology to accurately measure dd-cfDNA levels without the need for donor genotyping.

The Prospera test has been clinically and analytically validated for performance independent of donor type, rejection type, and clinical presentation. In repeatability and reproducibility studies, it showed superior precision with a coefficient of variation up to five times better than that of a competitive dd-cfDNA assay (1.85% vs. 9.2% within run; 1.99% vs. 4.5% across runs).[6, 9] In clinical validation, Natera reported higher sensitivity (89% vs. 59%) and higher area under the curve (0.87 vs. 0.74) than the competing dd-cfDNA assay.[5, 7]

About Natera

Natera (https://c212.net/c/link/?t=0&l=en&o=2417818-1&h=2504883060&u=https%3A%2F%2Fwww.natera.com%2F&a=Natera) is a global leader in cell-free DNA testing. The mission of the company is to change the management of disease worldwide. Natera operates an ISO 13485-certified and CAP-accredited laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) in San Carlos, Calif. It offers a host of proprietary genetic testing services to inform physicians who care for pregnant women, researchers in cancer including bio pharmaceutical companies, and genetic laboratories through its cloud-based software platform. For more information, visit natera.com (https://c212.net/c/link/?t=0&l=en&o=2417818-1&h=48113666&u=https%3A%2F%2Fwww.natera.com%2F&a=natera.com).

Forward-Looking Statements

All statements other than statements of historical facts contained in this press release are forward-looking statements and are not a representation that Natera's plans, estimates, or expectations will be achieved. These forward-looking statements represent Natera's expectations as of the date of this press release, and Natera disclaims any obligation to update the forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual results to differ materially, including with respect to our efforts to develop and commercialize new product offerings, our ability to successfully increase demand for and grow revenues for our product offerings, our ability and expectations regarding obtaining, maintaining and expanding third-party payer coverage of, and reimbursement for, our tests, whether the results of clinical studies will support the use of our product offerings, our expectations of the reliability, accuracy and performance of our tests, or of the benefits of our tests and product offerings to patients, providers and payers. Additional risks and uncertainties are discussed in greater detail in "Risk Factors" in Natera's recent filings on Forms 10-K and 10-Q and in other filings Natera makes with the SEC from time to time. These documents are available at www.natera.com/investors (https://c212.net/c/link/?t=0&l=en&o=2417818-1&h=4261593523&u=http%3A%2F%2Finvestor.natera.com%2Fphoenix.zhtml%3Fc%3D254055%26p%3Dirol-irhome&a=www.natera.com%2Finvestors) and www.sec.gov (https://c212.net/c/link/?t=0&l=en&o=2417818-1&h=370807822&u=http%3A%2F%2Fwww.sec.gov%2F&a=www.sec.gov).

The test was developed by Natera, Inc. a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA). This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Although FDA does not currently clear or approve laboratory-developed tests in the U.S., certification of the laboratory is required under CLIA to ensure the quality and validity of the tests.

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References

1. Kidney Disease Statistics for the United States. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease (https://c212.net/c/link/?t=0&l=en&o=2417818-1&h=2033551111&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2383031-1%26h%3D3137488059%26u%3Dhttps%253A%252F%252Fc212.net%252Fc%252Flink%252F%253Ft%253D0%2526l%253Den%2526o%253D2311473-1%2526h%253D473521873%2526u%253Dhttps%25253A%25252F%25252Fwww.niddk.nih.gov%25252Fhealth-information%25252Fhealth-statistics%25252Fkidney-disease%2526a%253Dhttps%25253A%25252F%25252Fwww.niddk.nih.gov%25252Fhealth-information%25252Fhealth-statistics%25252Fkidney-disease%26a%3Dhttps%253A%252F%252Fwww.niddk.nih.gov%252Fhealth-information%252Fhealth-statistics%252Fkidney-disease&a=https%3A%2F%2Fwww.niddk.nih.gov%2Fhealth-information%2Fhealth-statistics%2Fkidney-disease). Published Dec. 1, 2016.
2. Organ Donation Statistics. U.S. Department of Health and Human Services. U.S. Government Information on Organ Donation and Transplantation. https://www.organdonor.gov/statistics-stories/statistics.html (https://c212.net/c/link/?t=0&l=en&o=2417818-1&h=1553292152&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2383031-1%26h%3D3259530997%26u%3Dhttps%253A%252F%252Fc212.net%252Fc%252Flink%252F%253Ft%253D0%2526l%253Den%2526o%253D2311473-1%2526h%253D3614975809%2526u%253Dhttps%25253A%25252F%25252Fwww.organdonor.gov%25252Fstatistics-stories%25252Fstatistics.html%2526a%253Dhttps%25253A%25252F%25252Fwww.organdonor.gov%25252Fstatistics-stories%25252Fstatistics.html%26a%3Dhttps%253A%252F%252Fwww.organdonor.gov%252Fstatistics-stories%252Fstatistics.html&a=https%3A%2F%2Fwww.organdonor.gov%2Fstatistics-stories%2Fstatistics.html). Published March 31, 2016.
3. Stegall MD, Gaston RS, Cosio FG, Matas A. Through a glass darkly: seeking clarity in preventing late kidney transplant failure. J Am Soc Nephrol. 2015;26(1):20-9.
4. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. Am J Transplant. 2011;11(3):450-62.
5. Sigdel TK, Archila FA, Constantin T, et al. Optimizing detection of kidney transplant injury by assessment of donor-derived cell-free DNA via massively multiplex PCR. J Clin Med. 2019;8(1):19.
6. Altuğ Y, Liang N, Ram R, et al. Analytical validation of a single-nucleotide polymorphism-based donor-derived cell-free DNA assay for detecting rejection in kidney transplant patients. Transplantation, 2019
7. Bloom RD, Bromberg JS, Poggio ED, et al. Cell-free DNA and active rejection in kidney allografts. J Am Soc Nephrol. 2017;28(7):2221-2232. doi: 10.1681/ASN.2016091034.
8. Choi BS, Shin MJ, Shin SJ, et al. Clinical significance of an early protocol biopsy in living-donor renal transplantation: Ten-year experience at a single center. Am J Transplant. 2006;5:1354-1360.
9. Grskovic M, Hiller DJ, Eubank LA, et al. Validation of a clinical-grade assay to measure donor-derived cell-free DNA in solid organ transplant recipients. J Mol Diagn. 2016;18(6):890-902.

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