IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,	)	
Plaintiffs,	)	
v.	)	C.A. No. 19-567 (CFC) (CJB) CONSOLIDATED
NATERA, INC.,	)	
Defendant.	)	

NATERA INC.'S OPENING BRIEF IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT UNDER 35 U.S.C. § 101

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GLOSSARY OF TERMS

TERM	DEFINITION
the Patents	Collectively, U.S. Patent Nos. 8,703,652; 9,845,497; and 10,329,607
the ’652 patent	U.S. Patent No. 8,703,652
the ’497 patent	U.S. Patent No. 9,845,497
the ’607 patent	U.S. Patent No. 10,329,607
the Claims	The asserted claims of the Patents: ’652 patent: claims 1-3, 6, 11-12, 14-15 ’497 patent: claims 1-6, 9-10, 12, 15, 17, 19-21, 23, 25, 27 ’607: all claims
the Patentees	The named inventors on the face of the Patents.
CareDx	Collectively, plaintiffs CareDx, Inc. and The Board of Trustees of the Leland Stanford Junior University
Natera	Defendant Natera, Inc.
FAC	First Amended Complaint (D.I. 74)
DNA	Deoxyribonucleic Acid
cfDNA	Cell Free DNA
UF-#	Uncontested Statement of Facts
A-¶#	Appendix A, Declaration of Professor John A. Quackenbush, Ph.D.
B#	Appendix of Exhibits

I. NATURE AND STAGE OF THE PROCEEDINGS

On March 6, 2019, CareDx filed a Complaint against Natera (D.I. 1) alleging that Prospera, Natera's Kidney Transplant Rejection Test, infringes the '652 patent and the '497 patent. On March 12, 2020, CareDx filed the FAC and added the '607 patent to the case. D.I. 74.[1] At the Court's invitation (Apr. 30, 2020 Oral Order), Natera brings this motion for summary judgment pursuant to Federal Rule of Civil Procedure 56 and requests an order that the Claims are invalid because they are unpatentable under 35 U.S.C. § 101.

II. SUMMARY OF THE ARGUMENT

The Claims are unpatentable under 35 U.S.C. § 101 because they are directed to detecting an undisputedly natural phenomenon using techniques the patentee concedes are conventional. The natural phenomenon is the presence of foreign genetic material—donor-specific cell-free nucleic acid or cfDNA—that is

[1] Natera previously moved to dismiss the Complaint and FAC on the grounds that the Patents are invalid under 35 U.S.C. § 101. The parties' briefing and Magistrate Judge Burke's Report and Recommendation ("RR") on Natera's motion to dismiss the initial Complaint are filed at D.I. 9, 10, 15, 19, 53, 63, and 68. After Judge Burke issued his RR, CareDx filed the FAC. D.I. 74. While Natera's motion to dismiss the initial Complaint was pending, the Court vacated the RR and denied Natera's motion to dismiss as moot. Natera thereafter moved to dismiss the FAC (D.I. 86, 87) but then withdrew the motion. D.I. 97. Upon withdrawing Natera's motion to dismiss the FAC, the Court stayed the case and scheduled early summary judgment briefing on patentability under 35 U.S.C. § 101. *See* Apr. 30, 2020 Oral Order.

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released from a transplanted organ into a transplant recipient's body.[2] The conventionality of the claimed techniques used to detect this cfDNA cannot be disputed. The Patents' written description admits "[t]he practice of the present invention employs, unless otherwise indicated, ***conventional techniques*** ... which are within the skill of the art."[3] Nowhere does the written description or claims "otherwise indicate" that the claimed techniques are anything other than conventional. And the prior and contemporaneous scientific literature from 2009 and before confirms the same.

The conventional techniques are:

(i) "obtaining" a "sample" from the recipient that contains cfDNA;

(ii) "genotyping" the transplant donor and/or recipient to develop genetic profiles (or "genotypes");

(iii) "sequencing" the cfDNA from the sample using "multiplex" or "high-throughput" sequencing; and

(iv) "determining" / "quantifying" the amount of donor cfDNA.

These techniques have been and are used to detect the natural differences ("polymorphisms") between a donor's cfDNA and a recipient's cfDNA. But the Patents do not describe any non-conventional practice of these techniques or any

[2] The '652 patent is directed to the related but equally natural correlation between donor-specific cfDNA and the likelihood that the transplanted organ is failing or being rejected.

[3] UF-10; B0012 at 5:36-48. All emphasis in this Motion is added unless otherwise noted.

improvement or modification of them. The Patents' written description admits these techniques—taken individually or together as a whole—were routinely practiced by 2009 using commercially available equipment.

The scientific literature also shows the claimed techniques were routinely used before November 2009. For example, the claimed techniques were used to detect cell-free nucleic acids from analogous natural phenomena such as fetal cfDNA in a pregnant woman's blood, tumor cfDNA in a cancer patient's blood, and bacterial or viral cfDNA in an infected person's blood. Both the Patentees and numerous other scientists realized that the claimed techniques could be applied to detect any of these natural phenomena because they share the same fundamental feature: the presence of cfDNA in a patient's blood from different sources with different polymorphisms and different genotypes.

Accordingly, the Patents here claim detecting yet another naturally occurring example of this phenomenon in the transplant context—a context that many scientists before 2009 recognized as a suitable application for these methods. That is the only distinction from the prior art that CareDx identifies. But that distinction is not enough to survive summary judgment. Claiming conventional methods to predictably detect a different (but analogous) natural phenomenon does not render the Claims patentable.

Further, the U.S. Supreme Court and Federal Circuit opinions in every

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analogous case confirm the Claims are unpatentable. In those cases, the courts invalidated claims directed to detecting or correlating natural relationships between:

i. naturally metabolized drugs and safe treatment therewith (*Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012));

ii. naturally inherited paternal genes and naturally occurring fetal cfDNA in a pregnant mother's blood (*Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015));

iii. coding and non-coding sequences in the human genome (*Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369 (Fed. Cir. 2016));

iv. natural inflammatory enzymes and cardiovascular disease (*Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352 (Fed. Cir. 2017)); and

v. naturally occurring autoimmune antibodies and autoimmune disease (*Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743 (Fed. Cir. 2019)).

Because there is no material fact in dispute, summary judgment holding the Claims unpatentable under 35 U.S.C. § 101 is warranted.

III. STATEMENT OF FACTS

A. Technological Background

1. The Structure Of Nucleic Acids

Nucleic acids, such as the well-known DNA and RNA, are present in all living things and encode information needed for cellular growth and function. A-

¶39. While there are many types of nucleic acids, DNA[4] is the most relevant nucleic acid to the Patents. A-¶39. DNA is a double-stranded nucleic acid, and each strand is made up of a sequence of naturally occurring nucleotide bases. A-¶40. There are four possible bases that make up DNA—adenine ("A"), cytosine ("C"), guanine ("G"), and thymine ("T"). A-¶40. The sequence of bases on the strands is unique to every individual (except identical twins). A-¶43.

2. Genes, Genotypes, And Polymorphisms

Certain sequences of DNA nucleotides comprise genes that provide a code or blueprint for producing other molecules (such as proteins) enabling cell function. A-¶42. All DNA is normally located on chromosomes (threads of nucleic acid and protein) that are stored in the nuclei of cells. A-¶41. A specific nucleotide sequence that codes for a particular trait in individuals is called a "genotype," and the sum of an individual's DNA is called a "genome." A-¶43. There are naturally occurring differences in genotypes, called "polymorphisms," that make each individual's genotype unique. A-¶43. One type of polymorphism is a "single nucleotide polymorphism" ("SNP"), wherein a different nucleotide base is present at a single position ("locus") in different individuals. A-¶43.

3. Zygosity: Homozygosity And Heterozygosity

Every human normally has two copies of each chromosome, one inherited

[4] The pertinent properties of nucleic acids, such as DNA, are well-understood. *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 582 (2013).

from its mother and another from its father. A-¶44. "Zygosity" describes the similarity or difference between maternally and paternally inherited chromosomes at any given locus. A-¶44. An individual is "homozygous" for a particular locus if it has the same sequence on both its maternally inherited and paternally inherited chromosomes at that locus. A-¶44. An organism is "heterozygous" for a particular locus if the sequence on its maternally inherited chromosome differs from that of its paternally inherited chromosome at that locus. A-¶44.

4. Cell-Free DNA ("cfDNA")

DNA is typically found inside cells, but when cells die (via a process called "apoptosis") their DNA is broken up into small fragments and released into circulating bodily fluids as "cell-free DNA" or "cfDNA." UF-4; A-¶47. The existence of cfDNA was discovered as early as 1948. UF-3. Since that time, cfDNA has been studied in various contexts, including cancer, pregnancy, infectious disease, and transplant. UF-3-7; A-¶¶50-56.

5. cfDNA Genotypes In The Transplant, Prenatal, Infectious Disease And Cancer Contexts

In a variety of situations, cells in a patient having DNA that is different from most of a patient's own DNA may die and release their unique genetic material into the patient as cfDNA. UF-4; A-¶49. For example, tumor cells in a patient naturally die and release abnormally mutated cfDNA into the patient's blood. UF-6; A-¶54. These mutations are unique to the tumor and render its cfDNA distinct

from the patient's normal cells. UF-6; A-¶¶54-55. Similarly, in pregnant women, cells from the fetus or placenta will naturally die and release the fetus' unique cfDNA into the mother's blood. UF-5; A-¶¶52-53. The same is true in patients with an infectious disease—bacterial or viral agents will naturally die and release their unique cfDNA into the blood of an infected patient. UF-4; A-¶56. Organ transplants are no different. UF-7; A-¶¶50-51. The cells of a transplanted donor organ will naturally die and release the donor's unique cfDNA into the transplant recipient's blood. UF-7; A-¶50. In each of these cases, the genotype of the foreign cfDNA (tumor, fetus, virus/bacteria, donor) will differ from the genotype of the patient's own cfDNA (which also is regularly released into the patient's blood). UF-5-7; A-¶57; *e.g.*, B0013 at 7:37-46. And in each case, routine and conventional methods for detecting differences in the genotypes of the cfDNA can be used to determine their different sources. UF-5-7; A-¶57.

In the case of organ transplants, the body of the recipient may reject the transplanted organ, or the organ may fail for some other reason. UF-7; A-¶51. In the case of rejection, the immune system of the recipient attacks the transplanted organ, causing the organ's cells to die more rapidly than normal. UF-7; A-¶51. In the event of transplant failure, increased rates of cell death in the organ prompt the release of more donor-specific cfDNA into the recipient's circulation than would be expected if the transplanted organ was healthy. UF-7; A-¶51. Thus, heightened

cell death in the transplanted organ corresponds to heightened donor-specific cfDNA in the recipient's circulation. UF-7; A-¶51. As such, detecting high quantities of donor cfDNA indicates a greater likelihood that the transplant is either failing or being rejected. UF-7; A-¶51.[5]

6. Genotyping

Genotyping is a process for determining the genetic make-up of an individual by examining particular portions of that individual's DNA sequences. A-¶43. Common variants of different sequences or genes are called "alleles." A-¶43, 127. Genotyping is the identification of the specific allele or alleles an individual has inherited. A-¶43. By 2009, genotyping—including SNP genotyping—was a well-known, commercially available process for analyzing DNA in a variety of applications. UF-13-15; A-¶¶67, 79-80; B0019 at 20:31-41 ("***[g]enotyping*** of the transplant donor and/or the transplant recipient ***may be performed by any suitable method known in the art***").[6]

[5] UF-4, 7; B0013 at 7:41-46 ("[A]s cell-free DNA or RNA often arises from apoptotic cells, the relative amount of donor-specific sequences in circulating nucleic acids should provide a predictive measure of on-coming organ failure in transplant patients for many types of solid organ transplantation including, but not limited to, heart, lung, liver, and kidney.").

[6] UF-8, 14-15; B0016 at 13:51-61 (explaining that genotyping including SNP genotyping could be performed using "existing genotyping platforms known in the art including the one described herein") (internal citations to scientific literature omitted).

7. Sequencing

Sequencing is the process of determining the exact order of the bases in a DNA fragment. A-¶100. As discussed earlier, sequences can be any ordered combination of the bases Adenine (A), Guanine (G), Cytosine (C), or Thymine (T), and a DNA molecule can be anywhere from a few bases to billions of bases in length. A-¶40. Like genotyping, sequencing was well-known and routinely used before the Patents were filed (UF-16, 19; B0017 at 15:8-16:41), as were methods for simultaneously sequencing multiple strands of DNA in a high-throughput instrument. UF-18-20, 22; A-¶¶100-02. Parallel, high-throughput sequencing also is called multiplex sequencing, and one way to perform multiplex sequencing is via "sequencing-by-synthesis." UF-22; A-¶101. Sequencing-by-synthesis involves enzymatically creating a DNA strand that is complementary to one being sequenced. A-¶101. This is done by adding one nucleotide at a time while keeping track of each nucleotide after it is added. A-¶101. All of these technologies were known as early as 1993 and have been available commercially since at least 1999. UF-18-20, 22; A-¶¶103-13; B0017 at 15:8-16:41 (describing commercial products for multiplex, high-throughput, and sequencing-by-synthesis).

B. The Claims

The Claims[7] are all directed to detecting donor-specific cfDNA circulating in a transplant recipient. A-¶¶27-38. In the case of the '652 patent, once this donor-specific cfDNA is detected, its measured quantity is then correlated to possible transplant failure. Claim 1 of the '652 patent recites a "method for detecting transplant rejection . . . or organ failure." Claim 1 of the '497 patent recites a "method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient." And claim 1 of the '607 patent recites a "method of quantifying kidney transplant-derived circulating cell-free deoxyribonucleic acids in a human kidney transplant recipient."

Although the Claims use different words at times, and some limitations use more words than others, the Claims nevertheless all recite the same steps for detection and correlation:

- **Obtaining/providing a biological sample containing cfDNA from a transplant recipient**
  - *See* '652 Patent Claim 1(a) ("providing a sample comprising [cfDNA]")[8]
  - *See* '497 Patent Claim 1(c) ("obtaining a biological sample")[9]
  - *See* '607 Patent Claims 1(a) and (b) ("providing a plasma sample" and "extracting circulating [cfDNA]")

[7] The Patents have a common written description and one independent claim each. UF-1.

[8] '652 patent claims 3 and 12-16 recite similar sampling and transplant-related limitations. A-¶¶65, 172, 186, 191.

[9] '497 patent claims 2, 9, 12-14, 27, and 28 recite similar sampling and transplant-related limitations. A-¶¶65, 175, 187, 192.

- **Genotyping the transplant donor and/or recipient to establish profiles of genetic polymorphisms (or SNPs)**
  - *See* '652 Patent Claim 1(b) ("obtaining a genotype … to establish a polymorphism profile")[10]
  - *See* '497 Patent Claims 1(a) and (b) ("genotyping … to obtain a SNP profile")[11]
  - *See* '607 Patent Claim 1(c) ("performing a selective amplification of [SNPs] … by [PCR]"); Claim 1(f) ("using markers distinguishable between said [recipient and donor] . . . [that] comprise [SNPs]")[12]
- **Performing multiplex or high-throughput sequencing of the cfDNA to detect the genotyped polymorphisms (or SNPs)**
  - *See* '652 Patent Claim 1(c) ("multiplex sequencing of the [cfDNA] in the sample followed by analysis of the sequencing results using the polymorphism profile")[13]
  - *See* '497 Patent Claim 1(d) ("determining an amount of donor-specific [cfDNA] by … high-throughput sequencing or [dPCR]")[14]
  - *See* '607 Patent Claims 1(d) and (e) ("performing a high throughput sequencing reaction … compris[ing] … sequencing-by-synthesis … [and] … providing sequences from said high throughput sequencing reaction")[15]

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[10] '652 patent claims 2 and 11 recite similar genotyping and polymorphism-related limitations. A-¶¶65, 170, 173.

[11] '497 patent claims 6, 15-18, 24, and 25 recite similar genotyping and polymorphism-related limitations. A-¶¶65, 171, 194.

[12] '607 patent claims 2-5 recite similar genotyping and polymorphism-related limitations. A-¶¶65, 172.

[13] '652 patent claims 4-6, and 10 recite similar sequencing-related limitations. A-¶¶65, 178.

[14] '497 patent claims 3-5, 10, 11, 26, and 30 recite similar sequencing-related limitations. A-¶¶65, 179, 189.

[15] '607 patent claim 6 recites similar sequencing-related limitations. A-¶¶65, 180.

- **Quantifying the transplant cfDNA in the sample by detecting the genetic differences in the sequences**
  - *See* '652 Patent Claim 1(d) ("determining a quantity of [transplant cfDNA] based on the detection of [donor and recipient cfDNA] by the multiplexed sequencing")
  - *See* '497 Patent Claim 1(d) ("determining an amount of [transplant cfDNA] … by detecting a homozygous or a heterozygous SNP within the [transplant cfDNA]")
  - *See* '607 Patent Claim 1(f) ("quantifying an amount of [transplant cfDNA] … using markers distinguishable between … recipient and … donor").

A-¶29.

IV. LEGAL STANDARD

A. Patentable Subject Matter

"'[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 70 (2012) (citation omitted). Only "innovative" or "inventive" uses of natural phenomena are afforded patent protection. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 595 (2013). In determining whether patent claims reciting natural phenomena are eligible for protection under 35 U.S.C. § 101, two questions are asked (*i.e.*, "steps"): (1) whether the patent is directed to the natural phenomenon, and if so, (2) whether the claims recite an inventive concept "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Mayo*, 566 U.S. at 72-73, 77-80; *Ariosa*

Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1375 (Fed. Cir. 2015). "The inventive concept necessary at step two of the *Mayo*/*Alice* analysis cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself. That is, under the *Mayo/Alice* framework, a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility[.]" *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016).

Further, "[t]he prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the formula to a particular technological environment or adding insignificant post solution activity." *Mayo*, 566 U.S. at 73 (internal quotation marks and citation omitted). Accordingly, "simply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable." *Id.* at 82.

B. Summary Judgment

"Patent eligibility under 35 U.S.C. § 101 is a question of law." *Genetic Techs.*, 818 F.3d at 1373. However, whether something is well-understood, routine and conventional is a factual question. *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1369 (Fed. Cir. 2018). Summary judgment is appropriate where there is no genuine

dispute of material fact as to that question. *Mortg. Grader, Inc. v. First Choice Loan Servs. Inc.*, 811 F.3d 1314, 1325 (Fed. Cir. 2016) (affirming grant of summary judgment of patent ineligibility under Section 101); *Accenture Global Servs., GmbH v. Guidewire Software, Inc.*, 728 F.3d 1336, 1346 (Fed. Cir. 2013) (same).

C. Representative Claims

A court need not individually address claims not identified by the non-moving party if the court identifies a representative claim and "all the claims 'are substantially similar and linked to the same abstract idea.'" *Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat. Ass'n*, 776 F.3d 1343, 1348 (Fed. Cir. 2014) (citations omitted).

V. ARGUMENT

The Claims are directed to detecting a natural phenomenon—donor-specific cfDNA from a transplanted organ that circulates in the blood of a transplant recipient. The '652 patent claims are directed to the additional unpatentable concept of correlating the detected quantity of donor-specific cfDNA to transplant health—another natural phenomenon. The Claims perform this detection using conventional techniques—an indisputable fact in view of the Patentees' admissions and the corroborating scientific literature. Settled Supreme Court and Federal Circuit precedent further confirm that the Claims are not patent

eligible,[16] while recent authority upholding the patentability of certain life-sciences patents are inapposite. *See infra* Section V(D).

A. The Claims Are Directed To Natural Phenomena

The Claims fail at Step One of the *Mayo/Alice* inquiry because they are directed to conventionally detecting natural phenomena—the presence of donor-specific cfDNA circulating in a transplant recipient's body, and in the case of the '652 patent, the relationship between that donor-specific cfDNA and the health or status of the donor organ. *See BSG Tech LLC v. Buyseasons, Inc.*, 899 F.3d 1281, 1287 (Fed. Cir. 2018) ("For an application of an abstract idea to satisfy step one [of the *Mayo* framework], the claim's focus must be on something other than the abstract idea itself.").

To start, the Patents admit that cfDNA occurs naturally as a result of cell death in a transplant recipient's body. The Patents further describe cell death in a transplanted organ (and the consequent release of donor-specific cfDNA) as something that naturally occurs more frequently when a transplant is failing. UF-7; B0013 at 7:40-46; 8:18-21. That admission cannot be disputed. A-¶63. The single nucleotide polymorphisms ("SNPs") recited in the Claims for distinguishing between donor-specific and recipient cfDNA also are—again by

[16] *See, e.g.*, *Alice Corp. Pty. Ltd v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014); *Mayo*, 566 U.S. at 77; *Ariosa*, 788 F.3d at 1373-76; *Cleveland Clinic*, 859 F.3d at 1361; *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 764 (Fed. Cir. 2014).

the Patents' own admission—naturally occurring genetic differences that were conventionally used prior to the Patents to distinguish different DNA samples to determine their source. UF-8-9; B0012 at 6:61-64; B0013 at 7:40-46. This admission also cannot be disputed. A-¶¶59-66. Detecting those natural phenomena, or correlating the presence of donor-specific cfDNA in a patient's circulation to that patient's transplant health, are mere observations of natural phenomena and nothing more. A-¶¶59-66.

The Claims "begin and end" with the very natural phenomena they observe, and are thus "directed to matter that is naturally occurring." *Ariosa*, 788 F.3d at 1376. They do not create anything new or unnatural, such as new or altered DNA sequences, or unnatural DNA preparations. Instead, the Claims detect what already exists in nature.[17] A-¶¶59-66. For example, claim 1(a) of the '652 patent starts with "a sample comprising cell-free nucleic acids from a subject who has received a transplant," and element 1(d) ends with "diagnosing, predicting, or monitoring a transplant status or outcome of the subject … by determining a quantity of the donor cell-free nucleic acids based on the detection

[17] *See, e.g.*, *Genetic Techs.*, 818 F.3d at 1375-76 (finding that "the claims are directed to matter that is naturally occurring," and the method resulted in "no creation or alteration of DNA sequences"); *cf. Rapid Litig. Mgmt. Ltd. v. CellzDirect*, 827 F.3d 1042, 1047-50 (Fed Cir. 2016) (claiming new methods for generating a preparation with unnaturally high quantities of fetal cdDNA); *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 952 F.3d 1367, 1371-74 (Fed. Cir. 2020) (claiming new methods for preparing a select and unnatural population of liver cells).

of the donor cell-free nucleic acids and subject cell-free nucleic acids" in the sample. B0023 at 27:41-43; 27:59-63. In the '497 patent, the preamble of claim 1 starts with "detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient," and ends in element 1(d) with "determining an amount of donor-specific circulating cell-free nucleic acids from the solid organ transplant in the biological sample." B0045 at 28:2-3; 28:24-26. And in the '607 patent, claim 1(a) begins with "providing a plasma sample from said human kidney transplant recipient" and ends in element 1(e) with "quantifying an amount of said kidney transplant-derived circulating cell-free deoxyribonucleic acid in said plasma sample from said human kidney transplant recipient to obtain a quantified amount." B0072 at 28:59-60; B0073 at 29:39-42. Accordingly, the Claims are directed to a natural phenomenon and do not pass Step One.[18]

B. The Claims Recite Only Standard, Unimproved Techniques For Detecting Or Quantifying Donor-Specific cfDNA

Patent claims that purport to "detect[] a natural law 'with no meaningful

[18] *See, e.g.*, B0013 at 7:40-46; *see Mayo*, 566 U.S. at 77 (finding the claims ineligible because they "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a [] drug will prove ineffective or cause harm"); *Ariosa*, 788 F.3d at 1373-76 (invalidating claims "directed to detecting the presence of a naturally occurring thing or a natural phenomenon, [cell-free fetal DNA] in maternal plasma or serum"); *Cleveland Clinic*, 859 F.3d at 1361 (finding unpatentable claims detecting enzyme in order to diagnose cardiovascular risk); *23andMe, Inc. v. Ancestry.com DNA, LLC*, 356 F. Supp. 3d 889, 904-06 (N.D. Cal. 2018) (finding unpatentable claims that detected correlation that exists in nature).

non-routine steps'" are "directed to" that natural law and are unpatentable. *Athena*, 915 F.3d at 752 (quoting *Cleveland Clinic*, 859 F.3d at 1361). Here, the Claims only recite routine steps, in a routine order, to detect naturally occurring donor-specific cfDNA. A-¶¶67-128. This renders the Claims unpatentable.

1. The Claims As A Whole Recite No Inventive Concept

There is nothing in the Claims as a whole that gives rise to an inventive concept "sufficient to ensure that the patent in practice amounts to ***significantly more*** than a patent upon the natural law itself." *Mayo*, 566 U.S. at 73. "To save a patent" under *Alice/Mayo*, "an inventive concept 'must be evident in the claims.'" *WhitServe LLC v. Dropbox, Inc.*, No. 18-665-CFC, 2019 WL 3342949, at *5 (D. Del. July 25, 2019) (quoting and citing *Two-Way Media Ltd. v. Comcast Cable Commc'ns, LLC*, 874 F.3d 1329, 1338 (Fed. Cir. 2017)). Here, there is nothing evident in the written description or Claims to save them. A-¶¶67-72.

The Patents claim only the application of conventional techniques and previously used combinations for detecting and quantifying cfDNA from multiple sources. *See infra* Section V(B)(2); A-¶¶67-72. In fact, the Patents readily admit there is nothing inventive about the techniques used to practice the Claims: "[t]he practice of the present invention employs, unless otherwise indicated, conventional techniques ... which are within the skill of the art." B0012 at 5:36-48. The Patents further explain that genotyping and quantitation can be performed by sequencing,

which as explained in detail below, was a conventional technique performed with off-the-shelf commercial devices by 2009:

> ***Genotyping*** donor and recipient nucleic acids, and/or detection, identification and/or ***quantitation of the donor-specific nucleic acids*** after transplantation (e.g. ***polymorphic markers such as SNPs***) ***can be performed by sequencing*** such as whole genome sequencing or exome sequencing.

B0017 at 15:2-6; A-¶¶78-81. The Patents also acknowledge that its techniques were being used for diagnosing other conditions where DNA sequences that are different from a patient's normal genotype are present in a patient's sample, such as in pregnancy or cancer. B0012-B0013 at 6:57-7:46; A-¶137. The Patents explain:

> ***In all these applications of circulating nucleic acids, the presence of sequences differing from a patient's normal genotype has been used to detect disease***. In ***cancer***, mutations of genes are a tell-tale sign of the advance of the disease; in ***fetal diagnostics***, the detection of sequences specific to the fetus compared to maternal DNA allows for analysis of the health of the fetus.

B0013 at 7:30-36 (emphasis added).

Moreover, there is no evidence the Patentees modified the techniques the Patents describe as routine, conventional, and widely used in the cancer and fetal diagnostic fields, and even if they did, the Claims do not contain any such limitations. A-¶¶68-69. In fact, the evidence proves the opposite. Inventors Stephen Quake and Hannah Valantine admitted in a Stanford publication that their

transplant-focused technique was based upon a well-known combination of techniques used to detect fetal cfDNA in a pregnant patient:

> The current study began when Valantine noticed research by Quake in 2008 showing that it is possible to detect fetal chromosomal abnormalities by sequencing cell-free DNA fragments in a maternal blood sample.
>
> "When I saw that, I thought, wow, ***this technique*** could probably be used to monitor heart rejection," said Valantine, noting that cells damaged during rejection also release DNA into the circulatory system.

B00390; A-¶138. Stanford published the same admission:

> The ***cell-free DNA technique*** hinges on the existence in the genome of ***naturally occurring regions*** of variation called single nucleotide polymorphisms, or SNPs. In 2008, Hannah Valantine, then a Stanford professor of cardiology, realized that ***a DNA-sequencing technique*** developed in Quake's lab to pick out small quantities of fetal DNA from a pregnant woman's blood might also be useful to track the fate of a transplanted organ.

B0393. If the claimed techniques were being used in analogous fields before the Patents were filed, then their unmodified use in the transplant context cannot be non-conventional. A-¶139.

2. The Patents And Contemporaneous Literature Establish The Conventionality Of The Claimed Techniques

The Patents repeatedly admit the conventionality of the recited methods of "obtaining a sample" of cfDNA, "genotyping," "sequencing," and "detecting" / "quantifying" cfDNA.[19] As discussed above, the Patents even state that "[t]he

[19] The Court previously recognized that the "language in the written descriptions of the . . . asserted patents suggests that the patented steps are neither new nor

practice of the present invention employs, unless otherwise indicated, conventional techniques ... which are within the skill of the art." UF-10; B0012 at 5:36-48. The Patents also state that each claimed step is "conventional" without "otherwise indicat[ing]" that any step is beyond the ordinary skill. UF-10; A-¶4. Indeed, there is no evidence in the record the Patents claim any improvements to or non-conventional uses of any of the claimed techniques. A-¶69.

In fact, by November 6, 2009, the claimed techniques were a standard way of detecting DNA sequences that, like the donor-specific cfDNA in a transplant patient, differ from a patient's normal genotype. UF-10; A-¶68. The Patents recount numerous "applications of circulating nucleic acids, [in which] the presence of sequences differing from a patient's normal genotype has been used to detect disease." B0012-B0013 at 6:67-7:29; 7:30-32; 7:40-46; 8:18-21; A-¶137. The Patents explain polymorphisms (including SNPs) were routinely used for distinguishing between and detecting one genome from another, noting "any donor and recipient will vary at roughly three million SNP positions if fully genotyped." B0016 at 13:42-44; B0017 at 16:3-7; A-¶¶93-96. These genetic variations are readily assessed from a biological sample containing cfDNA, and the Patents do not recite any new or improved laboratory techniques for observing them. UF-11-32; A-¶¶129-35. Each claimed step recites techniques that were common practice

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unconventional[.]" *CareDx, Inc. v. Eurofins Viracor, Inc., et al.*, Case No. 1:19-cv-01804-CFC-CJB, D.I. 53 at 2 (D. Del. Apr. 21, 2020).

by November 2009, and the techniques were performed in a standard order. UF-11-32; A-¶¶129-35.

i. Obtaining a Sample

The Patents recite no improvements for "***obtaining***" or "***providing***" a sample containing cfDNA. UF-12, 30-31; A-¶¶73-77. Rather, the Patents state "[t]o obtain a blood sample, any technique known in the art may be used…" UF-12; B0014 at 10:11-12; B0010 at 1:14-17; B0012 at 6:57-67; B0014 at 9:4-14; B0014 at 10:7-10; A-¶75. CareDx has never argued otherwise, and there is no evidence showing the Claims recite any non-conventional way of obtaining or providing a sample. UF-12, 30-31; A-¶77.

ii. Genotyping / Polymorphism Profile

The Patents—along with contemporaneous literature—establish the claimed "***genotyping***" also was well-known and conventional by November 2009. UF-13, 16; A-¶¶78-81. The Patents state "[g]enotyping of the transplant donor and/or the transplant recipient may be performed by any suitable method known in the art including those described herein such as sequencing … or PCR." B0019 at 20:31-37; B0016 at 13:51-67; B0019 at 20:31-51; B0022 at 26:38-41; A-¶80. The particular methodology of genotyping in '607 element 1(c), "***selective amplification***" to "***amplif[y] … at least 1,000 [homozygous and heterozygous SNPs] … by PCR***," also is described in the Patents as a routine technique scientists

performed in 2009 using off-the-shelf equipment:

> Usable SNPs may comprise approximately 500,000 heterozygous donor SNPs and approximately 160,000 homozygous donor SNPs. Companies … currently offer both standard and custom-designed TaqMan probe sets for SNP genotyping that can in principle target any desired SNP position for a PCR-based assay …. With such a large pool of potential SNPs to choose from, a usable subset of existing or custom probes can be selected to serve as the probe set for any donor/recipient pair.

B0016 at 13:55-67; A-¶82.

The Patents likewise describe obtaining and using the "***polymorphism"*** or ***"SNP" "profile***" of '652 element 1(b) and '497 elements 1(a) and 1(b), or "***using markers distinguishable between [recipient and donor] … compris[ing] [SNPs]***" of '607 element 1(f), as standard, stating "after genotyping a transplant donor and transplant recipient, using existing genotyping platforms know [sic] in the art including the ones described herein, one could identify approximately 1.2 million total variations between a transplant donor and transplant recipient." B0016 at 13:51-55; B0013 at 7:30-36 ("In all these applications of circulating nucleic acids, the presence of sequences differing from a patient's normal genotype has been used to detect disease."); A-¶82.

Consistent with the Patents' disclosures, the contemporaneous literature is replete with examples of commercial products for carrying out the claimed "genotyping," including for profiling up to thousands of homozygous and heterozygous SNPs, as of the Patents' November 2009 filing date. UF-32; A-¶¶81,

83-86. The Patents' claims recite no improvements over or non-conventional ways of performing these established approaches to genotyping and polymorphism/SNP profiling. UF-13, 16, 33; A-¶¶78-87.

iii. High-Throughput / Multiplex Sequencing

The record also shows that the claimed sequencing techniques were routine and conventional by November 2009. UF-18-22, 34, 42. The Patents list numerous established commercial providers for "***multiplex***" and "***high-throughput sequencing***" (B0017-B0018 at 15:22-67; 16:58-17:3) and incorporate literature describing the standard use of these techniques. B0017-18 at 15:53-17:14; *see also* B0013 at 7:23-28; B0014 at 9:8-14; B0016 at 14:58-67; B0017-18 at 15:22-17:14; B0020 at 21:5-8; UF-18, 22, 34; A-¶¶100-122. Contemporaneous literature also confirms the conventionality of using these sequencing methods as claimed, including for detecting and quantifying cfDNA. UF-34, 42; A-¶100-122. Nothing in the Claims modifies or improves those conventional multiplex or high-throughput sequencing techniques. UF-23, 34, 42; A-¶123.

iv. Quantification

The Patents' claimed steps of detecting and quantifying cfDNA were conventional as well. The Patents state that "[d]etection, identification, and/or quantification of the donor-specific markers (e.g., polymorphic markers such as SNPs) can be performed using [numerous techniques]… as well as other methods

known in the art including the methods described herein." B0014 at 9:8-14; B0018 at 17:41-18:53; B0018-19 at 18:56-19:2 ("Methods for quantifying nucleic acids are known in the art…"); B0020 at 21:5-9; A-¶125. These existing, conventional methods also are described in the contemporaneous literature reporting quantification of cfDNA, including quantification of SNPs to detect different genotypes (*e.g.*, in DNA from a fetus, tumor, or infectious disease) in a patient's sample. UF-16, 22; A-¶¶126-28. Again, the Claims do not modify or claim any improvement over those techniques. UF-16, 22; A-¶128.

v. Sensitivity And Error Rate Limitations In The Claims Are Inherent To The Conventional Tools Described In The Patents

Each Claim recites limitations describing test-sensitivity, detection thresholds, and sequencing error rates, but none of these limitations renders any of the Claims patent eligible. Every one of these limitations is inherent to the technologies described in the Patents as routine, conventional, and commercially available. UF-25-29, 39; A-¶¶114-21.

First, the sensitivity limitation in claim 1 of the '652 patent, which recites the "***sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for … CAV***," is conventional. UF-25; A-¶114-21. Assuming for purposes of this motion this limitation is not indefinite, it would refer to a degree of sensitivity inherent in the conventional methods of the claims.

Id. It was well-known by 2009 that the number of molecules analyzed is one component of sensitivity, and that higher sensitivity could be achieved by sequencing more molecules. UF-26-27. The Patents, in fact, disclose standard ways to achieve higher sensitivities using the commercially available sequencing equipment without any claimed modification or improvement of that equipment. UF-29; B0018 at 17:12-15; 17:22-25; A-¶¶114-22. The Patents do not disclose or claim any non-conventional uses of this known sequencing equipment. UF-25-29, 35-39.

Second, elements 1(d) of the '497 patent and 1(f) of the '607 patent—each reciting a minimum detection threshold for donor-specific cfDNA—are conventional for similar reasons.[20] UF-38; A-¶114. Each Claim recites detection wherein donor-specific cfDNA is "***at least 0.03% of the total circulating [cfDNA] in the biological sample***." UF-37; A-¶114. The threshold itself describes yet another natural phenomenon—a naturally occurring percentage of cfDNA. A-¶114. The ability to detect that percentage is an inherent property of the commercially available sequencing equipment described in the Patents, a fact the Patents acknowledge when noting that this "[h]igher sensitivity can be achieved ***simply by sequencing more molecules***." B0018 at 17:1-3; 17:7-13 (also disclosing that the commercially available equipment can detect "donor molecules when the donor

[20] '497 patent claims 19-23, and 31-33 and '607 patent claims 7-10 recite similar cfDNA concentration limitations. A-¶¶144, 179, 195-96.

fraction is as low as 0.03%"); A-¶118. And as discussed above, it was well-known by 2009 that by sequencing more molecules, sensitivity will necessarily increase. UF-37-39. The Patents do not disclose or claim any non-conventional laboratory techniques for performing this element.[21] UF-37-39.

Finally, the '607 patent's recitation of a "***sequencing error rate of less than 1.5%***" is likewise just an inherent property of the commercial sequencers readily available in 2009. B0017 at 16:20-21; A-¶120. In the context of the Patents, the sequencing error rate is an estimate of the proportion of all bases (often expressed as a decimal) sequenced by a sequencer that are incorrect. A-¶¶120-21. These errors can be caused by a combination of problems, for example, during sample preparation, misidentification of single base additions by the sequencer, background noise, or some combination of these and other factors. *See* A-¶¶119-20, 183. As of 2009, it was well-known that typical sequencing error rates for base substitutions varied between sequencing platforms at a rate of 0.5%-1.5%. UF-35. It also was well-known that it was possible to lower the sequencing error rate by resequencing a sample multiple times. UF-36. The Claims recite no improvement

[21] *See Intellectual Ventures I LLC v. Capital One Fin. Corp.*, 850 F.3d 1332, 1342 (Fed. Cir. 2017) (explaining that "[o]ur law demands more" than claim language that "provides only a result-oriented solution, with insufficient detail for ***how*** a computer accomplishes it") (emphasis added); *see also Two-way Media Ltd.*, 874 F.3d at 1337 (finding claims patent ineligible that did "not sufficiently describe ***how*** to achieve these results in a nonabstract way"); *Credit Acceptance Corp. v. Westlake Servs.*, 859 F.3d 1044, 1057 (Fed. Cir. 2017) (same).

or modification of the commercially available sequencers, and the record does not show that the Patentees developed (let alone claimed) any improvement or unique modification for reducing error rates. A-¶¶114-21.

3. The Prosecution History Establishes The Conventionality Of The Claimed Techniques

The prosecution history further confirms that all of the claimed steps were conventional. A-¶98. During prosecution of the '652 patent, the applicants submitted a declaration stating the steps can be performed using "commercially available kits" and "standard protocols":

- "DNA from the samples was purified ***using commercially available kits***."
- "Sequencing libraries were constructed from cell-free DNA ***using commercially available kits*** and sequenced ***following standard protocols*** using an Illumina GAII sequencer."
- "Genotypes of the transplant recipients were obtained from genomic DNA using the Illumina Omni1-Quad Beadchip ***following standard protocols***."

B0260-61; A-¶98.[22] The Patentees did not argue that obtaining a sample, genotyping, sequencing, or detecting/quantifying were non-conventional or new

[22] The PTO recently rejected a pending patent application related to the Patents that is directed to detecting the presence of donor-specific cfDNA on the grounds that claimed detection steps were directed to an abstract "calculative analysis of data" and that claimed diagnosing steps were directed to an abstract "mental step that is the correlation of data and information." B1314-16 (2019-02-13 Final Rejection, Application No. 14/658,061) at 4-5. The Examiner also determined that recited steps including "steps of providing cell-free DNA and sequencing SNPs" were directed to conventional, well-known elements. B1315.

methods. A-¶98.[23]

4. CareDx's Statements In This Litigation Establish The Conventionality Of The Claimed Techniques

CareDx's counsel also confirmed at the Motion to Dismiss hearing the Patents did not "introduce a whole new concept that was never known before to science":

> [Judge Burke:] Would you acknowledge that individually, not only were each of those things known in the art, but that each of them had actually been utilized by way of trying to detect or measure for cell-free DNA?
>
> MR. REINES [CareDX Counsel]: I'm tempted to say that if you isolate down each step or aspect of a step—not each step at the element level, but if you take it ***word by word that there's no new concept, that we have not introduced a whole new concept that never was known before to science in any way on a per word basis, I'm tempted to say, yes.***

B1383, Nov. 21, 2019 Hearing Tr. at 74:2-11.

5. Contemporaneous And Prior Literature Establishes The Conventionality Of The Claims As A Whole

Corroborating the Patentees' admissions,[24] prior and contemporaneous literature further confirms that other scientists were applying the claimed techniques to detect DNA sequences that differ from a patient's normal genotype

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[23] During the prosecution of the '607 patent, the Patentees traversed a Section 101 rejection, but that bears no weight here because (i) the prior art references cited by and relied on by the Examiner are different from the references relied on here, and (ii) the Examiner applied the wrong legal standard—obviousness under 35 U.S.C. § 103—to evaluate those references. *See* B1330.

[24] *See supra* Section V(B)(1).

in a cfDNA sample, and the same techniques could be used to detect different genotypes regardless of the natural phenomenon. A-¶¶129-98. For example, in a U.S. Patent Application filed February 28, 2006 and published September 6, 2007, Cantor *et al.* described a method "***used to detect*** fetal nucleic acid in maternal blood sample; circulating tumor-specific nucleic acids in a blood, urine, or stool sample; and ***donor-specific nucleic acids in transplant recipients***" as well as "viral, bacterial, fungal, or other foreign nucleic acids in a biological sample." B0401 (U.S. 2007/0207466) at Abstract; A-¶¶148-50. Cantor disclosed an exemplary practice of the Patents' Claims to detect and quantify foreign (in this case fetal) cfDNA, including by using the same steps claimed in the Patents of obtaining a sample, genotyping to obtain an SNP profile, multiplex/high throughput sequencing, and quantifying the information. B0426-B0427 (Cantor); A-¶¶148-50.

Similarly, in a U.S. Patent Application filed July 23, 2008 and published on April 2, 2009, Lo *et al.* described a method that "***relates to the detection of*** cancer, the ***monitoring of transplantation***, and the monitoring of infectious diseases." B1251 (Lo U.S. 2009) at ¶ [0003]; A-¶151. Lo used analyzed "maternal and fetal DNA in [a] ***plasma sample***"[25] and stated the method could be used to detect cancer, monitor transplantation, or monitor infectious disease. B1251 (Lo U.S.

[25] B1274 (Lo U.S. 2009) at ¶ [0289]; A-¶152.

2009) at ¶ [0003]; A-¶152. And the prior art method disclosed the same conventional steps claimed here. B1251, B1254, B1258, B1263, B1271-74 (Lo U.S. 2009) at ¶¶ [0003], [0059-60], [0100], [0176], [0262], [0278]; [0289]; A-¶153.

There are numerous other examples showing the Claims' techniques together as a whole were known and conventional by 2009 that are further discussed in the Quackenbush declaration. *See* B0428-B0435 (Dhallan 2007); B0436-B0444 (Beck 2009); B0454-B0460 (Gordon 2009); B0461-B0462 (Holt 2009); A-¶¶154-68. Accordingly, there is nothing non-conventional about the Claims' recitation, as a whole, of well-known scientific techniques,[26] and there is no evidence to the contrary. *See, e.g.*, *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1334 (Fed. Cir. 2012); A-¶¶154-68.

6. The Dependent Claims Do Not Recite Inventive Concepts

None of the dependent limitations are described in the written description as non-conventional. To the contrary, according to the specification and as confirmed by Natera's expert Dr. Quackenbush, the dependent limitations all either add information about the natural phenomenon or recite conventional laboratory techniques. A-¶¶169-99.

[26] *Bascom Glob. Internet Servs., Inc. v. AT&T Mobility LLC*, 827 F.3d 1341, 1348-49 (Fed. Cir. 2016).

- *Dependent Claims Reciting Different Polymorphisms* ('652 patent at claims 2, 11; '497 patent at claims 6, 17, 25; '607 patent at claims 2, 3, 4, 5). As explained above, genotyping to obtain a polymorphism profile comprising SNPs of various quantities was well-understood, routine and conventional as of November 2009. UF-13-22; A-¶¶78-79, 170-73.

- *Dependent Claims Reciting Types Of cfDNA and cfRNA* ('652 patent at claim 3; '497 patent at claim 12). As the Patents admit, it was routine and conventional as of November 2009 to assay any of the recited types of natural occurring nucleic acids using the claimed methods. UF-3-6, 16-17; A-¶¶174-77.

- *Dependent Claims Reciting Certain Concentrations Of Cell-Free Nucleic Acids In The Sample* (*See* '497 patent at claim 20; '607 patent at claims 7, 8). As explained above, detecting the claimed concentrations of cell-free nucleic acids was an inherent feature of the standard and conventional methods and instruments disclosed by the Patents. *See supra* Section V(B)(2); UF-12, 34, 37-39; A-¶¶195-97.

- *Dependent Claims Reciting Certain Common Modifications, Error Rates, Or Quality Scores Associated With Multiplexed Or High Throughput Sequencing* ('652 patent at claim 6;'497 patent at claims 3, 4, 5, 19, 21, 23; '607 patent at claim 6). It is evident from the Patents, literature, and equipment manuals that all of these limitations were either conventional methods or features inherent to the techniques of the independent claims. UF-34-32; A-¶¶178-85 (discussing each limitation).

- *Dependent Claims Reciting Further Genotyping Prior To Or Simultaneously With Quantifying Cell-Free Nucleic Acids* ('497 patent at claims 15). The written description and Claims do not disclose or claim any non-conventional application of these genotyping limitations. A-¶194. Nor do they disclose or claim improvements to conventional genotyping techniques as of 2009 that make this claim inventive. *Id.*

- *Dependent Claims Reciting Organ or Species Limitations* (*See* '652 patent at claims 14, 15; '497 patent at claim 9). The Patents do not disclose or claim anything non-conventional or inventive about selecting a particular type of transplant organ (*e.g.*, kidney, pancreas, heart, etc.). UF-10, 12, 17; A-¶¶186-88. Nor do the Patents state or claim they

invented analyzing the bodily fluid samples of human transplant recipients as opposed to those of some other species. *Id.*

- *Dependent Claims Reciting Conventional PCR Or Amplification Methods* (*See* '497 patent at claim 10). As explained above, digital PCR, real-time PCR, and use of arrays were well-understood, routine and conventional as of November 2009. UF-13, 15-24; A-¶¶189-90. And performing an amplification reaction on donor cfDNA prior to quantifying it also was routine and conventional. *Id.*

- *Dependent Claims Reciting Different Sample Types* ('652 patent at claims 12; '497 patent at claims 2, 27). Using patient samples from naturally occurring sources such as blood, serum, urine, stool, or plasma to extract cfDNA does not confer patentability either. UF-3-5; 11-23; A-¶¶191-93. Obtaining a biological sample from a patient—from whatever natural source—and using it with the claimed methods was standard and routine by 2009. *Id.*

C. The Claims Do Not Become Patentable By Limiting The Field Of Use

By CareDx's admission, the only purported innovation in the Claims is the application of the claimed method ***to the particular field of transplant cfDNA***.[27] But that is not enough to confer patentability. "As the Supreme Court has held, 'the prohibition against patenting abstract ideas [or natural phenomena] cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.'" *Molecular Pathology*, 689 F.3d at 1334 (citing *Bilski v. Kappos*, 561 U.S. 593, 610 (2010)) (finding that "[l]imiting [a] comparison to just the *BRCA* genes or … the identification of particular alterations," *i.e.*,

[27] D.I. 17 (Furneaux Decl.) at ¶ 25 ("It was not well-known or conventional to use these techniques ***together***, in 2009, ***in the context of non-invasive diagnostic tests for organ transplant rejection***.").

particular manifestations of natural phenomena regarding genetic mutations, "fails to render the claimed process patent-eligible."). Accordingly, CareDx's field of use argument cannot render the Claims patentable.

Numerous other courts have found that limiting the field of use of conventional techniques to specific categories of natural phenomenon—like the category of donor-specific cfDNA here—is insufficient to confer patentability.[28] *Genetic Techs*. and *Ariosa* are particularly analogous. In both cases, the Federal Circuit held that various "physical steps" such as the "physical steps of DNA amplification and analysis of the amplified DNA" and "PCR to amplify and detect [the cell-free DNA]" were all well-understood and conventional—much like the physical steps of PCR/amplification, sequencing, and genotyping here. *See Genetic Techs.*, 818 F.3d at 1377-78; *Ariosa*, 788 F.3d at 1377. This is why, in *Ariosa*, the court evaluated whether it was "well-understood, routine, and conventional activity" to combine the recited method steps to detect DNA in blood ***generally***, not whether it was routine to apply those steps to a particular kind of DNA—***maternal and fetal cfDNA***—which was the natural phenomenon at issue there.

[28] *See, e.g.*, *Alice*, 573 U.S. at 222-23; *Mayo*, 566 U.S. at 84; *Bilski*, 561 U.S. at 612; *Affinity Labs of Texas, LLC v. DIRECTV, LLC*, 838 F.3d 1253, 1259 (Fed. Cir 2016); *Content Extraction*, 776 F.3d at 1348; *buySAFE, Inc. v. Google, Inc.*, 765 F.3d 1350, 1355 (Fed. Cir. 2014); *Exergen Corp. v. Thermomedics, Inc.*, 132 F. Supp. 3d 200, 207 (D. Mass. 2015).

Ariosa, 788 F.3d at 1377.[29]

The same result is warranted here. The Claims are directed to a particular natural phenomenon—donor-specific cfDNA that circulates in the blood of a transplant recipient—and recite standard laboratory techniques to detect that natural phenomenon. A-¶¶59-199. But, as in *In re BRCA*, "[n]othing is added by identifying the techniques to be used . . . because those . . . techniques were the well-understood, routine, and conventional techniques that a scientist would have thought of when instructed" to detect and analyze cfDNA in a transplant recipient's body. 774 F.3d at 764; A-¶66.

D. The Claims Are Analogous To Diagnostic Claims The Supreme Court And Federal Circuit Have Invalidated

1. Analogous Cases Confirm Unpatentability Of The Claims

As this Court has recognized, "[t]o determine whether claims are directed to an abstract idea courts generally 'compare the claims at issue to those claims already found to be directed to an abstract idea in previous cases.'" *In-Depth Test, LLC v. Maxim Integrated, Prods., Inc.*, C.A. No. 14-887-CFC, 2018 WL 6617142, at *4 (D. Del. Dec. 18, 2018) (quoting *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1334 (Fed. Cir. 2016)). Here, comparing the Claims to those

[29] *See also In re BRCA*, 774 F.3d at 764 (finding unpatentable claims that recited "detecting," "amplifying," and "sequencing" genes because those techniques did "nothing more than spell out what practitioners already knew—how to compare gene sequences using routine, ordinary techniques").

previously found unpatentable by the Supreme Court and Federal Circuit further confirms the Claims are directed to a natural phenomenon and add no inventive concept. *See Illumina*, 952 F.3d at 1371 ("[W]e have consistently held diagnostic claims unpatentable as directed to ineligible subject matter.").

In *Mayo*, the Supreme Court invalidated claims "set[ting] forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a [] drug will prove ineffective or cause harm." 566 U.S. at 77. Here too, the Claims set forth laws of nature—namely relationships between the amounts of donor-specific cfDNA detected in the blood and, in the case of the '652 patent, the likelihood that a transplanted organ is being rejected or failing. A-¶¶59-66.

In *Athena*, the Federal Circuit found methods for detecting auto-antibodies produced in patients suffering from a certain autoimmune disease to be "directed to" a natural law, holding "[c]laiming a natural cause of an ailment and well-known means of observing it is not eligible for a patent because such a claim in effect only encompasses the natural law itself." 915 F.3d at 752-53. Similarly here, the Patents claim a natural correlation to an ailment—increased levels of transplant donor-specific cfDNA circulating within a transplant recipient—and only well-known means of observing it. A-¶¶59-199.

Similarly in *Cleveland Clinic*, the Federal Circuit found that claims

detecting "elevated levels" of a natural inflammatory enzyme called "MPO," and the correlation of this MPO to the likelihood of cardiovascular disease—were "directed to" a natural phenomenon. 859 F.3d at 1360-61. The court found they were not directed to a patentable laboratory method for detecting MPO because "[t]he specifications of the testing patents confirm that known testing methods could be used to detect [the natural phenomenon], and that there were commercially available testing kits for [the natural phenomenon] detection." *Id.* at 1361. The same is true here, where the Claims recite detecting elevated levels of donor-derived cfDNA in a transplant recipient's blood, but again recite no improvements over the known—and commercially available—methods recited in the Claims. A-¶¶73-168.

In *Ariosa Diagnostics*, the Federal Circuit found claims for detecting naturally occurring fetal cfDNA in a pregnant woman's blood using "method steps [that] were well-understood, conventional and routine" to be directed to a natural phenomenon. 788 F.3d at 1376-77. Specifically, the claims recited steps such as "PCR to amplify and detect cffDNA" that the court found conventional as of 1997. *Id.* at 1377. Here, as well, the Claims recite detecting naturally occurring quantities of donor-specific cfDNA in a transplant recipient's blood without reciting any improvement over the well-understood, conventional, and routine detection methods recited in the claims. A-¶¶73-127.

And in *Genetic Techs.*, the Federal Circuit invalidated a claim for detecting compilations of genetic sequences by taking advantage of how certain sequences were naturally "linked" to others. 818 F.3d at 1374-76. The Court found that claim to be "directed to" a natural law because it "does not purport to identify novel detection techniques." *Id.* at 1376. Similarly here, the Patents claim methods for detecting selected compilations, or profiles, of genetic sequences (polymorphisms or SNPs) in cfDNA of a transplant recipient without identifying any new or improved techniques for the detection. A-¶¶67-199; *see also Genetic Veterinary Scis., Inc. v. LABOKLIN GmbH & Co. KG*, 933 F.3d 1302, 1315-18 (Fed. Cir. 2019) (claim reciting "method for genotyping" with steps of "obtaining" a sample, "genotyping" a gene sequence and "detecting" specific nucleotide replacement were directed to natural law).

2. *CellzDirect* And *Illumina* Are Not Applicable

In two recent life sciences cases, the Federal Circuit upheld the patentability of certain non-analogous claims. *See Rapid Litig. Mgmt. Ltd. v. CellzDirect*, 827 F.3d 1042 (Fed Cir. 2016); *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 952 F.3d 1367 (Fed. Cir. 2020). Those cases do not apply here for at least two reasons.

a. Unlike *CellzDirect* and *Illumina*, The Claims Here Do Not Lead To An Unnatural Result Or Preparation

First, the claims upheld in *CellzDirect* and *Illumina* claimed the use of a

natural phenomenon to arrive at an unnatural result, which is not true here. In *Illumina*, the claims were directed to "methods for preparing ***a fraction*** of cell-free DNA ***that is enriched in fetal DNA***" by taking advantage of the fact that fetal cfDNA tends to be smaller than maternal cfDNA. *Illumina*, 952 F.3d at 1372. The *Illumina* claims recited "specific process steps" for performing DNA size discrimination and selectively removing DNA fragments that were above a specific size threshold, which thereby increased the relative amount of fetal DNA as compared to maternal DNA in the sample. *Id.* The claimed process "***change[d] the composition of the mixture***, resulting in a DNA fraction that is ***different from the naturally-occurring fraction*** in the mother's blood." *Id.*

In *CellzDirect*, the claimed methods took advantage of the ability of certain liver cells to survive multiple cycles of freezing and thawing. 827 F.3d at 1045-46. The claimed methods took advantage of this natural survivability and claimed a process for preserving liver cells by preparing a select and unnatural population of liver cells resilient to cryopreservation. *Id.* at 1050-52. Specifically, the improved process involved freezing cells, thawing cells, removing non-viable cells, and then refreezing the viable cell. *Id.* The result of this process created an unnatural composition of cells not found in nature. *Id.* at 1048-51.

In contrast to *Illumina* and *CellzDirect*, the Claims here do not result in any unnatural "preparation" or "composition." Unlike *Illumina* and *CellzDirect*, the

Claims do not selectively remove, alter, or modify cfDNA to change the composition of the samples into something else. Altering the samples in the ways claimed by *Illumina* and *CellzDirect* would, in fact, stifle the purpose of the Claims, which is to detect naturally occurring levels of donor and recipient cfDNA in a transplant patient and compare naturally occurring differences between them to assess transplant status. A-¶¶59-66. The Claims thus do not produce something "different from the naturally-occurring [cfDNA] fraction," but instead do the opposite—they observe a naturally occurring cfDNA fraction. *Illumin*a, 952 F.3d at 1372.

b. <u>Unlike CellzDirect and Illumina, The Claims Here Do Not Disclose Any New Or Improved Laboratory Technique</u>

Second, in *CellzDirect* and *Illumina*, the Federal Circuit held the claims recited new and improved laboratory techniques, which the Claims here do not recite. A-¶¶69-199. Notably, the Federal Circuit itself in *Athena* and *Cleveland Clinic* distinguished *CellzDirect* on grounds that apply equally here—the *CellzDirect* claims were targeted to a "new and useful laboratory technique." *See Cleveland Clinic*, 859 F.3d at 1361 (distinguishing *CellzDirect*); *Athena*, 915 F.3d at 751-52 (same); *see also* Section V(B) above (demonstrating standard use of Patents' recited laboratory methods). In *CellzDirect*, the improvement involved freezing and thawing viable liver cells more than once (as well as pooling cells)—

techniques the contemporaneous literature discouraged. *CellzDirect*, 827 F.3d at 1048-49, 1051 ("Repeating a step that the art taught should be performed only once can hardly be considered routine or conventional"). In *Illumina*, the improvement involved setting size thresholds to segregate the cfDNA such that fetal cfDNA was enriched in the final preparation. *Illumina*, 952 F.3d at 1375. But here, the Patents recite no improvements or non-conventional techniques—only the routine and conventional techniques of obtaining a sample, genotyping, sequencing cfDNA, and determining/quantifying donor-specific cfDNA. That is confirmed by the Patentees own admission that "***[t]he practice*** of the present invention employs, unless otherwise indicated, ***conventional techniques*** ... which are within the skill of the art." B0012 at 5:36-49.

VI. CONCLUSION

For the foregoing reasons, Natera requests the Court find the Claims of the Patents unpatentable under 35 U.S.C. § 101 and dismiss the FAC in its entirety with prejudice.

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CERTIFICATE OF COMPLIANCE

I hereby certify that this brief has been prepared in Times New Roman 14-point typeface using Microsoft Word, and contains 9,668 words as determined by the Word Count feature of Microsoft Word.

June 11, 2020

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CERTIFICATE OF SERVICE

I hereby certify that on June 11, 2020, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on June 11, 2020, upon the following in the manner indicated:

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