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. NATERA, INC., Defendant.	)	Civil Action No. 19-567-CFC-CJB (CONSOLIDATED)
CAREDX, INC., Plaintiff, v. EUROFINS VIRACOR, INC., Defendant, and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Nominal Defendant.	)	Civil Action No. 19-1804-CFC-CJB

REPORT AND RECOMMENDATION

1. Presently pending before the Court in these patent infringement cases are motions filed by Defendant Natera, Inc. ("Natera") and Defendant Eurofins Viracor, Inc. ("Eurofins," and collectively with Natera, "Defendants") pursuant to Federal Rule of Civil Procedure 12(b)(6) (the "Motions"). (Civil Action No. 19-567-CFC-CJB, D.I. 9; Civil Action No. 19-1804-CFC-CJB, D.I. 6) With their Motions, Defendants argue that the patents asserted against them (the "asserted patents") by Plaintiffs CareDx, Inc. ("CareDx") and The Board of Trustees of the

Leland Stanford Junior University ("Plaintiffs")—United States Patent Nos. 9,845,497 (the "'497 patent," which is asserted against Natera by both Plaintiffs) and 8,703,652 (the "'652 patent," which is asserted against Natera by both Plaintiffs and against Eurofins by CareDx)—are directed to patent-ineligible subject matter pursuant to 35 U.S.C. § 101.[1] For the reasons that follow, the Court recommends that the Motions be DENIED.[2]

2. The Court has often set out the relevant legal standards for review of a Rule 12(b)(6) motion premised on a claim of patent ineligibility, including in *Genedics, LLC v. Meta Co.*, Civil Action No. 17-1062-CJB, 2018 WL 3991474, at *2-5 (D. Del. Aug. 21, 2018). The Court hereby incorporates by reference its discussion in *Genedics* of these legal standards and will follow those standards herein. To the extent consideration of the Motions necessitates discussion of other, related legal principles, the Court will set out those principles below.

3. The asserted patents recite methods to help predict the status or outcomes of transplant recipients through the sequencing of cell-free nucleic acids ("cfDNA") found in the bodily fluids of a recipient. If an organ transplant is rejected or fails in a recipient, a significant number of cells in that organ will die, and the donor's DNA found in those dead cells will be

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[1] These two cases have been referred to the Court by United States District Judge Colm F. Connolly to hear and resolve all matters up to expert discovery. (Civil Action No. 19-567-CFC-CJB, Nov. 25, 2019 Oral Order; Civil Action No. 19-1804-CFC-CJB, Nov. 25, 2019 Oral Order) The Motions were fully briefed as of November 6, 2019, (Civil Action No. 19-1804-CFC-CJB, D.I. 16), and the Court held oral argument on November 21, 2019, (Civil Action No. 19-567-CFC-CJB, D.I. 47 (hereinafter, "Tr.")). Unless otherwise noted below, citations will be to the docket in Civil Action No. 19-567-CFC-CJB.

[2] With its Motion, Natera had also argued that Plaintiffs' allegations that Natera's Kidney Test infringes the '652 patent failed to meet the *Twombly/Iqbal* pleading standard. (D.I. 10 at 19-20) The Court issued a Report and Recommendation on November 25, 2019 recommending that this portion of Natera's Motion be denied, (D.I. 36); the Report and Recommendation was adopted by the District Court on December 10, 2019, (D.I. 38).

released into the recipient's bloodstream; the asserted claims are to methods meant to help reliably detect the amount of donor cfDNA in a transplant recipient's body, and (in some cases) to use that information to help diagnose or predict whether the transplanted organ is failing or not. ('497 patent; '652 patent; Tr. at 10-11)

4. For purposes of the Motions, Defendants have asserted that claim 1 of the '652 patent (which relates to both Motions) and claim 1 of the '497 patent (which relates to Natera's Motion) are representative. (D.I. 10 at 2-3; Civil Action No. 19-1804-CFC-CJB, D.I. 7 at 5-6) Thus, the Court will focus below on those two claims, understanding that if the Motions are not well taken as to those claims, they will also not be successful as to the remaining asserted claims in the cases. Claim 1 of the '652 patent recites as follows:

> **1.** A method for detecting transplant rejection, graft dysfunction, or organ failure, the method comprising:
>
> (a) providing a sample comprising cell-free nucleic acids from a subject who has received a transplant from a donor;
>
> (b) obtaining a genotype of donor-specific polymorphisms or a genotype of subject-specific polymorphisms, or obtaining both a genotype of donor-specific polymorphisms and subject-specific polymorphisms, to establish a polymorphism profile for detecting donor cell-free nucleic acids, wherein at least one single nucleotide polymorphism (SNP) is homozygous for the subject if the genotype comprises subject-specific polymorphisms comprising SNPs;
>
> (c) multiplex sequencing of the cell-free nucleic acids in the sample followed by analysis of the sequencing results using the polymorphism profile to detect donor cell-free nucleic acids and subject cell-free nucleic acids; and
>
> (d) diagnosing, predicting, or monitoring a transplant status or outcome of the subject who has received the transplant by determining a quantity of the donor cell-free nucleic acids based on the detection of the donor cell-free nucleic acids and subject cell-free nucleic acids by the multiplexed sequencing, wherein an

increase in the quantity of the donor cell-free nucleic acids over time is indicative of transplant rejection, graft dysfunction or organ failure, and wherein sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV).

('652 patent, cols. 27:39-28:40) Claim 1 of the '497 patent recites as follows:

1. A method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient, the method comprising:

(a) genotyping a solid organ transplant donor to obtain a single nucleotide polymorphism (SNP) profile of the solid organ transplant donor;

(b) genotyping a solid organ transplant recipient to obtain a SNP profile of the solid organ transplant recipient, wherein the solid organ transplant recipient is selected from the group consisting of: a kidney transplant, a heart transplant, a liver transplant, a pancreas transplant, a lung transplant, a skin transplant, and any combination thereof;

(c) obtaining a biological sample from the solid organ transplant recipient after the solid organ transplant recipient has received the solid organ transplant from the solid organ transplant donor, wherein the biological sample is selected from the group consisting of blood, serum and plasma, and wherein the biological sample comprises circulating cell-free nucleic acids from the solid organ transplant; and

(d) determining an amount of donor-specific circulating cell-free nucleic acids from the solid organ transplant in the biological sample by detecting a homozygous or a heterozygous SNP within the donor-specific circulating cell-free nucleic acids from the solid organ transplant in at least one assay, wherein the at least one assay comprises high-throughput sequencing or digital polymerase chain reaction (dPCR), and
wherein the at least one assay detects the donor-specific circulating cell-free nucleic acids from the solid organ transplant when the donor-specific circulating cell-free nucleic acids make up at least 0.03% of the total circulating cell-free nucleic acids in the biological sample.

('497 patent, cols. 28:2-29:5)

5. Here, the Motions can be resolved at *Alice*'s step one. Defendants argue at step one that the claims are directed to natural phenomena, specifically (as Eurofins puts it) "the correlation between transplant rejection and the presence of naturally occurring [cfDNA] in the bodily fluids of transplant recipients[,]" (Civil Action No. 19-1804-CFC-CJB, D.I. 7 at 11; *see also* Eurofins' Hearing Presentation, Slides 3, 24), or (as Natera puts it) "taking [] two [measurements of cfDNA] from the body . . . correlating that and then using that correlation to make an assessment of whether the transplant is being rejected or not[,]" (Tr. at 15-16).

6. In order to determine what a patent claim is really directed to at step one, the United States Court of Appeals for the Federal Circuit has indicated a court may consider the content of the patent's specification.[3] In this case, however, the patents' specification[4] repeatedly and consistently states that this basic "correlation" between the presence of increased levels of donor-specific cfDNA and transplant rejection (hereinafter, "the correlation")—i.e., the thing that, according to Defendants, the asserted claims are purportedly "directed to"—had already been well-known in the art for quite a long time. (*Id.* at 18-19, 59) To that end, the patents explain that studies published decades ago in the 1990s and 2000s revealed that "much of the circulating nucleic acids in blood arise from necrotic or apoptotic cells[.]" ('652 patent, col.

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[3] *Cf. Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1337 (Fed. Cir. 2016) (indicating that it is appropriate to look to a patent's specification to determine whether a claim of the patent is "directed to" a particular concept, and that if a claim contains a particular element that is described by the patent's specification as what the "present invention comprises[,]" this suggests that the claim may be directed to that element or concept) (internal quotation marks and citation omitted); *Internet Patents Corp. v. Active Network, Inc.*, 790 F.3d 1343, 1348 (Fed. Cir. 2015) (same, and noting that if a concept is described in the patent as being "the innovation over the prior art" or the "the essential, most important aspect" of the patented invention, that suggests that the claim is directed to that concept) (internal quotation marks and citation omitted).

[4] The two patents at issue here share a nearly identical specification, and the Court will cite to the '652 patent's specification unless otherwise noted, for ease of reference.

6:57-63) The patents go on to state that "the presence of [genetic] sequences differing from a patient's normal genotype has been used to detect disease[,]" and that it was known that because "cell-free DNA . . . often arises from apoptotic cells, the relative amount of donor-specific sequences in circulating nucleic acids [could] provide a predictive measure of on-coming organ failure in transplant patients[.]" (*Id.*, col. 7:30-32, 40-46) Thus, the patent explains, scientists had for years been attempting to find ways to test for and detect the presence of such donor-specific cfDNA. (*Id.*, cols. 7:40-8:44) One initial approach described in the specification involved a focus on gender-mismatched transplant scenarios (i.e., where a female recipient received an organ from a male donor). In these studies, researchers looked to see if Y chromosome sequences from the male donors were present to a great degree in the female patients; the patents note that certain of the results from one such study "establish that for heart transplant patients, donor-derived DNA present in plasma can serve as a potential marker for the onset of organ failure." (*Id.*, cols. 7:48-8:21) However, according to the patents, these efforts were limited in their usefulness, because: (a) sometimes, it was hard to identify the necessary Y-chromosome specific sequences; (b) even if the methods of detection were successful, they were not helpful in cases where the gender of the donor and the recipient was the same and (c) if the female patient had had prior blood transfusions from men, that might "lead to Y-chromosome specific signals from sources other than the transplanted organ." (*Id.*, cols. 7:57-8:31) The patents also describe how scientists had tried to use detection of donor-specific human leukocyte antigen ("HLA") alleles in circulating DNA as a signal for organ rejection. (*Id.*, col. 8:34-45) That strategy too was limited, as researchers were at times confronted with the "inability to distinguish HLA alleles between all donors and recipients, particularly for common HLA types"

and due to the above-referenced complication of microchimerism resulting from blood transfusions. (*Id.*)

7. This begs the question: How could it be the case that the "basic thrust" or "character as a whole" or "focus"[5] of the purportedly representative claims of the patents is to a naturally-occurring correlation, when the patentee repeatedly states that this very correlation was already well-known in the art? To ask the question is to answer it. It does not, in fact, make a lot of sense to think that the claims are directed to something that the patent repeatedly says the claims are not directed to. And indeed, in the specification, the patentee tells us that what it thinks was really invented here—the purported claimed advance that is what the patent is really about—is something *other than* the correlation itself:

> [T]he invention provides a universal approach to noninvasive detection of graft rejection in transplant patients which circumvents the potential problems of microchimerism from DNA from other foreign sources and is general for all organ recipients without consideration of gender. In some embodiments, a genetic fingerprint is generated for the donor organ. This approach allows for a reliable identification of sequences arising solely from the organ transplantation that can be made in a manner that is independent of the genders of donor and recipient.

(*Id.*, col. 8:45-54; *see also* Tr. at 19-20) In other words, the patent is saying that what the inventors were focused on here was how to develop a new, more accurate and useful analytic method of determining whether significant amounts of cfDNA were present in a transplant recipient's body (so that one could *then* make use of the known correlation between that fact and indication of transplant rejection). (D.I. 15 at 10; Tr. at 38 (Natera's counsel acknowledging that what the specification is stating is that the inventors came up with "a new test that hadn't been

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[5] *Elec. Power Grp., LLC v. Alstom S.A.*, 830 F.3d 1350, 1353 (Fed. Cir. 2016).

done before . . . that's measuring for transplant rejection"); *id.* at 69-70 (Plaintiffs' counsel noting that the patent states that its "claimed advance" is "not the correlation [but a] new analytical method for differentiating between the DNA")) The specification goes on to describe how, *inter alia*, using digital polymerase chain reaction ("PCR") or high-throughput sequencing or multiplex sequencing,[6] the invention could "quantitate the presence of specific polymorphisms that have already been identified in [an] initial genotyping step" and "quantitate the fraction of donor DNA in a transplant patient using probes targeted to several SNPs"[7] without the need to rely on, for example, "a specific gender relationship between donor and recipient." ('652 patent, col. 14:55-67; *see also id.*, col. 9:8-14; Tr. at 22-23, 35, 37)

8. That said, claims claim, and if there were not much more in these purportedly representative claims than a reference to the well-known correlation itself, then perhaps Defendants' Motions would have legs. But here, the claims *do* make reference to the claimed advance described by the specification: the use of digital PCR/high-throughput sequencing/multiplex sequencing, at certain levels of sensitivity, to identify homozygous or heterozygous SNPs in the blood of a transplant recipient (all in order to determine the amount of donor-specific cfDNA in the recipient). (Tr. at 56-57)[8] For example, Claim 1 of the '497 patent

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[6] According to Defendants, "sequencing" is simply "identifying the sequence of the bases in the DNA[,]" "multiplexed sequencing" is "sequencing multiple samples or multiple things together at the same time" and "[h]igh-throughput sequencing" is "an automated form of this multiplexed sequencing." (Tr. at 11-12; *see also* '652 patent, col. 15:1-21)

[7] According to Defendants, "polymorphisms" "are places in the genetic sequence where individuals differ" and SNPs are "places in the genome where individuals may vary at a single base [or nucleotide] position." (Tr. at 8; D.I. 10 at 5; *see also* Natera's Hearing Presentation, Slide 6; Eurofins' Hearing Presentation, Slide 7)

[8] Defendants repeatedly assert that this aspect of the claims amounts to the use of conventional methods well-known in the art to determine the presence of donor cfDNA in the

states that the claimed method involves genotyping a transplant donor and recipient to obtain a "SNP[] profile[,]" obtaining a biological sample containing cfDNA from the recipient, and then determining an amount of donor-specific cfDNA in the recipient's sample by "detecting a homozygous or a heterozygous SNP within the donor-specific circulating cell-free nucleic acids" in an assay comprising either "high-throughput sequencing or digital [PCR,]" with certain sensitivity requirements. ('497 patent, cols. 28:5-29:5) And claim 1 of the '652 patent states that the claimed method obtains a genotype of donor-specific or subject-specific polymorphisms (or both) to establish a polymorphism profile for detecting donor cfDNA, wherein "at least one . . . SNP . . . is homozygous for the subject if the genotype comprises subject-specific polymorphisms comprising SNPs"; from there, it requires that "multiplex sequencing" of the cfDNA be used to determine the quantity of donor cfDNA in the blood, such that "sensitivity of the method is greater than 56%" compared to certain "current surveillance methods for cardiac allograft vasculopathy." ('652 patent, cols. 27:44-28:40) It is these purportedly new, unconventional combination of steps that the claims are directed to, not the natural law itself.

9. For all of the above reasons,[9] Defendants have failed to meet their burden to demonstrate that, at *Alice*'s step one, the representative claims here are directed a natural

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body. That may be, or it may be that (as Plaintiffs suggest) these amount to an unconventional ordered combination of known steps (i.e., a non-conventional arrangement of known, conventional pieces) that are being used to obtain this end. (*See, e.g.*, D.I. 15 at 13, 17) The Court comes to no conclusions as to who is right or who is wrong on this front. But regardless, the key point here for purposes of *Alice*'s step one is that the claims appear to be "directed to" *these particular methods for detecting*—and not to the *fact or existence of the natural phenomenon* itself.

[9] In the case against Eurofins, CareDx attached to its Complaint a declaration from its expert, Dr. Henry Furneaux, which contains material supportive of the Court's conclusions here. (Civil Action No. 19-1804-CFC-CJB, D.I. 1, ex. 12) Dr. Furneaux's declaration was not included as an exhibit to the Complaint in the Natera action. Because the declaration thus could

phenomenon. *See Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1045-50 (Fed. Cir. 2016) (concluding at *Alice*'s step one that the claims were "simply not directed to" a natural law—the ability of hepatocytes to survive multiple freeze-thaw cycles—because it was clear that the claims were instead directed to a "new and useful laboratory technique for preserving hepatocytes"; this could be seen by the "plain claim language" and by the patent specification, which explained why the new technique "had a number of advantages over the prior art" cryopreservation techniques).[10] Thus, the Court recommends that the Motions be DENIED.[11]

10. This Report and Recommendation is filed pursuant to 28 U.S.C. § 636(b)(1)(B), Fed. R. Civ. P. 72(b)(1), and D. Del. LR 72.1. The parties may serve and file specific written objections within fourteen (14) days after being served with a copy of this Report and Recommendation. Fed. R. Civ. P. 72(b)(2). The failure of a party to object to legal conclusions may result in the loss of the right to de novo review in the district court. *See Henderson v. Carlson*, 812 F.2d 874, 878-79 (3d Cir. 1987); *Sincavage v. Barnhart*, 171 F. App'x 924, 925 n.1 (3d Cir. 2006). The parties are directed to the Court's Standing Order for Objections Filed

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only be considered in deciding one of these two Rule 12 Motions, *see In re Burlington Coat Factory Secs. Litig.*, 114 F.3d 1410, 1426 (3d Cir. 1997), and because the Court does not need to rely on the declaration in order to reach the decision above, the Court will not explicitly rely on the declaration here. That said, as noted above, the content of the declaration would only bolster the Court's decision herein. (Civil Action No. 19-1804-CFC-CJB, D.I. 1, ex. 12 at ¶¶ 11-23)

[10] *Cf. Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 750-51 (Fed. Cir. 2019) (concluding at *Alice*'s step one that the claims were directed to a natural law—the correlation between the presence of naturally occurring muscle-specific tyrosine kinase ("MuSK") autoantibodies in bodily fluid and MuSK-related neurological diseases—in significant part because the "patent describes the claimed invention principally as a discovery of [this] natural law, not as an improvement in the underlying immunoassay technology").

[11] Plaintiffs' motion for leave to file a sur-reply brief in Civil Action No. 19-567-CFC-CJB is DENIED. (D.I. 21)

Under Fed. R. Civ. P. 72, dated October 9, 2013, a copy of which is available on the District Court's website, located at http://www.ded.uscourts.gov.

Dated: February 10, 2020

Christopher J. Burke
UNITED STATES MAGISTRATE JUDGE