No. 22-

In the Supreme Court of the United States

CAREDX, INC., AND THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, PETITIONERS

v.

NATERA, INC.

CAREDX, INC., AND THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, PETITIONERS

v.

EUROFINS VIRACOR, INC.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Congress has provided that any "new and useful process" is eligible for patent protection, and that "any new and useful improvement thereof" is also eligible for patent protection. 35 U.S.C. 101. The question presented is whether a new and useful method for measuring a natural phenomenon, that improves upon prior methods for measuring that very same phenomenon, is eligible for patent protection under Section 101.

CORPORATE DISCLOSURE STATEMENT

Petitioner CareDx, Inc. is a publicly traded company. No parent or publicly held company owns 10% or more of petitioner CareDx, Inc.'s stock. The Leland Stanford Junior University is a non-profit corporation. No parent or publicly held company owns any interest in it.

RELATED PROCEEDINGS

United States District Court for the District of Delaware:

CareDx, Inc. and The Board of Trustees of the Leland Stanford Junior University v. *Natera, Inc.*, No. 19-567-CFC-CJB (Sept. 28, 2021)

CareDx, Inc. and The Board of Trustees of the Leland Stanford Junior University v. *Eurofins Viracor, Inc.*, No. 19-1804-CFC-CJB (Sept. 28, 2021)

United States Court of Appeals for the Federal Circuit:

CareDx, Inc., The Board of Trustees of the Leland Stanford Junior University v. *Natera, Inc.*, No. 22-1027 (July 18, 2022)

CareDx, Inc., The Board of Trustees of the Leland Stanford Junior University v. *Eurofins Viracor, Inc.*, No. 22-1028 (July 18, 2022)

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ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

CareDx, Inc., and The Board of Trustees of the Leland Stanford Junior University respectfully petition for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit in these consolidated cases.

OPINIONS BELOW

The opinion of the court of appeals is published at 40 F.4th 1371 (App., *infra*, 1a-21a). The memorandum opinion of the district court is reported at 563 F. Supp. 3d 329 (App., *infra*, 22a-57a).

JURISDICTION

The court of appeals entered judgment on July 18, 2022, App., *infra*, 2a, and denied a timely petition for rehearing on December 2, 2022, *id.* at 84a. On February 17, 2023, this Court extended the time within which to file a petition for a writ of certiorari to and including May 1, 2023. The Court has jurisdiction under 28 U.S.C. 1254(1).

STATUTORY PROVISIONS INVOLVED

Section 101 of the Patent Act of 1952, 35 U.S.C. 101, provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

STATEMENT

A. Legal Background

1. The Constitution empowers Congress "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to … Inventors the exclusive Right to their respective … Discoveries." U.S. Const. Art. I, § 8, Cl. 8. Section 101 of the Patent Act of 1952 provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. 101.

Section 101 thus defines the subject matter that may be patented. See, *e.g.*, *Bilski* v. *Kappos*, 561 U.S. 593, 601 (2010). This Court has described Section 101 as "expansive" and as showing that "the patent laws would be given wide scope." *Ibid.* "Congress took this permissive

approach … to ensure that 'ingenuity should receive a liberal encouragement.'" *Ibid.* (quoting 5 Writings of Thomas Jefferson 75–76 (H.A. Washington ed. 1861)). To obtain a patent, an inventor must also satisfy the Patent Act's many additional requirements, "includ[ing] that the invention be novel, nonobvious, and fully and particularly described." *Id.* at 602 (citations omitted); see 35 U.S.C. 102, 103, 112.

2. Despite Section 101's broad language, this Court has long held that "[l]aws of nature, natural phenomena, and abstract ideas are not patentable." *Alice Corp. Pty.* v. *CLS Bank Int'l*, 573 U.S. 208, 216 (2014). "The concern that drives this exclusionary principle [is] one of pre-emption," a "concern that patent law not inhibit further discovery by improperly tying up the future use of the[] building blocks of human ingenuity." *Ibid.* (internal quotation marks omitted). But because "[a]t some level, all inventions embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," this Court "tread[s] carefully in construing" the limitation on Section 101's scope "lest it swallow all of patent law." *Id.* at 217 (cleaned up). This Court's precedents thus distinguish between claims that "[m]onopoliz[e]" or "risk disproportionately tying up" phenomena that are not themselves patentable, while permitting claims that "apply" those phenomena "to a new and useful end" and "pose no comparable risk of pre-emption." *Id.* at 216-217; see also *Mayo Collaborative Servs.* v. *Prometheus Lab'ys, Inc.*, 566 U.S. 66, 70-78 (2012).

To that end, this Court has set out a two-step inquiry to determine whether a patent impermissibly claims a law of nature, natural phenomenon, or abstract idea. "First," the Court "determine[s] whether the claims at

issue are directed to one of those patent-ineligible concepts." *Alice*, 573 U.S. at 217. If not, the invention is eligible for patenting. *Ibid.* If so, the Court proceeds to "step two" and "search[es] for an inventive concept" by "consider[ing] the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application." *Ibid.* (cleaned up). If the Court finds such an inventive concept, the invention is patent eligible. *Ibid.*

B. Scientific Background

Organ rejection is a life-threatening complication of organ transplantation. App., *infra*, 25a. Early detection of organ rejection is thus crucial to preventing serious adverse outcomes, including death. *Ibid.* Traditionally, testing for organ rejection required invasive and expensive tissue biopsies from the organ. *Ibid.*; C.A.J.A. 120, 281. There was therefore a long-recognized "pressing need" for improved methods for diagnosing rejection. C.A.J.A. 120.

By 1998, scientists had discovered a natural correlation that, if properly measured, could allow for early and non-invasive detection of rejection. App., *infra*, 14a-15a; C.A.J.A. 121. Specifically, fragments of a person's DNA can be found in their bloodstream, outside of any cell, and thus are known as "cell-free DNA." Scientists discovered that, when a patient receives a transplant, fragments of the donor's DNA from the donated organ also release into the recipient's bloodstream, and that, during organ rejection, the proportion of cell-free DNA from the donor increases. See App., *infra*, 75a; C.A.J.A. 1491-1492. Scientists recognized that, if they could measure the proportion of the donor's cell-free DNA relative to

the recipient's, they could diagnose organ rejection without a biopsy. App., *infra*, 75a; C.A.J.A. 121, 281.

For a decade, scientists struggled to develop optimal methods for measuring the proportion of the donor's cell-free DNA. App., *infra*, 75a-76a. The first method was to look for fragments of Y-chromosomal DNA, which is unique to males. *Id.* at 76a; C.A.J.A. 121. But that approach only works when the donor is male and the recipient female. *Ibid.* And even then, that method sometimes fails because Y-chromosome fragments are sometimes found in the cell-free DNA of women who were once pregnant with males. *Ibid.*

In 2006, scientists developed another method that relied on human leukocyte antigen (HLA) alleles in circulating cell-free DNA as a signal for organ rejection. App., *infra*, 76a; C.A.J.A. 121. But that approach also has shortcomings, including the inability to distinguish HLA alleles between all donors and recipients. *Ibid.*

In 2008, after ten years of unsuccessful attempts, an article concluded that "the use of [cell] free DNA for the detection of organ rejection [is] difficult and impractical." C.A.J.A. 648.

C. The Stanford Patents

Just as the scientific community was announcing defeat in its collective effort to improve upon those "difficult and impractical" methods, three Stanford University scientists—Professor Stephen Quake, Professor Hannah Valantine and their research associate, Tom Snyder—were designing improved methods of measuring donor and recipient cell-free DNA in a recipient's bloodstream. See App., *infra*, 26a; C.A.J.A. 109-181.

These scientists developed a method using cutting-edge next-generation sequencing (also referred to as

"high-throughput" and "multiplex" sequencing) and digital polymerase chain reaction (digital PCR) techniques to measure and quantify single nucleotide polymorphisms (SNPs), a specific kind of minuscule mutation in a person's DNA. See App., *infra*, 3a-9a; *id.* at 78a-80a & n.7; Pet. C.A. Br. 44 n.3. Because every individual has unique SNPs, finding enough donor SNPs in the DNA fragments in a recipient's bloodstream allows scientists to distinguish the donor's cell-free DNA from the recipient's. See App., *infra*, 78a; C.A.J.A. 124-126. If enough of those SNP-containing fragments are measured and quantified, doctors can ascertain the proportion of cell-free donor DNA in the recipient's bloodstream and diagnose organ rejection. See *ibid.*; App., *infra*, 3a. This new method improved upon the Y-chromosome method, as it worked for all patients, regardless of gender, and represented a marked improvement in sensitivity over the HLA allele method. See App., *infra*, 77a; C.A.J.A. 119, 121.

The scientists described and claimed their inventions in U.S. Patent Nos. 8,703,652, 9,845,497, and 10,329,607 ("Stanford Patents"). See C.A.J.A. 109-181. For example, claim 1 of the '607 patent claims:

> (1) providing a plasma sample from the recipient;
>
> (2) extracting cell-free DNA from the sample;
>
> (3) performing "selective amplification" of target DNA sequences, wherein that amplification "amplifies a plurality of genomic regions comprising at least 1,000 [SNPs]" using PCR;
>
> (4) performing "high throughput sequencing" comprising a "sequencing-by-synthesis reaction" with an error rate of less than 1.5%;

(5) providing sequences comprising "at least 1,000 [SNPs]"; and

(6) quantifying the proportion of donor-derived DNA, using distinguishing biomarkers drawn from those at least 1,000 SNPs, and wherein the donor's cell-free DNA comprises at least 0.03% of the total in the sample. App., *infra*, 6a-8a; C.A.J.A. 180-181.

The Stanford Patents' common specification explains the history set forth above, with the decade-long struggle to effectively measure the proportion of donor cell-free DNA to detect organ rejection. See C.A.J.A. 121; App., *infra*, 75a-76a. It then claims to solve the longstanding measurement problem by providing a "universal approach to noninvasive detection of graft rejection in transplant patients," that is sufficiently "sensitive, rapid and inexpensive." C.A.J.A. 118, 121; see also App., *infra*, 77a.

D. CareDx's Investment and Respondents' Infringement

Petitioner CareDx, Inc. is a leading innovator in the transplant organ health business and the exclusive licensee of the Stanford Patents. C.A.J.A 374-375, 382; App., *infra*, 9a. CareDx invested heavily in its AlloSure® product in reliance on patent protection: It (1) sponsored a prospective clinical study to establish the test's efficacy, (2) funded a campaign to persuade clinicians of the benefits of its approach, and (3) obtained Medicare approval to gain insurance coverage. Pet. C.A. Br. 14-15.

In 2019, however, respondent Natera, Inc., released a copycat product, Prospera, using the same donor-cell-free-DNA measurement techniques the Stanford inventors had spent years developing. See C.A.J.A. 377-382. Respondent Eurofins Viracor, Inc., likewise introduced

its copycat product, the TRAC Kidney test, in 2020. See C.A.J.A. 368-370.

E. Procedural History

1. Petitioners brought two patent infringement suits, one against Natera and the other against Eurofins. The cases were marked as related and the district court partially coordinated their pretrial filings. Respondents moved to dismiss, arguing the Stanford Patents were ineligible for patent protection under Section 101 on the theory that they claim a natural phenomenon—specifically, the correlation between increased donor cell-free DNA and organ rejection. See *Natera* D. Ct. Doc. 10, at 10-19; *Eurofins* D. Ct. Doc. 7, at 11-20. In response, petitioners explained that the Patents did not claim the correlation because the patents *disclaim* discovery of that natural phenomenon, *disclaim* the preexisting methods for measuring it, and instead claim only new and improved measurement methods. See *Natera* D. Ct. Doc. 15, at 10-19; *Eurofins* D. Ct. Doc. 15, at 9-19.

The magistrate judge agreed with petitioners. He issued a report and recommendation that the motions should be denied at *Alice* step one because the Stanford Patents are not "directed to" the cell-free DNA-organ rejection correlation. App., *infra*, 69a-81a. The magistrate judge explained that the patents are each "directed to" "a new, more accurate and useful analytic method of determining whether significant amounts of [cell-free] DNA were present in a transplant recipient's body," a problem that "scientists had for years been attempting to" address. *Id.* at 74a-77a. He further explained that the patents could not be directed to the "correlation" (*i.e.*, the underlying natural phenomenon) because, as "the patents' specification repeatedly and consistently

states," that correlation "had already been well-known in the art for quite a long time." *Id.* at 75a (footnote omitted).

The district court denied Eurofins' motion to dismiss, stating that resolving the Section 101 question would be "premature." App., *infra*, 67a. Natera subsequently withdrew its motion to dismiss. See *id.* at 38a.

2. The district court initially denied motions for summary judgment on Section 101 grounds. App., *infra*, 60a-65a. The court found that there was substantial record evidence that the measurement techniques claimed in the Stanford Patents were not conventional, including "six scientific articles that discuss the limitations and nascent nature of some of the specifically disclosed techniques," as well as an expert declaration. *Id.* at 61a, 64a. The court thus found a dispute of material fact and denied the motions. *Id.* at 61a, 65a.

The district court later reconsidered its decision *sua sponte* and granted summary judgment to respondents. App., *infra*, 22a-57a. The court began by criticizing "the state of § 101 law" as "fraught, incoherent, unclear, inconsistent, and confusing, and indeterminate and often leading to arbitrary results." *Id.* at 36a-37a (cleaned up). The court then collapsed the two-step *Alice* inquiry into a single dispositive question: "where a patent claims a method for detecting a natural phenomenon, the dispositive inquiry under both steps of the *Alice* inquiry is whether the asserted method uses more than standard or conventional techniques of detection." *Id.* at 44a. Like countless other specifications, the Stanford Patents' common specification includes a statement that the methods "employ[], unless otherwise indicated, conventional techniques." C.A.J.A. 120; see App., *infra*, 50a;

Pet. C.A. Br. 47 n.4. Notwithstanding the qualifier "unless otherwise indicated," the court understood that statement to mean that the Stanford Patents as a whole employed only conventional techniques in a conventional manner. App., *infra*, 46a-47a. The district court determined that this "end[ed] the matter." *Id.* at 47a.

3. The court of appeals affirmed. App., *infra*, 1a-21a. At *Alice* step one, the court maintained that even an "improved" measurement method that disclaims discovery of the natural law is "directed to natural phenomena" if it relies upon "conventional" techniques. *Id.* at 17a-18a. The court rejected the argument that conventionality was irrelevant at step one, emphasizing that the Federal Circuit had "repeatedly analyzed conventionality at step one." *Id.* at 17a.

At *Alice* step two, the court agreed with the district court that the disclosure in the specification meant that "each step in the purported invention requires only conventional techniques." App., *infra*, 19a. It determined that the patents' application of existing techniques using a new and specific combination of steps to solve a problem that had plagued scientists for over a decade was nothing more than a "logical combination" of those "standard, well-known techniques" and that the patents therefore lacked an "inventive concept." *Id.* at 18a-20a.

The court of appeals denied a timely petition for en banc review. App., *infra*, 83a.

REASONS FOR GRANTING THE PETITION

1. This Court needs to take another Section 101 case. Over the last five years, this Court has called for the views of the Solicitor General five times to find an appropriate vehicle for clarifying the scope of Section 101 of the Patent Act of 1952, 35 U.S.C. 101 *et seq.* The Solicitor General has consistently responded by urging

this Court to grant certiorari in an appropriate Section 101 case. And the Solicitor General has recently recommended that this Court grant certiorari in two such cases. See U.S. Br. 1, *Tropp* v. *Travel Sentry, Inc.*, No. 22-22, *Interactive Wearables, LLC* v. *Polar Electro Oy*, No. 21-1281 (Apr. 5, 2013), 2023 WL 2817859 (U.S. *Tropp* Br.).

2. Petitioners respectfully submit that this case is an even better vehicle for clarifying the scope of Section 101. It raises many of the same problems as *Tropp* and *Interactive Wearables*, including the Federal Circuit's chronic, improper reliance on obviousness considerations in step two of the *Alice* framework. See U.S. *Tropp* Br. 17-18. But the problems here are even worse.

First, *Tropp* and *Interactive Wearables* involve the application of the abstract-ideas exception to patents in fields (luggage processing and wearable technology) that have not been the source of considerable controversy. By contrast, this case lies at the epicenter of the controversy at the Federal Circuit: This case involves applying the natural-phenomenon exception to medical diagnostics, the field where the need for this Court's review is most pressing. The Federal Circuit's judges and the Solicitor General have both called on this Court to grant a diagnostic-method case. And the confusion in applying this Court's Section 101 jurisprudence has caused significant practical harm in this field: The Federal Circuit has invalidated every single diagnostic-method patent it has encountered since *Mayo Collaborative Services* v. *Prometheus Laboratories, Inc.*, 566 U.S. 66, 70-78 (2012), powerfully undercutting the incentive to innovate and invest in life-saving medical diagnostics. Granting certiorari thus would enable this

Court to clarify that there is no basis for what has become a virtually per se rule of invalidity.

Second, this case gives the Court an opportunity to refocus the Section 101 inquiry on the statutory text, where statutory analysis must begin. The statute protects "new and useful improvement[s]" upon preexisting "process[es]." 35 U.S.C. 101. And that describes the Stanford Patents perfectly: They claim an improved method for measuring a previously known natural phenomenon (the correlation between the proportion of a donor's DNA in the recipient's blood and organ rejection) for a useful purpose (to diagnose organ rejection). The patents explain that the scientific community had known of that correlation for a decade, and its relevance to diagnosing organ rejection, but had developed only limited ways to measure it.

Pioneering researchers at Stanford University invented a new and improved test. Their methods use human-made tools (next-generation sequencing and digital PCR) to identify a specific class of mutations that uniquely correspond to the donor and the recipient, in sufficient quantities, and then to differentiate the donor's DNA fragments from the recipient's to measure their relative proportion. Those new and improved measurement methods are a significant advance: They work for all patients and are more accurate and thus mark a dramatic "improvement" upon the prior methods. They are therefore eligible for patent protection as "improve[d]" methods. 35 U.S.C. 101.

The Stanford Patents' focus on specific improved methods for measuring the relative proportion of the donor's DNA likewise ensures the absence of any preemption concerns. Patents that claim specific improvements upon preexisting processes for applying a previously-

known natural phenomenon cannot monopolize the underlying phenomenon itself, because other methods already exist to apply it and thus remain outside the scope of the patent. This case would accordingly enable this Court to reinvigorate the role of Section 101's statutory text in a manner consonant with the preemption concerns that animate this Court's precedents.

Third, this case is an ideal vehicle for clarifying the role (or lack thereof) that "conventionality" plays at both steps in the *Alice* framework. The Solicitor General recommended certiorari in *Interactive Wearables* in part because the Federal Circuit erred in overly relying on considerations of novelty and obviousness at step two of the *Alice* inquiry. See U.S. *Tropp* Br. 17. "Section 101 should not be understood to incorporate by reference [those] other restrictions on patentability." *Id.* at 18.

Here, the Federal Circuit made that same mistake at step two—and also made a similar mistake at step one. At step one, the Federal Circuit held that the claims were "directed to" the natural phenomenon on the theory that even an "improved" measurement method fails at *Alice* step one if it relies upon "conventional" techniques. App., *infra*, 17a-18a. Indeed, the Federal Circuit emphasized that it had "repeatedly analyzed conventionality at step one." *Id.* at 17a. That conflicts with *Alice* and *Mayo*, which direct that the step one inquiry centers on the claims' focus and associated preemption concerns, not the "conventionality" of the techniques utilized. Granting certiorari would enable this Court to correct that mistake.

At step two, the Federal Circuit determined that the patents' novel application of a combination of existing techniques to solve a problem that had plagued scientists for over a decade was nothing more than a "logical

combination" of "standard, well-known techniques" and that the patents therefore lacked an "inventive concept." App., *infra*, 18a-20a. But that is wrong on several levels. It disregards that the patents are for improved methods that plainly include an "inventive concept" because they depart from the conventional ways of measuring the same phenomenon for the same purpose (such as the Y-chromosome technique). It also disregards that the "inventive concept" can lie in combining a particular series of steps *and* applying it to solve a particular problem: "[A]n *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Diamond* v. *Diehr*, 450 U.S. 175, 187-188 (1981); *Mayo*, 566 U.S. at 71 (same); *Bilski*, 561 U.S. at 611 (same).

Even worse, the Federal Circuit's casual dismissal of these patents as merely a "logical combination" is tantamount to a finding of obviousness and improperly uses Section 101 to circumvent this Court's obviousness jurisprudence. When interpreting Section 103, this Court has required courts to engage in "factual inquiries" to "guard against slipping into use of hindsight" and help "resist the temptation to read into the prior art the teachings of the invention." *Graham* v. *John Deere Co.*, 383 U.S. 1, 17, 36 (1966). Here, the lower courts could not have granted summary judgment on obviousness—the district court initially *denied* summary judgment because of record evidence that the techniques at issue were cutting edge. And applying those techniques to solve this particular problem, using this specific combination of steps, was even more inventive. If these methods were truly conventional, scientists would have found them years earlier. This case is thus a uniquely good vehicle to clarify that Section 101 cannot be used

as an end-run around the protections built into Section 103.

3. This case is accordingly an even better vehicle for this Court's review than *Tropp* or *Interactive Wearables*. This Court should grant certiorari or call for the views of the Solicitor General. At a minimum, this Court should hold this petition pending the outcome of *Tropp* and *Interactive Wearables*.

I. This Court Needs To Take Another Section 101 Case

This Court has called for the views of the Solicitor General in Section 101 cases five times over the past five Terms. In each invitation brief, the Solicitor General has urged this Court to grant review in an appropriate case. U.S. Br. 8, *Hikma Pharm.* v. *Vanda Pharm., Inc.*, 140 S. Ct. 911 (2020) (No. 18-817), 2019 WL 6699397 (urging plenary review "in an appropriate case" to resolve "confusion"); U.S. Br. 10-11, *HP Inc.* v. *Berkheimer,* 140 S. Ct. 911 (2020) (No. 18-415), 2019 WL 6715368 (similar); U.S. Br. 9-10, *Am. Axle & Mfg., Inc.* v. *Neapco Holdings LLC*, 142 S. Ct. 2902 (2022) (No. 20-891), 2022 WL 1670811 (recommending the Court grant to "provid[e] greater clarity"). The Solicitor General has now recommended that this Court grant certiorari in *Tropp* and *Interactive Wearables*. U.S. *Tropp* Br. 1.

The Federal Circuit's judges have similarly urged this Court to take another Section 101 case. They have described *Alice* and *Mayo* as "baffling," *Athena Diagnostics, Inc.* v. *Mayo Collaborative Servs., LLC* (*Athena II*), 927 F.3d 1333, 1371 (Fed. Cir. 2019) (O'Malley, J., dissenting from the denial of the petition for rehearing en banc), leaving them "at a loss as to how to uniformly apply § 101." *Am. Axle & Mfg., Inc.* v. *Neapco Holdings LLC* (*Am. Axle III*), 977 F.3d 1379, 1382 (Fed. Cir. 2020) (Moore, J., concurring). Judges have remarked that it is

"near impossible to know with any certainty whether [an] invention is or is not patent eligible." *Interval Licensing LLC* v. *AOL, Inc.*, 896 F.3d 1335, 1348 (Fed. Cir. 2018) (Plager, J., concurring-in-part and dissenting-in-part). That reality "ha[s] a serious effect on the innovation incentive in all fields of technology," *Am. Axle & Mfg., Inc.* v. *Neapco Holdings LLC* (*Am. Axle II*), 966 F.3d 1347, 1357 (Fed. Cir. 2020) (Newman, J., dissenting from denial of the petition for rehearing en banc), and in 2019 led "every judge on [the Federal Circuit] to request Supreme Court clarification," *Am. Axle III,* 977 F.3d at 1382 (Moore, J., concurring).

District court judges too have widely bemoaned the lack of clarity in this area of the law. For example, the district court in this very case described Section 101 law as "fraught, incoherent, unclear, inconsistent, and confusing, and indeterminate and often leading to arbitrary results." App., *infra*, 36a-37a (cleaned up). As another district court put it, "[t]he only thing clear about the appropriate test for patent-eligible subject matter is that it is unclear." *PPS Data, LLC* v. *Jack Henry & Assocs., Inc.*, 404 F. Supp. 3d 1021, 1039 n.8 (E.D. Tex. 2019).

The U.S. Patent and Trademark Office (PTO) has agreed that "[p]roperly applying the *Alice/Mayo* test in a consistent manner has proven to be difficult, and has caused uncertainty." 2019 Revised Patent Subject Matter Eligibility Guidance, 84 Fed. Reg. 50, 50 (Jan. 7, 2019). A prior PTO Director called Section 101 "the most important substantive patent law issue in the United States today." Ryan Davis, *Courts Can Resolve Patent Eligibility Problems, Iancu Says*, Law360 (Apr. 11,

2019).[1] Another prior PTO Director testified that "patent eligibility law truly is a mess" and has produced "decisions that are irreconcilable, incoherent, and against our national interest." David J. Kappos, Testimony Before the S. Subcomm. on Intell. Prop. at 1 (June 4, 2019).[2]

The practical impact of the uncertainty is severe. The current state of Section 101 law has "reduced investment in new technologies." Barbara Fiacco, President-Elect, Am. Intellectual Prop. Law Ass'n, Testimony Before the S. Subcomm. on Intell. Prop. at 2 (June 5, 2019);[3] see also National Security Commission on Artificial Intelligence, Final Report 469 (2021).[4] And worse, it has "driven industry to foreign jurisdictions." Fiacco, *supra*, at 2. The prevailing law makes it "easier to secure patent protection for critical life sciences and information technology inventions in the People's Republic of China and in Europe, than in the U.S." Kappos, *supra*, at 2.

In sum, the Court's guidance on the correct application of Section 101 is overdue.

II. This Case Is A Better Vehicle Than *Tropp* And *Interactive Wearables*

This case is an even better vehicle to clarify Section 101's application than *Tropp* and *Interactive Wearables*

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[1] https://www.law360.com/articles/1149185/courts-can-resolve-patent-eligibility-problems-iancu-says

[2] https://www.judiciary.senate.gov/imo/media/doc/Kappos%20Testimony.pdf

[3] https://www.judiciary.senate.gov/imo/media/doc/Fiacco%20Testimony.pdf

[4] https://www.nscai.gov/wp-content/uploads/2021/03/Full-Report-Digital-1.pdf

because it involves many of the same analytic errors—and much more. In particular, this case gives the Court the opportunity (1) to clarify the application of Section 101 in a medical diagnostics case involving the natural-phenomenon exception, where the Federal Circuit is applying a virtually per se rule of invalidity and thus sharply undermining the incentive to invest in life-saving medical technologies; (2) to refocus the inquiry on the statutory text; and (3) to clarify that considerations of "conventionality" have no role to play in step one of the *Alice* analysis and also cannot be used at step two to deny patent protection to new and improved processes that apply natural phenomena to useful ends and to circumvent the protections against hindsight bias that this Court has long established under Section 103.

A. The Need For This Court's Review Is Most Pressing In The Field Of Medical Diagnostics

The problems with Section 101 have "had particularly significant practical effects with respect to medical-diagnostic methods." U.S. *Hikma* Br. 22. The Solicitor General has urged that "further guidance from this Court is amply warranted" in a "diagnostic-method case[]." *Id.* at 22-23; see also U.S. *Am. Axle* Br. 20 ("Problems arising from the application of Section 101 have attracted particular attention in certain fields, such as medical diagnostics.").

Innovations in medical diagnostics "are of substantial public benefit"—improving patient outcomes and "greatly reduc[ing] associated costs." *Athena II*, 927 F.3d at 1363, 1369 (Newman, J., dissenting from denial of the petition for rehearing en banc). But as the decision below illustrates, the Federal Circuit has adopted a virtually per se rule that all such "life-saving inventions" are invalid. *Id.* at 1370 (Stoll, J., dissenting from denial of

the petition for rehearing en banc). "Under *Mayo*, [the Federal Circuit] ha[s] consistently held diagnostic claims unpatentable." *Illumina, Inc.* v. *Ariosa Diagnostics, Inc.*, 967 F.3d 1319, 1325 (Fed. Cir. 2020), cert. dismissed, 142 S. Ct. 2707 (2022). Indeed, since *Mayo*, the Federal Circuit has invalidated "every single diagnostic claim in every case." *Athena II*, 927 F.3d at 1352 (Moore, J., dissenting from denial of the petition for rehearing en banc); Eurofins C.A. Br. 3 (same).

For example, the Federal Circuit invalidated a patent for an invention enabling early diagnosis of heart disease, an often-treatable malady that is responsible for almost one in every five deaths in the United States. See *Cleveland Clinic Found.* v. *True Health Diagnostics LLC*, 859 F.3d 1352 (Fed. Cir. 2017); *Heart Disease Facts*, CDC (Oct. 14, 2022).[5] It also invalidated a diagnostic method for tuberculosis, a treatable disease that causes over 1.5 million deaths annually. See *Roche Molecular Sys., Inc.* v. *CEPHEID*, 905 F.3d 1363, 1374 (Fed. Cir. 2018); *Tuberculous Fact Sheet*, World Health Org. (Apr. 21, 2023).[6] Here, the Federal Circuit invalidated patents that play a crucial role in preventing death from organ rejection. See App., *infra*, 21a, 25a.

The aim of U.S. patent law is to "promote the progress of science and useful arts." U.S. Const., Art. I, § 8, Cl. 8. But denying protection for diagnostic methods sharply undermines the incentive to invest in new and improved methods, lest the advance be cheaply copied by knock-off competitors. Diagnostics are "very expensive to develop but relatively cheap to reproduce," An-

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[5] https://www.cdc.gov/heartdisease/facts.htm

[6] https://www.who.int/news-room/fact-sheets/detail/tuberculosis

atole Krattiger, *Promoting Access to Medical Innovation,* World Intellectual Prop. Org. (Sept. 2013),[7] making patent protection particularly important. Unsurprisingly, innovators have proceeded with caution. Faced with the Federal Circuit's pattern of invalidating any and all diagnostic methods, the industry is "not moving forward diagnostic discoveries to translate them into commercial products the way [it] would do otherwise." State of Patent Eligibility in America, Part III, 116th Cong. 1:22:12–1:22:35 (June 11, 2019) (testimony of Peter O'Neill, Executive Director of Cleveland Clinic Innovations Before the S. Subcomm. on Intell. Prop.).[8]

This case is therefore a particularly good vehicle. It is a natural-phenomenon case involving a diagnostic method, the field where the need for this Court's review is most pressing. And the Federal Circuit's decision further solidifies its virtually per se rule of invalidity and thus further undermines the incentive to innovate.

B. This Case Would Enable The Court To Refocus The Inquiry On The Statutory Text

This case is also a particularly good vehicle for returning the focus of the eligibility analysis to Section 101's statutory text. As a matter of textual interpretation, this case is easily resolved.

1. "Statutory interpretation … always … begins with the text." *Ross* v. *Blake*, 578 U.S. 632, 638 (2016). This Court's Section 101 precedents have focused on whether a patent is for a "new and useful process, machine, manufacture, or composition of matter," 35

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[7] https://www.wipo.int/wipo_magazine/en/2013/05/article_0002.html

[8] https://www.senate.gov/isvp/?auto_play=false&comm=judiciary&filename=judiciary061119p

U.S.C. 101, or instead is effectively a claim upon a preexisting natural phenomenon. *E.g.*, *Mayo*, 566 U.S. at 70-80. The Court's Section 101 decisions have at times appeared to interpret the statute's terms, and more recently this Court has characterized its jurisprudence as an exception to those terms. See U.S. *Tropp* Br. 3-4 (documenting this shift). But Section 101 also includes an additional clause that provides threshold eligibility to any "new and useful *improvement* thereof." 35 U.S.C. 101 (emphasis added). This Court has not considered the application of Section 101 to an "improvement" upon a preexisting useful process. This case would accordingly give the opportunity to focus on the text of that clause, which provides a clear textually-grounded answer in a natural-phenomenon case.

When a patent claims an "improvement" upon prior useful methods for measuring a particular natural phenomenon, that is a dispositive indicator that the patent does not claim or monopolize the phenomenon itself and instead is patent eligible under Section 101. First, a claim to an "improvement" necessarily does not claim a natural phenomenon. Natural phenomena are preexisting and cannot be improved upon while still remaining natural. See *Ass'n for Molecular Pathology* v. *Myriad Genetics, Inc.*, 569 U.S. 576, 595-596 (2013). Nature is what it is. Second, in such a case, the preemption concerns that "drive[]" this Court's Section 101 precedents, *Alice*, 573 U.S. at 216, are absent because there can be no serious risk that the claimed improvement will preempt the underlying natural phenomenon. By definition, such a patent cannot claim the phenomenon itself, because the phenomenon was previously known and other methods already existed for using that same

phenomenon for the same purpose. Moreover, such a patent cannot claim the preexisting methods either, because otherwise it would be invalid for lack of novelty. See 35 U.S.C. 102. Such a patent thus inherently avoids concerns of monopolizing the natural phenomenon.

2. Consider the patents in this case, which are "improvement[s]" upon prior human-devised "process[es]" for doing something "useful." 35 U.S.C. 101. The specification *disclaims* discovery of the natural phenomenon at issue, crediting other scientists with identifying the correlation between donor-cell free DNA and organ rejection a decade earlier. C.A.J.A. 121; App. 75a-76a. It also identifies and *disclaims* prior useful methods for measuring that same phenomenon, namely, the preexisting Y-chromosome and HLA allele methods for measuring the proportion of donor/recipient cell-free DNA in order to detect organ rejection. *Ibid.*

The only claimed advance of each Stanford Patent is to improve upon those prior useful processes by devising a new and better test for measuring that very same correlation for the same purpose. See App., *infra*, 76a-78a; C.A.J.A. 121. As the magistrate judge explained, the Stanford Patents, on their face, are drawn to "a new, more accurate and useful analytic method of determining whether significant amounts of [cell-free] DNA [are] present in a transplant recipient's body." App., *infra*, 77a. The claims teach a method wherein a blood sample is obtained, and specific human-made technology (next-generation sequencing or digital PCR) is used to identify a specific kind of genetic information (SNPs), in sufficient quantities, and then to quantify the SNPs in the blood sample. *Id.* at 3a-9a, 79a-80a. It is "th[ose] particular *methods* for detecting" the donor cell-free DNA that the claims describe and are therefore "directed to," "not

to the fact or existence of the natural phenomenon itself." *Id.* at 79a n.8.

In these respects, the Stanford Patents mirror the patent this Court declared valid in *Tilghman* v. *Proctor*, 102 U.S. 707 (1880). In upholding Tilghman's patent for a process for separating "glycerine" from fatty acids, the Court explained that "[t]he chemical principle or scientific fact upon which [the patent was] founded … was not discovered by Tilghman." *Id.* at 729. Nor did Tilghman "claim every mode of accomplishing th[e] result" his patented process produced, as he "d[id] not claim" three methods that had been invented previously. *Ibid.* Thus, this Court concluded, Tilghman's patent was "not [a claim] for *a mere principle*," but was rather an eligible claim for "*a particular mode* of bringing about [a] desired result." *Ibid.* (emphasis added)

So too here. The Stanford Patents' singular focus on claiming specific improvements upon prior methods eliminates any risk of claiming and "disproportionately tying up the use of the underlying" phenomenon. *Alice*, 573 U.S. at 217. The "building block[]" of the correlation between donor cell-free DNA and organ rejection remains on the table for further advances of "human ingenuity." *Id.* at 216-217. Scientists may still use the Y-chromosome and HLA allele methods to diagnose organ rejection. And scientists are free to devise new methods that are different and even better than the claimed SNP-based methods.

This case accordingly presents a uniquely good vehicle for this Court to reinvigorate the role of the statutory text. As the Stanford Patents illustrate, when a claim is for an improved method for measuring a natural phenomenon, that is sufficient to establish that the patent does not claim or monopolize the phenomenon itself.

Such a patent instead claims only a specific patent-eligible "improvement" upon a prior useful process. 35 U.S.C. 101. The patent may ultimately fail for other reasons, such as for lack of novelty, obviousness, or enablement. See 35 U.S.C. 102, 103, 112; see also U.S. *Tropp* Br. 17-18 (emphasizing this problem). But a lack of patent eligibility is not one of them.

C. This Case Would Enable The Court To Clarify Both *Alice* Steps And Prevent Lower Courts From Circumventing This Court's Obviousness Jurisprudence

In recommending that this Court grant review in *Tropp* and *Interactive Wearables*, the Solicitor General emphasized that the Federal Circuit in *Interactive Wearables* had improperly relied on obviousness considerations in step two of its Section 101 analysis. See U.S. *Tropp* Br. 17-18. The Solicitor General explained that the Federal Circuit's "heavy emphasis on prior art was misplaced," because Section 101 turns "not on *when* the patent is filed, but on whether the claim represents a 'patent-eligible *application*' of a natural law or phenomenon or abstract idea." *Id.* at 17 (citation omitted). In this case, the Federal Circuit made this same type of mistake at *both* step one and step two.

1. At step one, the Federal Circuit concluded that even an "improved" measurement method fails at *Alice* step one if it relies upon "conventional" techniques. App., *infra*, 17a-18a. The panel emphasized that the Federal Circuit has "repeatedly analyzed conventionality at step one." *Id.* at 17a; see, *e.g.*, *Athena Diagnostics, Inc.* v. *Mayo Collaborative Servs., LLC* (*Athena I*), 915 F.3d 743, 751 (Fed. Cir. 2019); *Universal Secure Registry LLC* v. *Apple Inc.*, 10 F.4th 1342, 1349-1350, 1352 (Fed. Cir. 2021), cert. denied 142 S. Ct. 2707 (2022). The

Federal Circuit thus has made considerations of "conventionality" critical at both step two *and* step one. See App., *infra*, 14a-20a. That is a serious analytical error.

This Court's precedents establish that it is only at "step two" that courts take into account that "[s]imply appending conventional steps, specified at a high level of generality, [is] not enough to supply an inventive concept" sufficient to "transform" the claim "into a patent-eligible application." *Alice*, 573 U.S. at 221-222 (cleaned up); see also *id.* at 225 (determining, at *step two*, whether "each step of the process is purely conventional" (cleaned up)). A court reaches that inquiry "[i]f," but only "[i]f," the court has already finished step one and determined that the patent, for other reasons, is "drawn to" ineligible subject matter and thus may claim "the ineligible concept itself." *Id* at 217-218 (cleaned up).

Particularly given the Federal Circuit's emphasis on obviousness-like considerations at step two, giving those same considerations a starring role at step one as well collapses the entire Section 101 inquiry into "a search for an inventive concept," *Alice*, 573 U.S. at 217 (cleaned up), effectively conflating Section 101 with the statutory requirements of novelty, 35 U.S.C. 102, nonobviousness, 35 U.S.C. 103, and enablement, 35 U.S.C. 112. That cannot be right. "Section 101 should not be understood to incorporate by reference other restrictions on patentability." U.S. *Tropp* Br. 18.

The Federal Circuit's heavy reliance on conventionality has also been coupled with its disregard for consideration of preemption: the concern that "drives" and "undergirds" this Court's Section 101 jurisprudence. *Alice*, 573 U.S. at 216, 223. The Federal Circuit has adopted a virtually per se approach, under which it has consistently invalidated diagnostic-method patents

without even identifying any serious risk of preemption. See, *e.g.*, *Athena I*, 915 F.3d at 752; *Roche*, 905 F.3d at 1374; *Cleveland Clinic*, 859 F.3d at 1363; *Ariosa Diagnostics, Inc.* v. *Sequenom, Inc.*, 788 F.3d 1371, 1378-1379 (Fed. Cir. 2015). Indeed, the Federal Circuit invalidated the improved methods here even though they plainly do not preempt the underlying natural phenomenon. See pp. 22-23, *supra*.

The Federal Circuit has reasoned that preemption concerns "are fully addressed and made moot" when claims are found invalid "under the [*Alice*] framework." *E.g.*, *Ariosa*, 788 F.3d at 1379. But that logic breaks down when the Federal Circuit fails even to consider the preemption concerns that drive this Court's Section 101 jurisprudence and instead allows "conventionality" to take the wheel even at step one. See, *e.g.*, App, *infra*, 14a-18a. That approach leads to results like this one, in which important patents are invalidated under Section 101 without any significant preemption concern.

This case accordingly would be an unusually good vehicle for reorienting step one of the *Alice* test away from conventionality and back towards the key goal of ferreting out risks of preemption.

2. The Federal Circuit also improperly imported obviousness considerations into *Alice* step two. As noted above, the Solicitor General recommended certiorari in *Tropp* and *Interactive Wearables* in part to clarify the differences between Section 101 and other statutory requirements, including novelty, nonobviousness, and enablement. See U.S. *Tropp* Br. 17-18. Here, the Federal Circuit made the same mistake of relying on obviousness considerations at step two, but its errors were even more stark.

At the outset, the Federal Circuit once again overlooked that these are improved methods for measuring a known phenomenon (the natural correlation) for a known purpose (diagnosing organ rejection). The patents thus plainly contain an "inventive concept": to use particular human-made tools (next-generation sequencing or digital PCR) to identify fragments of a particular kind of mutation (SNPs), in sufficient quantity, to differentiate DNA fragments from the donor and the recipient, measure the proportion, and in turn diagnose organ rejection.

That is not, as the Federal Circuit held, a "conventional" or "standard" method for measuring that phenomenon. *Id.* at 19a-20a. It is brand new and had eluded a decade of motivated efforts by the scientific community. The "conventional" and "standard" methods for measuring cell-free DNA to diagnose organ rejection were *the Y-chromosome and HLA allele methods that the Stanford Patents affirmatively disclaim*. The Stanford Patents thus consist of a "patent-eligible application" of a natural phenomenon, namely, a new and better diagnostic test. *Alice*, 573 U.S. at 221.

The Federal Circuit nonetheless determined that the claims lack an "inventive concept" because (1) the court understood a boilerplate statement in the specification to "admit[]" that each laboratory technique used in the claims involved "only conventional techniques and off-the-shelf technology," App., *infra*, 18a-19a; and (2) the court determined that the application of the specific combination of steps at issue, to solve a measurement problem that had remained unsolved for a decade, was merely a "standard" and "logical combination" of those "standard, well-known techniques," *Id.* at 18a.

Petitioners strongly disagree with the Federal Circuit's understanding of the specification's language, but the panel's errors at the second stage of its analysis are deeper and purely legal. Even if each step of the Stanford Patents' methods involved "conventional" or "off-the-shelf" tools, App., *infra*, 19a, these methods would still be eligible for patent protection under Section 101.

As this Court has explained, "an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187; see also *Mayo*, 566 U.S. at 71 (same); *Bilski*, 561 U.S. at 611 (same). Likewise, "applications of [ineligible subject matter] to a new and useful end … [are] eligible for patent protection." *Alice*, 573 U.S. at 217 (cleaned up); see also *Myriad*, 569 U.S. at 596 ("new *applications* of knowledge about" natural phenomena are patentable). Indeed, when a patent, "considered as a whole," discloses "a new combination of steps" that achieves "a result heretofore unknown in the art," it remains eligible under Section 101 "even [if] all the constituents of the combination were well known and in common use before the combination was made." *Diehr*, 450 U.S. at 188, 193 n.15; see U.S. *Am. Axle* Br. 18-19 (stating that "[c]larification of this point is especially important"); see also, *e.g.*, *Tilghman*, 102 U.S. at 718 (upholding a patent for a chemical process when the apparatus for performing it "was well known"): *Le Roy* v. *Tatham*, 55 U.S. (14 How.) 156, 175 (1852) (providing that inventions that "apply[]" natural phenomena "to useful objects" are patentable "whether the machinery used be novel, or [the inventions] consist of a new combination of parts known").

Under those precedents, the Stanford Patents are clearly patent eligible. They apply the natural phenomenon (the correlation between the proportion of donor cell-free DNA and organ rejection) in a new way. They use a new combination of steps—*i.e.*, employ next-generation sequencing or digital PCR tools to identify fragments of a particular kind of mutation (SNPs), in sufficient quantity, to differentiate DNA fragments from the donor and the recipient—to produce a new and improved diagnostic test for organ rejection.

Furthermore, by invalidating the Stanford Patents on the ground that they merely involve a "logical" combination of known techniques, the Federal Circuit circumvented important protections guaranteed by this Court's obviousness precedents under Section 103. This Court's precedents establish that obviousness depends on underlying questions of fact. *E.g., Graham*, 383 U.S. at 17-18. And this Court has crafted numerous protections to "guard against slipping into use of hindsight" and help "resist the temptation to read into the prior art the teachings of the invention." *Id.* at 36; see also *KSR Int'l Co.* v. *Teleflex Inc.*, 550 U.S. 398, 421 (2007). Among other things, courts must consider objective evidence that the advance was not obvious, such as evidence of "differences between the prior art and the claims at issue," "long felt but unsolved needs," and "failure of others." *Graham*, 383 U.S. at 17-18; *Teleflex*, 550 U.S. at 406.

The lower courts did not grant, and could not have granted, summary judgment on obviousness on this record because ample evidence shows that these claims are nonobvious. The methods eluded motivated scientists for a decade: Scientists struggled to operationalize the discovery regarding donor cell-free DNA into a robust

diagnostic test and viewed "the use of [cell-]free DNA for the detection of organ rejection [as] difficult and impractical." C.A.J.A. 648. And the district court initially *denied* summary judgment because of substantial record evidence that the methods were a significant step forward. See App., *infra*, 61a, 64a.

The Federal Circuit thus did not merely reduce "analytical rigor" by putting a Section 103 inquiry into the wrong analytical box. U.S. *Tropp* Br. 18. It reached a result that this Court's Section 103 precedents foreclose. This case would therefore be a particularly good vehicle for clarifying the differences between Section 101 and Section 103 and the appropriate role (if any) of "conventionality" under Section 101.

The decision below is accordingly wrong on several levels. It disregards the statutory text. It misapprehends the nature of the patent and disregards the lack of preemption. It improperly puts considerations of obviousness into step one and step two. In doing so, it ignores the fundamental axiom that applying known techniques to a natural phenomenon may well be worthy of patent protection. And it reaches a result on "conventionality" that this Court's obviousness precedents would foreclose. The decision below is accordingly an ideal vehicle for this Court's review.

III. At A Minimum, This Court Should Hold This Case Pending The Outcome Of *Tropp* And *Interactive Wearables*

For the reasons set forth above, this Court needs to take another Section 101 case and this is a perfect vehicle. This Court accordingly should grant certiorari. In the alternative, this Court should call for the views of the Solicitor General as to whether this case warrants plenary review.

At a minimum, this Court should hold this case pending the outcome of *Tropp* and *Interactive Wearables*. This case involves the same statute (Section 101) and the same precedents (including *Alice*) regarding the same issue (eligibility). Moreover, as set forth above, this case involves overlapping analytical issues, including as to the role of conventionality and related concerns in the *Alice* inquiry. In *Tropp* or *Interactive Wearables*, this Court could illuminate the role of the statutory text and clarify or refine either or both of the two steps of the *Alice* inquiry, including by clarifying the differences between Section 101, on one hand, and Sections 102, 103, and 112, on the other. See U.S. *Tropp* Br. 17-18. And although those cases involve the abstract-ideas exception, whereas this case involves the natural-phenomenon exception, there is only a single statute and statutory test. Accordingly, this Court at a minimum should hold this case pending the outcome of those cases.

CONCLUSION

For the foregoing reasons, the Court should grant the petition of certiorari, call for the views of the Solicitor

General, or hold this petition pending the outcome of *Tropp* and *Interactive Wearables*.

Respectfully submitted,

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MAY 2023

APPENDIX

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APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2022-1027

CAREDX, INC., THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs-Appellants

v.

NATERA, INC.,

Defendant-Appellee

Appeal from the United States District Court for the District of Delaware in Nos. 1:19-cv-00567-CFC-CJB, 1:20-cv-00038-CFC-CJB, Chief Judge Colm F. Connolly.

2022-1028

CAREDX, INC., THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs-Appellants

v.

EUROFINS VIRACOR, INC.,

Defendant-Appellee

Appeal from the United States District Court for the District of Delaware in No. 1:19-cv-01804-CFC-CJB, Chief Judge Colm F. Connolly.

Decided: July 18, 2022

EDWARD R. REINES, Weil, Gotshal & Manges LLP, Redwood Shores, CA, argued for plaintiffs-appellants. Also represented by DEREK C. WALTER; ANNA DWYER, New York, NY; ZACHARY TRIPP, Washington, DC.

GABRIEL K. BELL, Latham & Watkins LLP, Washington, DC, argued for defendant-appellee Natera, Inc. Also represented by ASHLEY FRY, FAN ZHANG.

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for defendant-appellee Eurofins Viracor, Inc. Also represented by JORDAN BOCK, KEVIN JON DEJONG, Boston, MA; DARRYL M. WOO, San Francisco, CA.

Before LOURIE, BRYSON, and HUGHES, *Circuit Judges*.

LOURIE, *Circuit Judge*.

CareDx, Inc. and The Board of Trustees of the Leland Stanford Junior University ("Stanford") (collectively, "CareDx") appeal from a decision of the United States District Court for the District of Delaware holding that U.S. Patents 8,703,652 (the "'652 patent"), 9,845,497 (the "'497 patent"), and 10,329,607 (the "'607 patent") are ineligible for patent under 35 U.S.C. § 101. *See CareDx, Inc. v. Natera, Inc.*, 563 F. Supp. 3d 329 (D. Del. 2021) ("*Decision*"). We affirm.

BACKGROUND

Stanford owns the '652, '497, and '607 patents. All three patents share the same specification and are entitled "Non-Invasive Diagnosis of Graft Rejection in Organ Transplant Patients." These patents discuss diagnosing or predicting organ transplant status by using methods to detect a donor's cell-free DNA ("cfDNA"). When an organ transplant is rejected, the recipient's body, through its natural immune response, destroys the donor cells, thus releasing cfDNA from the donated organ's dying cells into the blood. These increased levels of donor cfDNA—which occur naturally as the organ's condition deteriorates—can be detected and then used to diagnose the likelihood of an organ transplant rejection. Claim 1 of each patent is representative. Claim 1 of the '652 patent reads as follows:

> 1. A method for detecting transplant rejection, graft dysfunction, or organ failure, the method comprising:
>
> (a) *providing a sample* comprising [cfDNA] 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 [cfDNA], 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 [cfDNA] in the sample followed by analysis of the sequencing results using the polymorphism profile to *detect donor [cfDNA] and subject [cfDNA]*; 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 [cfDNA]* based on the detection of the donor [cfDNA] and subject [cfDNA] by the multiplexed sequencing, wherein an *increase in the quantity of the donor [cfDNA] 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 at col. 27 l. 39–col. 28 l. 40 (emphases added).

Claim 1 of the '497 patent is similar, except that it recites high-throughput sequencing or digital polymerase chain reaction ("PCR") instead of multiplex sequencing for "determining" the amount of donor cfDNA.

> 1. A method of detecting donor-specific circulating [cfDNA] 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 [cfDNA] from the solid organ transplant; and

(d) determining an amount of donor-specific circulating [cfDNA] from the solid organ transplant in the biological sample by detecting a homozygous or a heterozygous SNP within the donor-specific circulating [cfDNA] 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 [cfDNA] from the solid organ transplant when the donor-specific circulating [cfDNA] make

> up at least 0.03% of the total circulating [cfDNA] in the biological sample.

'497 patent at col. 28 l. 2–col. 29 l. 5 (emphasis added).

Claim 1 of the '607 patent is also similar, except that it recites selective amplification of the cfDNA by PCR before high-throughput sequencing.

> 1. A method of quantifying kidney transplant-derived circulating [cfDNA] in a human kidney transplant recipient, said method comprising:
>
> (a) providing a plasma sample from said human kidney transplant recipient, wherein said human kidney transplant recipient has received a kidney transplant from a kidney transplant donor, wherein said plasma sample from said human kidney transplant recipient comprises kidney transplant-derived circulating [cfDNA] and human kidney transplant recipient-derived circulating [cfDNA];
>
> (b) extracting circulating [cfDNA] from said plasma sample from said human kidney transplant recipient in order to obtain extracted circulating [cfDNA], wherein said extracted circulating [cfDNA] comprises said kidney transplant-derived circulating [cfDNA] and human kidney transplant recipient-derived circulating [cfDNA];
>
> (c) *performing a selective amplification of target [DNA] sequences*, wherein said selective amplification of said target [DNA] sequences is of said extracted

circulating [cfDNA], wherein said selective amplification of said target [DNA] sequences amplifies a plurality of genomic regions comprising at least 1,000 single nucleotide polymorphisms, wherein said at least 1,000 single nucleotide polymorphisms comprise homozygous single nucleotide polymorphisms, heterozygous single nucleotide polymorphisms, or both homozygous single nucleotide polymorphisms and heterozygous single nucleotide polymorphisms, and wherein said selective amplification of said target deoxyribonucleic acid sequences is by polymerase chain reaction (PCR);

(d) performing a high throughput sequencing reaction, wherein said high throughput sequencing reaction comprises performing a sequencing-by-synthesis reaction on said selectively-amplified target [DNA] sequences from said extracted circulating [cfDNA], wherein said sequencing-by-synthesis reaction has a sequencing error rate of less than 1.5%;

(e) providing sequences from said high throughput sequencing reaction, wherein said provided sequences from said high throughput sequencing reaction comprise said at least 1,000 single nucleotide polymorphisms; and

(f) quantifying an amount of said kidney transplant-derived circulating [cfDNA] in said plasma sample from said human kidney transplant recipient to obtain a quantified amount, wherein said quanti-

> fying said amount of said kidney transplant-derived circulating [cfDNA] in said plasma sample from said human kidney transplant recipient comprises using markers distinguishable between said human kidney transplant recipient and said kidney transplant donor, wherein said markers distinguishable between said human kidney transplant recipient and said kidney transplant donor comprises single nucleotide polymorphisms selected from said at least 1,000 single nucleotide polymorphisms identified in said provided sequences from said high throughput sequencing reaction, and wherein said quantified amount of said kidney transplant-derived circulating [cfDNA] in said plasma sample from said human kidney transplant recipient comprises at least 0.03% of the total circulating [cfDNA] from said plasma sample from said human kidney transplant recipient.

'607 patent at col. 28 l. 56–col. 30 l. 2 (emphasis added).

In summary, the methods disclosed in the representative claims have four steps for detecting a donor's cfDNA in a transplant recipient:

1. "obtaining" or "providing" a "sample" from the recipient that contains cfDNA;
2. "genotyping" the transplant donor and/or recipient to develop "polymorphism" or "SNP" "profiles";

3. "sequencing" the cfDNA from the sample using "multiplex" or "high-throughput" sequencing; or performing "digital PCR"; and
4. "determining" or "quantifying" the amount of donor cfDNA.

CareDx is the exclusive licensee of the '652, '497, and '607 patents. It sued Natera, Inc. ("Natera"), alleging that Natera's kidney transplant rejection test infringed the '652, '497, and '607 patents. CareDx also sued Eurofins Viracor, Inc. ("Eurofins"), alleging that Eurofins' various organ transplant rejection tests infringed the '652 patent. Natera and Eurofins both moved to dismiss the complaints for failure to state a claim due to lack of patent-eligible subject matter under § 101.

The motions to dismiss were referred to a magistrate judge, who recommended that they be denied. The magistrate judge held that the claims were a "purportedly new, unconventional combination of steps" to detect natural phenomena. *Decision* at 336–37 (quoting J.A. 12). In light of an amendment in CareDx's complaint against Natera, the district court vacated the magistrate judge's recommendation in Natera's action. The court then adopted the magistrate judge's recommendation in the Eurofins action but modified the reasoning. The court noted that "language in the written description[] of the asserted patent[] suggests that the patented steps are neither new nor unconventional" and that the "specifications raise[d] doubts about the patents' validity." *Id.* at 337 (alterations in original). However, the court was cautious about ruling prematurely, and denied the motion to dismiss so that the parties could conduct limited discovery and develop the record on conventionality.

After expert discovery relating to § 101 had concluded, Natera and Eurofins each moved for summary judgment of ineligibility. The district court denied the motions, concluding that there was a factual dispute as to the conventionality of the techniques for performing the claimed methods. Natera and Eurofins then moved for certification of interlocutory appeals from the court's order denying summary judgment. Following a conference with the parties regarding the motion, the court stated it would reconsider its summary judgment decision in view of case law cited in the certification motion.

Following reconsideration, the district court granted the summary judgment motions of ineligibility. The court first determined that the asserted claims were directed to the detection of natural phenomena, specifically, the presence of donor cfDNA in a transplant recipient and the correlation between donor cfDNA and transplant rejection. The court concluded that, based on the specification's numerous admissions, the claims recited only conventional techniques.

CareDx appealed the district court's grant of Natera's and Eurofins' summary judgment motions. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review the district court's grant of summary judgment *de novo* under Third Circuit law. *SRI Int'l, Inc. v. Cisco Sys., Inc.*, 930 F.3d 1295, 1306 (Fed. Cir. 2019). Summary judgment is appropriate when "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). Patent eligibility under § 101 is ultimately a question of law that this court reviews *de*

novo. *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1365 (Fed. Cir. 2018).

I

Section 101 provides that "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. Given the expansive terms of § 101, "Congress plainly contemplated that the patent laws would be given wide scope"; the legislative history likewise indicated that "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 308–09 (1980) (internal citation omitted).

The Supreme Court has held that § 101 "contains an important implicit exception. '[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo Collaborative Servs. v. Prometheus Lab'ys, Inc.*, 566 U.S. 66, 70 (2012) (alteration in original) (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). These exceptions exist because monopolizing the basic tools of scientific work "might tend to impede innovation more than it would tend to promote it." *Id.* at 71. However, the Supreme Court has advised that these exceptions must be applied cautiously, as "too broad an interpretation of this exclusionary principle could eviscerate patent law." *Id.*

Laws of nature and natural phenomena are not patentable, but applications and uses of such laws and phenomena may be patentable. A claim to otherwise eligible statutory subject matter does not become ineligible by its use of a law of nature or natural

phenomenon. *See Diehr*, 450 U.S. at 187; *Parker v. Flook*, 437 U.S. 584, 590 (1978). On the other hand, adding "conventional steps, specified at a high level of generality," to a law of nature or natural phenomenon does not make a claim to the law or phenomenon patentable. *Mayo*, 566 U.S. at 82.

To distinguish claims to patent-eligible applications of laws of nature and natural phenomena from claims that impermissibly tie up such laws and phenomena, we apply the two-part test set forth by the Supreme Court. First, we examine whether the claims are "directed to" a law of nature or natural phenomenon. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014). If—and only if—they are, then we proceed to the second inquiry, where we examine whether the limitations of the claim apart from the law of nature or natural phenomenon, considered individually and as an ordered combination, "'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo*, 566 U.S. at 78).

II

CareDx argues that, regarding *Alice*/*Mayo* step one, the patents' claimed advance is not the discovery of a natural correlation between organ rejection and the donor's cfDNA levels in the recipient's blood. Rather, the claimed advance is improved measurement methods spelled out in the claims as superior to the inadequate prior art measurement techniques. CareDx adds that the district court did not properly perform the step one analysis because it concluded that step one is essentially the same as step two and centers on conventionality. It asserts that there is no basis in the law for a one-step application of *Alice*/*Mayo*.

Regarding *Alice*/*Mayo* step two, CareDx argues that using digital PCR and next-generation sequencing ("NGS") to identify and measure donor-specific SNPs was an inventive breakthrough and that the patents claim this specific and useful application. CareDx notes that the district court itself acknowledged that there was a factual dispute as to the conventionality of the claimed techniques when it initially denied summary judgment. Lastly, CareDx asks us to reverse the court's decision rather than remand because of what it refers to as a record of irregular proceedings, such as the court backtracking on its denial of summary judgment and improperly making credibility determinations.

Natera responds that CareDx's asserted claims are directed to detecting natural phenomena—the presence of an organ donor's cfDNA in the blood of a transplant recipient and the correlation between elevated levels of that cfDNA and organ transplant rejection. It adds that the claims recite performing this detection using collection and measurement techniques that the specification admits are conventional and further admits can be performed using existing technology without modification. As such, Natera argues, these claims are indistinguishable from other diagnostic method claims that the Supreme Court found ineligible in *Mayo* and that we found ineligible on multiple occasions. Natera's Resp. at 17 (citing *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743 (Fed. Cir. 2019); *Genetic Veterinary Scis., Inc. v. LABOKLIN GmbH & Co. KG*, 933 F.3d 1302 (Fed. Cir. 2018); *Roche Molecular Sys., Inc. v. CEPHEID*, 905 F.3d 1363 (Fed. Cir. 2018); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352 (Fed. Cir. 2017); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015)).

Natera adds that the district court properly applied *Alice* step one and relied on the express use of the word "detecting" in the claims, and our case law addressing similar "detecting" claims, to conclude that the claims are directed to a natural phenomenon. Natera further adds that the court recognized that *Alice* step one can overlap with step two.

Lastly, Natera asserts that the procedural background of this case confirms that we should affirm. Natera notes that early in this case, the district court determined that it was premature to resolve the eligibility question without affording the parties an opportunity to develop the record. Subsequently, the court recognized that CareDx's expert testimony and other extrinsic evidence was contrary to, and therefore could not overcome, the admissions in the specification. Natera points out that the court's reconsideration of its summary judgment decision demonstrates that it thoughtfully and thoroughly considered that issue. Eurofins largely echoes Natera's arguments.

We agree with Natera and Eurofins. This is not a case involving a method of preparation or a new measurement technique. *See Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 952 F.3d 1367, *opinion modified by* 967 F.3d 1319, 1327 (Fed. Cir. 2020) (holding that a new and improved "method for preparing" an unnaturally enriched fetal cfDNA fraction from a pregnant woman by separating smaller fetal cfDNA fragments from larger (and likely maternal) fragments was unlike claims merely "directed to starting with a sample that contains" cfDNA and "seeing that the [cfDNA] exists"). CareDx also concedes that it did not invent or discover the relationship between donor cfDNA and the likelihood of organ transplant rejection. *See* Appellant's Br. at 1 ("[S]ince at least 1998, scientists recognized that

higher concentrations of donor cfDNA in the organ recipient's bloodstream may be a marker for organ rejection."). Furthermore, as the district court noted, the patents' written description expressly states that the techniques referred to in the claimed steps are, "unless otherwise indicated, conventional techniques of immunology, biochemistry, chemistry, molecular biology, microbiology, cell biology, genomics, and recombinant DNA, which are well within the skill of art." *Decision* at 335 (citing '652 patent at col. 5 ll. 36–40). Specifically, the written description is replete with characterizations of the claimed techniques in terms that confirm their conventionality.[1] Thus, CareDx's

[1] *See, e.g.*, '652 patent at col. 9 ll. 8–14 (stating that "[d]etection, identification and/or quantitation of the donor-specific markers (e.g.[,] polymorphic markers such as SNPs) can be performed using real-time PCR, chips (e.g., SNP chips), high throughput shotgun sequencing of circulating nucleic acids (e.g.[,] [cfDNA]), as well as other methods known in the art"); *id.* at col. 10 ll. 11–12 (stating that, to obtain cfDNA samples, "any technique known in the art may be used, e.g. a syringe or other vacuum suction device"); *id.* at col. 13 ll. 51–53 (stating that step 2 of claimed methods can be performed "using existing genotyping platforms know[n] in the art"); *id.* at col. 15 ll. 6–8 (stating that techniques recited in step 2 of claimed methods "can be accomplished through classic Sanger sequencing methods which are well known in the art"); *id.* at col. 13 ll. 58–61 (stating that "[c]ompanies (such as Applied Biosystems, Inc.) currently offer both standard and custom-designed TaqMan probe sets for SNP genotyping that can in principle target any desired SNP position for a PCRbased assay"); *id.* at col. 20 ll. 31–34 (stating that genotyping recited in claimed methods "may be performed by any suitable method known in the art including those described herein such as sequencing, nucleic acid array or PCR"); *id.* at col. 15 ll. 22–65 (discussing commercial high throughput sequencing products); *id.* at col. 14 ll. 58–67 (citing articles from 2006 and 2007 as supporting the statement that "digital PCR is a much more accurate and reliable method to quantitate nucleic acid species"); *id.* at col. 18 l. 55–col. 19 l. 2 (stating that "[m]ethods for

patents apply conventional measurement techniques to detect a natural phenomenon—the level of donor cfDNA and the likelihood of organ transplant rejection.

The claimed methods are indistinguishable from other diagnostic method claims the Supreme Court found ineligible in *Mayo* and that we found ineligible on multiple occasions. *See Mayo*, 566 U.S. at 82 (applying conventional diagnostic methods to observe a natural correlation is not patent eligible subject matter). Similarly, *Ariosa* involved claims reciting methods for making a diagnosis of certain fetal characteristics based on detecting paternally inherited cell-free fetal DNA ("cffDNA") in the blood of a pregnant female. 788 F.3d at 1376. In *Ariosa*, as here, it was undisputed that the existence of cffDNA in maternal blood was a natural phenomenon. *Id.* And, as here, the recited steps in *Ariosa* included amplifying the cfDNA—in that case cffDNA in the mother's blood—using PCR. *Id.* at 1374. What followed was detecting the paternally inherited cffDNA, again a natural phenomenon. *Id.* at 1373–74. The specification asserted that analyzing cffDNA permitted more efficient determination of genetic defects and that a pregnant woman carrying a fetus with certain genetic defects will have more cffDNA in her blood than will a woman with a normal fetus. *Id.* We held that the claims were directed to a natural phenomenon, identifying the presence of cffDNA, at *Alice*/*Mayo* step one, and ultimately ineligible. *Id.* at 1376, 1378.

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quantifying nucleic acids," including high throughput genotyping, "are known in the art"); *id.* at col. 21 ll. 5–9 (stating that "[t]he presence or absence of one or more nucleic acids from the transplant donor in the transplant recipient may be determined by any suitable method known in the art including those described herein such as sequencing, nucleic acid arrays or PCR").

Here, as in *Ariosa*, the claims boil down to collecting a bodily sample, analyzing the cfDNA using conventional techniques, including PCR, identifying naturally occurring DNA from the donor organ, and then using the natural correlation between heightened cfDNA levels and transplant health to identify a potential rejection, none of which was inventive. The claims here are equally as ineligible as those in *Ariosa*.

CareDx's step one arguments are unavailing. Its argument that the district court "disregarded the [s]tep [o]ne analysis entirely," Appellant's Br. at 33–34, is contradicted by the record. The court reviewed the claim language (e.g., "detecting" and "quantifying" donor cfDNA in a transplant recipient), along with CareDx's own characterizations, and concluded that the claims recite methods for detecting natural phenomena. *Decision* at 341–42. Based on our precedent, the court noted that claims applying conventional methods "directed to" natural phenomena satisfy *Alice*/*Mayo* step one.

CareDx also incorrectly characterizes our precedent as limiting the conventionality inquiry to step two. On the contrary, and as the district court recognized, we have repeatedly analyzed conventionality at step one as well. *See Athena*, 915 F.3d at 751 (stating that, at step one "the specification describes the claimed concrete steps for observing the natural law as conventional"); *see also Cleveland Clinic*, 859 F.3d at 1361 (stating that, at step one the claims contained "no meaningful non-routine steps"). Indeed, we have explained that "the two stages are plainly related: not only do many of our opinions make clear that the two stages involve overlapping scrutiny of the content of the claims, but . . . there can be close questions about when the inquiry should proceed from the first stage

to the second." *Elec. Power Grp., LLC v. Alstom S.A.*, 830 F.3d 1350, 1353 (Fed. Cir. 2016) (citations omitted). As such, our precedent rejects CareDx's effort to draw a bright line between the two steps.

CareDx argues that the patents' claims are directed not to natural phenomena, but to improved laboratory techniques. CareDx contends that the "claimed advance" is "an improved, human-devised method for measuring increases in donor cfDNA in a recipient's body to identify organ rejection." Appellant's Br. at 27. In particular, CareDx identifies the use of digital PCR, NGS, and selective amplification to more accurately measure donor SNPs of cfDNA in transplant recipients. However, CareDx does not actually claim any improvements in laboratory techniques—rather, as previously discussed, the actual claims of the patent merely recite the conventional use of existing techniques to detect naturally occurring cfDNA. Furthermore, the specification admits that the laboratory techniques disclosed in the claims require only conventional techniques and off-the-shelf technology. *See supra* note 1.

For these reasons, we affirm the district court's holding that the '652, '497, and '607 patents' asserted claims are directed to natural phenomena under *Alice*/*Mayo* step one.

Regarding *Alice*/*Mayo* step two, we also agree with the district court and hold that the asserted claims add nothing inventive because they merely recite standard, well-known techniques in a logical combination to detect natural phenomena. The court thoroughly considered whether any of the claims' additional elements were unconventional and, based on the specification's admissions, properly found that they were not. *See Decision* at 345–46. The specification

admits that each step in the purported invention requires only conventional techniques and commercially available technology: (1) collecting the patient's sample using "any technique known in the art," '652 patent at col. 10 l. 11; (2) genotyping the donor and recipient to create SNP profiles using "any suitable method known in the art," *id.* at col. 20 ll. 31–33; (3) sequencing the cfDNA using "well known" techniques and off-the-shelf tools, *id.* at col. 15 ll. 6–8, col. 15 ll. 22–67; and (4) quantifying the donor cfDNA using methods "known in the art," *id.* col. 18 l. 55 col. 19 l. 2. *See supra* note 1. There is no genuine dispute that the claimed techniques add nothing inventive to the natural phenomenon being detected.

We have repeatedly held that applying standard techniques in a standard way to observe natural phenomena does not provide an inventive concept. In *Ariosa*, the specification stated that the preparation and amplification of DNA sequences in plasma, including by PCR were "standard" techniques. 788 F.3d at 1377. In *Athena*, the specification expressly described the recited immunoassay techniques as "standard" or "known per se in the art." 915 F.3d at 753–54. And in *Roche*, the specification stated that the methods for detecting the bacterium used "standard PCR techniques" and failed to disclose "any 'new and useful' improvement to PCR protocols or DNA amplification techniques." 905 F.3d at 1372.

As in each of these cases, CareDx's asserted claims add nothing inventive at step two because they recite detection methods that "simply append[] conventional steps, specified at a high level of generality" to natural phenomena. *Mayo*, 566 U.S. at 82. Each of the methods in the recited steps was already being performed by those in the art. Furthermore, the claimed combina-

tion of steps adds nothing inventive. The specification confirms that the claimed combination of steps—collecting a sample, genotyping, sequencing, and quantifying—was a straightforward, logical, and conventional method for detecting cfDNA previously used in other contexts, including cancer diagnostics and prenatal testing. *See* '652 patent at col. 6 l. 57–col. 7 l. 46. Thus, the practice of the asserted method claims does not result in an inventive concept that transforms the natural phenomena into a patentable invention. For these reasons, we affirm the district court's holding with regard to *Alice*/*Mayo* step two.

Lastly, we note that CareDx's procedural complaints are without merit. First, CareDx asserts that the district court did not "explain[] why it departed from the magistrate judge's reasoning." Appellant's Br. at 54. However, the court explained that it agreed with the magistrate judge insofar as he found it was premature to resolve § 101 on the pleadings. The court then went on to express doubt about the magistrate judge's recommendation on finding eligibility in light of the specification's disclosures suggesting the conventionality of the claimed methods. The court also indicated that it viewed CareDx's claims as akin to ineligible claims in *Athena*. J.A. 60. Moreover, the court's final decision explained why the claims are indeed ineligible.

Second, CareDx points out the irregularity of the district court backtracking on its initial denial of summary judgment and contends that the court erroneously decided issues of fact. However, as Natera and Eurofins argue, the court was entitled to reconsider its summary judgment decision. The court initially denied summary judgment because the warring extrinsic evidence from CareDx, Natera, and

Eurofins appeared to create a fact issue. However, the court later found this fact issue non-genuine due to the explicit contradiction between CareDx's extrinsic evidence and the numerous admissions of conventionality in the intrinsic record.

CONCLUSION

We have considered CareDx's remaining arguments but find them unpersuasive. Because the asserted claims in the '652, '497, and '607 patents are directed to a natural law together with conventional steps to detect or quantify the manifestation of that law, they are ineligible under § 101. For the foregoing reasons, we affirm the judgment of the district court.

AFFIRMED

APPENDIX B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civil Action No. 19-0567-CFC-CJB
CONSOLIDATED

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs,

v.

NATERA, INC.,

Defendant.

Civil Action No. 19-1804-CFC-CJB

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs,

v.

EUROFINS VIRACOR, INC.,

Defendant.

Brian Farnan, Michael Farnan, FARNAN LLP, Wilmington, Delaware; Derek Walter, Edward Reines, WEIL, GOTSHAL & MANGES LLP, Redwood Shores, California; Stephen Bosco, WEIL, GOTSHAL & MANGES LLP, Washington, District of Columbia

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Counsel for Defendant Eurofins Viracor, Inc.

MEMORANDUM OPINION

September 28, 2021
Wilmington, Delaware

/s/ Colm F. Connolly
COLM F. CONNOLLY
CHIEF JUDGE

Plaintiffs CareDx, Inc. and the Board of Trustees of the Leland Stanford Junior University (collectively, CareDx) have sued Defendants Natera, Inc. (CA. No. 19-0567) and Eurofins Viracor, Inc. (C.A. No. 19-1804) for patent infringement. On December 1, 2020, I denied Natera's and Eurofins's motions for summary judgment of invalidity of the asserted patents

under 35 U.S.C. § 101. C.A. No. 19-0567, D.I. 115; C.A. No. 19-1804, D.I. 76. I subsequently decided, after identifying material facts that may not be genuinely in dispute, to reconsider summary judgment of invalidity of the asserted patents on my own pursuant to Federal Rule of Civil Procedure 56(f)(3) and the Court's inherent authority.[1] I held an evidentiary hearing and permitted the parties to submit briefing after the hearing. I have now determined, for the reasons set forth below, that there are no genuine disputes of material fact and that summary judgments in Defendants' favor are warranted because the asserted patents claim patent-ineligible subject matter and are therefore invalid under § 101. *See* Fed. R. Civ. P. 56(a) ("The court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.").

I. THE ASSERTED PATENTS

CareDx has asserted three patents: U.S. Patent Numbers 8,703,652 (the #652 patent) (asserted

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[1] Pursuant to Federal Rule of Civil Procedure 56(0(3), "[a]fter giving notice and a reasonable time to respond, the court may consider summary judgment on its own after identifying for the parties the material facts that may not be genuinely in dispute." Under Third Circuit law, which governs the procedures by which this case is handled, a district court may revisit a prior decision *sua sponte* so long as it has not entered a final judgment depriving it of jurisdiction to reconsider the issue. *DeFranco v. Wolfe,* 387 F. App'x 147, 155 (3d Cir. 2010); *see also Escanio v. United Parcel Serv.,* 538 F. App'x 195, 199 (3d Cir. 2013) (judge may revisit earlier interlocutory denial of summary judgment). "In order to revisit a prior decision, the Court must explain on the record the reasoning behind its decision to reconsider the prior ruling, and it must take appropriate steps so that the parties are not prejudiced by reliance on the prior ruling." *DeFranco,* 387 F. App'x at 156.

against Natera and Eurofms); 9,845,497 (the #497 patent) (asserted against Natera); and 10,329,607 (the #607 patent) (asserted against Natera). As described by CareDx in the operative Amended Complaint against Natera, all three patents disclose "method[s] for determining organ transplant rejection" that "allow[ ] doctors to assess rejection through blood tests and without invasive biopsies." C.A. No. 19-0567, D.I. 74 ¶ 1.[2] An important determinant of the success or failure of an organ transplant is whether, and the extent to which, the recipient's body "rejects" the organ and attacks it with the body's immune system. Early detection of rejection is crucial to a transplant operation's success and the recipient's survival.

The methods disclosed in the patents, to use CareDx's words, "detect [particular concentrations of donor-specific, cell-free DNA in the bodies of donor recipients . . . ." D.I. 15 at 3. The linkage between concentrations of the organ donor's cell-free DNA (cfDNA) found in the recipient's blood after the organ transplant and the likelihood that the recipient will reject the newly transplanted organ was "long-known" before 2009, when the applications for the asserted patents were filed with the United States Patent and Trademark Office (PTO). D.I. 176 at 2. According to CareDx, attempts to detect the concentration of donor-specific cfDNA as of 2009 were "deficient," and the methods claimed by the asserted patents "improved on these deficiencies *[sic]* through the use of innovative, highly precise assays capable of detecting tiny increases in donor-specific DNA, thereby allowing doctors to recognize the onset of

[2] Unless otherwise noted, all docket citations that follow will be to C.A. No. 19-0567.

organ rejection before the damage becomes irreversible." D.I. 15 at 2.

The three asserted patents share a single written description and are all titled "Non-invasive Diagnosis of Graft Rejection in Organ Transplant Patients." Each patent has a priority date in November 2009. The shared written description states that the claimed "invention describes sensitive and non-invasive methods . . . for diagnosing or predicting transplant status or outcome (e.g. transplant rejection)." #657 patent at 3:52-55.[3] A detection method is said to be "sensitive" in two respects. Sensitivity can refer to the smallest absolute amount of change that can be detected by a method, Tr. of May 17, 2021 Hr'g at 96:25-97:14; or it can refer to the method's ability to correctly identify a patient with a particular disease, *id.* at 111:9-22.

CareDx alleged in its operative complaints that claim 1 of each asserted patent is "representative." See D.I. 74 ¶¶ 20, 23, 26; C.A. No. 19-1804, D.I. ¶ 17. Defendants assert, and CareDx does not dispute, that claim 1 in each patent is sufficiently similar to the respective patent's other claims to be deemed a representative claim for determining whether the patent claims patent-eligible subject matter.

Claim 1 of the #652 patent recites:

> A method for detecting transplant rejection, graft dysfunction, or organ failure, the method comprising:

[3] For the sake of simplicity, I will identify only the #652 patent when citing to the patents' shared written description.

(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).

Claim 1 of the #497 patent recites:

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 homozy-

gous 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.

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, said method comprising:

(a) providing a plasma sample from said human kidney transplant recipient, wherein said human kidney transplant recipient has received a kidney transplant from a kidney transplant donor, wherein said plasma sample from said human kidney transplant recipient comprises kidney transplant-derived circulating cell-free deoxyribonucleic acid and human kidney transplant recipient-derived circulating cell-free deoxyribonucleic acid;

(b) extracting circulating cell-free deoxyribonucleic acid from said plasma sample from said human kidney trans-

plant recipient in order to obtain extracted circulating cell-free deoxyribonucleic acid, wherein said extracted circulating cell-free deoxyribonucleic acid comprises said kidney transplant-derived circulating cell-free deoxyribonucleic acid and human kidney transplant recipient-derived circulating cell-free deoxyribonucleic acid;

(c) performing a selective amplification of target deoxyribonucleic acid sequences, wherein said selective amplification of said target deoxyribonucleic acid sequences is of said extracted circulating cell-free deoxyribonucleic acid, wherein said selective amplification of said target deoxyribonucleic acid sequences amplifies a plurality of genomic regions comprising at least 1,000 single nucleotide polymorphisms, wherein said at least 1,000 single nucleotide polymorphisms comprise homozygous single nucleotide polymorphisms, heterozygous single nucleotide polymorphisms, or both homozygous single nucleotide polymorphisms and heterozygous single nucleotide polymorphisms, and wherein said selective amplification of said target deoxyribonucleic acid sequences is by polymerase chain reaction (PCR);

(d) performing a high throughput sequencing reaction, wherein said high throughput sequencing reaction comprises performing a sequencing-by-synthesis reaction on said selectively-

amplified target deoxyribonucleic acid sequences from said extracted circulating cell-free deoxyribonucleic acid, wherein said sequencing-by-synthesis reaction has a sequencing error rate of less than 1.5%;

(e) providing sequences from said high throughput sequencing reaction, wherein said provided sequences from said high throughput sequencing reaction comprise said at least 1,000 single nucleotide polymorphisms; and

(f) 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, wherein said quantifying said amount of said kidney transplant-derived circulating cell-free deoxyribonucleic acid in said plasma sample from said human kidney transplant recipient comprises using markers distinguishable between said human kidney transplant recipient and said kidney transplant donor, wherein said markers distinguishable between said human kidney transplant recipient and said kidney transplant donor comprises single nucleotide polymorphisms selected from said at least 1,000 single nucleotide polymorphisms identified in said provided sequences from said high throughput sequencing reaction, and wherein said quantified amount of said kidney

> transplant-derived circulating cell-free deoxyribonucleic acid in said plasma sample from said human kidney transplant recipient comprises at least 0.03% of the total circulating cell-free deoxyribonucleic acid from said plasma sample from said human kidney transplant recipient.

Thus, the methods disclosed in the representative claims have four steps for detecting a donor's cfDNA in a transplant recipient:

1. "obtaining" or "providing" a "sample" from the recipient that contains cfDNA;
2. "genotyping" the transplant donor and/or recipient to develop "polymorphism" or "SNP" "profiles";
3. "sequencing" the cfDNA from the sample using "multiplex" or "high-throughput" sequencing; or performing "digital PCR"; and
4. "determining" or "quantifying" the amount of donor cfDNA.[4]

The patents' written description expressly states that the techniques referred to in these steps are, "unless otherwise indicated, conventional techniques of immunology, biochemistry, chemistry, molecular biology, microbiology, cell biology, genomics, and

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[4] Defendants, in their supplemental § 101 opening brief, provided this summary of the steps of the method disclosed in the independent claims. *See* D.I. 175 at 8. CareDx does not dispute this summary, *see* D.I. 176; and CareDx's expert—Dr. Brian Van Ness—characterized the claims in essentially the same way, *see* Tr. of May 17,2021 Hr'g at 169:19-170:5, 174:10-23, 175:25-176:10, 176:22-177:8.

recombinant DNA, which are within the skill of the art." #652 patent at 5:36-40. Nowhere in the written description do the patents "otherwise indicate" that any of these techniques are nonconventional. On the contrary, the written description is replete with characterizations of the techniques in terms that confirm their conventionality.[5] Thus, according to the

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[5] *See, e.g.,* #652 patent at 9:8-14 (stating that "[d]etection, identification and/or quantitation of the donor-specific markers (e.g. polymorphic markers such as SNPs) can be performed using real-time PCR, chips (e.g., SNP chips), high through-put shotgun sequencing of circulating nucleic acids (e.g. cell-free DNA), as well as other methods known in the art"); *id.* at 10:11-12 (stating that to obtain cfDNA samples "any technique known in the art may be used, e.g. a syringe or other vacuum suction device"); *id.* at 13:51-52 (stating that step 2 of claimed methods can be performed "using existing genotyping platforms know[n] in the *art"); id.* at 15:6-8 (stating that techniques recited in step 2 of claimed methods "can be accomplished through classic Sanger sequencing methods which are well known in the *art"); id.* at 13:58-61 (stating that "[c]ompanies (such as Applied Biosystems, Inc.) 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"); *id.* at 20:31-34 (stating that genotyping recited in claimed methods "may be performed by any suitable method known in the art including those described herein such as sequencing, nucleic acid array or PCR"); *id.* at 15:22-65 (discussing commercial high-throughput sequencing products); *id.* at 14:58-67 (citing articles from 2006 and 2007 as supporting the statement that "digital PCR is a much more accurate and reliable method to quantitate nucleic acid species"); *id.* at 18:55-19:2 (stating that "[m]ethods for quantifying nucleic acids," including high-throughput genotyping, "are known in the art"); *id.* at 21:59 (stating that "[t]he presence or absence of one or more nucleic acids from the transplant donor in the transplant recipient may be determined by any suitable method known in the art including those described herein such as sequencing, nucleic acid arrays or PCR").

patents themselves, the recited techniques disclosed in the claimed methods of detection were conventional as of 2009.

II. RELEVANT PROCEDURAL HISTORY OF THE CASE

CareDx filed its original complaint against Natera in March of 2019, alleging that Natera's kidney transplant rejection test infringed the #497 and #652 patents. D.I. 1. Five months later, CareDx filed its complaint against Eurofins, alleging that Eurofins's various organ transplant rejection tests infringed the #652 patent. C.A. No. 19-1804, D.I. 1. Defendants each moved to dismiss the complaints on the ground that the patents asserted against them were invalid under § 101 for claiming patent-ineligible subject matter. *See* D.I. 10; C.A. No. 19-1804, D.I. 7. The motions were referred to the Magistrate Judge, who issued in both actions a single Report and Recommendation in which he recommended that I deny the motions. *See* D.I. 53.

Defendants each filed objections to the Magistrate Judge's recommendation. While the objections were pending before me, CareDx amended its complaint against Natera to add a claim for infringement of the #607 patent, which had issued in June 2019. *See* D.I. 74. Because the filing of the Amended Complaint mooted the motion to dismiss, I issued an Order in the Natera action vacating the Report and Recommendation (in that case), denying without prejudice Natera's motion to dismiss, and stating that Natera was free to file a motion to dismiss the Amended Complaint. Natera subsequently filed a second motion to dismiss, alleging that all three patents asserted against it were invalid under § 101. *See* D.I. 76.

In the meantime, I issued an Order adopting the Magistrate Judge's recommendation to deny the motion to dismiss in the Eurofins action. I stated in the Order:

> Eurofins argued in support of its motion to dismiss that the claims of the [#652 patent] are directed to a natural phenomenon (i.e., the correlation between transplant rejection and the presence of naturally occurring ctDNA) and therefore are not eligible for patenting under 35 U.S.C. § 101. The Magistrate Judge disagreed, concluding that the claims are directed to a "purportedly new, unconventional combination of steps" to detect that natural phenomenon. [C.A. No. 19-1804,] D.I. 30 at 9. Although language in the written description[] of the . . . asserted patent[ ] suggests that the patented steps are neither new nor unconventional, *see generally Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC,* 915 F.3d 743, 757 (Fed. Cir. 2019) (claims that "recite only a natural law together with conventional steps to detect that law, . . . are ineligible under § 101"), I agree with the Magistrate Judge that it would be premature to make at this time a definitive ruling on whether the claims recite patent eligible subject matter. Accordingly, I will adopt the recommendation of the Magistrate Judge and deny Eurofins['s] motion to dismiss.
>
> Because the patents' specifications raise doubts about the patents' validity, and mindful of my obligation to facilitate the "just, speedy, and inexpensive determination

> of every action and proceeding," Fed. R. Civ. P. 1, I will entertain in this case early dispositive motion practice and, to that end, will convene a teleconference with the parties to discuss scheduling.

C.A. No. 19-1804, D.I. 53 at 2-3.

As evident from my observation in the Order that the written description of the asserted patents "suggests that the patented steps are neither new nor unconventional" and my citation of *Athena Diagnostics, I* had serious doubts that the Magistrate Judge's recommendation was correct. I was, however, mindful that the state of § 101 law is, to use the words of various Federal Circuit judges, "fraught,"[6] "incoherent,"[7] "unclear, inconsistent[,] . . . and confusing,"[8] and "indeterminate and often lead[ing] to

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[6] *See Athena Diagnostics,* 927 F.3d at 1337 (Hughes, J., concurring in the denial of the petition for rehearing en bane) ("The multiple concurring and dissenting opinions regarding the denial of en bane rehearing in this case are illustrative of how fraught the issue of § 101 eligibility, especially as applied to medical diagnostics patents, is.").

[7] *See Interval Licensing LLC v. AOL, Inc.,* 896 F.3d 1335, 1348 (Fed. Cir. 2018) (Plager, J., concurring in part and dissenting in part) (observing that the "incoherent body of doctrine" surrounding § 101 "renders it near impossible to know with any certainty whether [an] invention is or is not patent eligible" and that "the state of the law is such as to give little confidence" in the court's decisions).

[8] *See The State of Patent Eligibility in America, Part I: Hearing Before the Subcomm. on Intellectual Property of the S. Comm. on the Judiciary,* 116th Cong. 2 (2019) at 2 (retired Federal Circuit Chief Judge Paul Michel describing recent § 101 cases as "unclear, inconsistent with one another and confusing" and acknowledging that "courts alone created this problem").

arbitrary results."[9, 10] And so I was especially reluctant to overrule a § 101 decision of a well-respected colleague at the motion to dismiss stage.

On the other hand, I recognized (and remain of the view) that "[f]ailure to recite statutory subject matter is the sort of basic deficiency that can, and should, be exposed at the point of minimum expenditure of time and money by the parties and the court." *OIP Techs., Inc. v. Amazon.com, Inc.,* 788 F.3d 1359, 1364 (Mayer, J., concurring) (internal quotation marks and citation omitted). And I shared (and continue to share) Judge Mayer's view that "addressing 35 U.S.C. § 101 at the outset not only conserves scarce judicial resources and spares litigants the staggering costs associated with discovery and protracted claim construction litigation, it also works to stem the tide of vexatious suits . . . ." *Id.*

These competing concerns led me to a middle ground. I decided to follow the Magistrate Judge's

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[9] *See Smart Sys. Innovations, LLC v. Chicago Transit Auth.,* 873 F.3d 1364, 1377 (Fed. Cir. 2017) (Linn, J., dissenting in part and concurring in part) (characterizing § 101 jurisprudence as "indeterminate and often lead[ing] to arbitrary results").

[10] *See also Berkheimer v. HP Inc.,* 890 F.3d 1369, 1374 (Fed. Cir. 2018) (Lourie J., concurring in the denial of rehearing en banc) ("[Section 101] needs clarification by higher authority."); Daryl Lim, *The Influence of Alice,* 105 Minn. L. Rev. Headnotes 345, 346 (2021) (describing the standards for deciding patent eligibility as being "virtually indiscernible"); James Nurton, *Iancu Calls on Federal Circuit to Fix Section 101 Problem,* IP Watchdog (May 2, 2019) (former PTO director Andrei Iancu stating that "[r]ecent [§ 101] case law has created significant confusion"); *State of Patent Eligibility, Part I* at 1-2 (former PTO director David Kappos stating that "patent eligibility law truly is a mess" and calling Federal Circuit decisions "irreconcilable [and] incoherent").

recommendation and deny the motions to dismiss; but, at the same time, I stayed all aspects of the case except for expert discovery and summary judgment practice related to Defendants' § 101 challenge to the asserted patents. Natera thus withdrew its motion to dismiss, the parties engaged in expert discovery related to patent eligibility, and both Defendants filed motions for summary judgment of invalidity of the asserted patents under § 101.

The Scheduling Orders of both cases require that a concise statement of facts accompany any motion for summary judgment. The concise statements must detail the facts "essential for the Court's determination of the summary judgment." D.I. 45 at 14. As explained in the Scheduling Orders, the concise statements of fact "play an important gatekeeping role in the Court's consideration of summary judgment motions," and, as a result, "a party shall reference only the material facts that *are absolutely necessary* for the court to determine the limited issues presented in the motion for summary judgment *(and no other)."* D.I. 45 at 14 n.1, 14-15 (emphasis added). In the concise statement of facts submitted with each summary judgment motion, Defendants each alleged as an undisputed, essential fact that "[n]either the written description nor the claims of the Patents disclose nonconventional techniques for performing genotyping and/or multiplex/high-throughput sequencing, individually or in combination." D.I. 102 ¶ 23. In support of this alleged fact, the Defendants relied on the written description of the asserted patents and the opinions of their shared expert, Dr. John Quackenbush. D.I. 102 ¶ 23 and cited exhibits. CareDx denied that the patents' claims disclosed only conventional techniques and cited in support of its position opinions of its own expert, Dr. Brian Van

Ness, as well as six scientific articles that discussed the nascent nature of some of the specifically disclosed techniques. D.I. 104 ¶ 23 and cited exhibits. Faced with competing expert testimony on a fact the Defendants identified as being "absolutely necessary" for my determination, I denied the summary judgment motions in orders issued on December 1, 2020. D.I. 115; C.A. No. 19-1804, D.I. 76.

On January 13, 2021, Defendants moved for certifications of interlocutory appeals from these orders. In their joint opening brief filed in support of their certification requests, Defendants cited Federal Circuit case law that appeared on its face to hold that the articles and expert testimony relied on by CareDx in opposition to the summary judgment motions are incapable, as a matter of law, of raising a genuine issue of material fact in light of the statements in the patents' shared written description that the disclosed techniques in the claimed detection methods were, in fact, conventional.

Defendants had not made this argument in their summary judgment briefing, *see* D.I. 123; D.I. 136; Tr. of April 20, 2021 Hr'g at 5-14; and they had repeatedly cited in that briefing the opinions of their expert about the conventionality of the disclosed techniques, *see* D.I. 101 at 2-3, 14, 29-30; C.A. No. 19-1804, D.I. 62 at 3, 17-18. Accordingly, during a telephonic hearing on April 20, 2021, I denied the certification motions on the grounds that the parties had not put before me (and thus I had not addressed) the issue for which certification of the appeals was sought. Tr. of April 20, 2021 Hr'g at 14. But in light of the case law cited in support of the certification motions, it occurred to me that I may have prematurely decided that summary judgment in Defendants'

favor was not warranted. It also occurred to me that I had the authority to decide questions of fact underlying Defendants' § 101 challenge. *See Mortgage Grader Inc. v. First Choice Loan Servs. Inc.,* 811 F.3d 1314, 1325 (Fed. Cir. 2016) ("The mere existence in the record of dueling expert testimony does not necessarily raise a genuine issue of material fact" that precludes summary judgment.); *cf. Halliburton Energy Servs., Inc. v. M-I LLC,* 514 F.3d 1244, 1249-50 (Fed. Cir. 2008) (affirming grant of summary judgment of indefiniteness based on intrinsic evidence and noting in dictum that conflicting expert testimony does not preclude a finding of indefmiteness); *Capital Sec. Sys., Inc. v. NCR Corp.,* 725 F. App'x 952, 958-59 (Fed. Cir. 2018) (affirming district court's decision granting summary judgment of indefiniteness despite expert testimony that an artisan of ordinary skill would understand the disputed claim term with reasonable certainty); *HIP, Inc. v. Hormel Foods Corp.,* 796 F. App'x 748 (Fed. Cir. 2020) (summarily affirming district court's decision granting summary judgment of indefiniteness despite expert testimony that an artisan of ordinary skill would understand the disputed claim term with reasonable certainty).

For these reasons, and cognizant of my obligation to administer the Federal Rules of Civil Procedure "to secure the just, speedy, and inexpensive determination of every action", Fed. R. Civ. P. 1, I ruled *sua sponte* at the April 20 hearing that I would reconsider my denial of the previous summary judgment motions and schedule a hearing for the parties to adduce any evidence they thought I should consider in addressing the validity of the asserted patents under § 101. Tr. of April 20, 2021 Hr'g at 14-29. I then held in May 2021 an evidentiary hearing during which the parties presented competing expert testimony. And I permit-

ted briefing after the hearing on any topic the parties wished to address related to the asserted patents' validity under § 101.

III. PATENT-ELIGIBLE SUBJECT MATTER

Section 101 of the Patent Act defines patent-eligible subject matter. It provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101.

There are three judicially created limitations on the literal words of § 101. The Supreme Court has long held that laws of nature, natural phenomena, and abstract ideas are not patentable subject matter. *Alice Corp. Pty. v. CLS Bank Int'l,* 573 U.S. 208, 216 (2014). These exceptions to patentable subject matter arise from the concern that the monopolization of "the[se] basic tools of scientific and technological work" "might tend to impede innovation more than it would tend to promote it." *Id.* (internal quotation marks and citations omitted).

But "an invention is not rendered ineligible for patent simply because it involves" a law or phenomenon found in nature or an abstract idea. *Alice,* 573 U.S. at 217 As the Court noted in *Alice,* "[a]t some level, 'all inventions ... embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.' *Id.* (citation omitted). Applications of these concepts to "new and useful end[s]" remain eligible for patent protection. *Id.* (citation omitted).

Alice famously

> set forth a framework for distinguishing patents that claim laws of nature, natural

> phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, "[w]hat else is there in the claims before us?" To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent-eligible application. We have described step two of this analysis as a search for an "'inventive concept'"—i. e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Alice, 573 U.S. at 217-18 (citations omitted). Thus, under *Alice,* when faced with a § 101 challenge to a patent, the court first asks whether the asserted claims are "directed to" a patent-ineligible concept. If the answer to the "directed to" question (i.e., step one of the *Alice* inquiry) is no, then the patent is not invalid under § 101. If the answer to that question is yes, then the court proceeds to step two of the *Alice* inquiry and asks whether the individual or combined elements of the asserted claims contain an inventive concept.

In *Athena Diagnostics,* the Federal Circuit held that at step one of the *Alice* inquiry claims are directed to a natural law if they "recite only [a] natural law together with standard techniques for observing it." 915 F.3d at 752. This holding is consistent with at least two other Federal Circuit

decisions. *See Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.,* 827 F.3d 1042, 1048 (Fed. Cir. 2016) (holding that claims are "directed to" a patent-ineligible concept "when they amount[] to nothing more than observing or identifying the ineligible concept itself'); *Cleveland Clinic Found. v. True Health Diagnostics LLC,* 859 F.3d 1352, 1361 (Fed. Cir. 2017) (holding that method-of-detection claims were "directed to a natural law" at step one of the *Alice* inquiry where the claims "use[d] well-known techniques to execute the claimed method" and had "no meaningful non-routine steps"). Thus, under binding Federal Circuit case law, methods-of-detection claims are directed to a patent-ineligible concept if they "only involve detecting a natural law 'with no meaningful non-routine steps.'" *Athena,* 915 F.3d at 752 (quoting *Cleveland Clinic,* 859 F.3d at 1361). Accordingly, where a patent claims a method for detecting a natural phenomenon, whether the patent is "directed to" a natural phenomenon for purposes of *Alice* step one turns on whether the claimed methods of detection are standard or routine.

In *Berkheimer,* however, the Federal Circuit held that "[t]he second step of the *Alice* test is satisfied when the claim limitations involve more than performance of well-understood, routine, [and] conventional activities previously known to the industry." 881 F.3d at 1367 (internal quotation marks and citations omitted). This description of the test for *Alice* step two sounds a lot like—in my mind, exactly like—the description of the test for *Alice* step one articulated by the Federal Circuit in *Athena* and *Cleveland Clinic* for method-of-detection claims. And, indeed the Federal Circuit has recognized that the two steps of the *Alice* inquiry overlap. *See Amdocs (Isr.) Ltd v. Openet Telecom, Inc.,* 841 F.3d 1288, 1294 (Fed. Cir.

2016) ("Recent cases, however, suggest that there is considerable overlap between step one and step two, and in some situations this analysis could be accomplished without going beyond step one."); *Elec. Power Grp., LLC v. Alstom S.A.,* 830 F.3d 1350, 1353 (Fed. Cir. 2016) ("[T]he two stages involve overlapping scrutiny of the content of the claims[, and] . . . there can be close questions about when the inquiry should proceed from the first stage to the second." (citations omitted)); *see also Smart Sys. Innovations,* 873 F.3d at 1382 n.2 (Linn, J., dissenting in part and concurring in part) (expressing "serious[] doubt" that "the boundary between steps one and two can somehow be defined").

It follows, then, that where a patent claims a method for detecting a natural phenomenon, the dispositive inquiry under both steps of the *Alice* inquiry is whether the asserted method uses more than standard or conventional techniques of detection. And under either step, as the Supreme Court held in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.,* where the asserted

> claims inform a relevant audience about certain laws of nature; [and] any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately[,] . . . the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities.

566 U.S. 66, 79-80 (2012).

IV. ANALYSIS

The parties essentially agree, and I find, that the asserted claims are directed to detecting a donor's cfDNA in a transplant recipient. *See* #652 patent at claim 1 (claiming "[a] method for detecting transplant rejection . . . or organ failure."); #497 patent at claim 1 (claiming "[a] method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient"); #607 patent at claim 1 (claiming "[a] method of quantifying kidney transplant-derived circulating cell-free deoxyribonucleic acids in a human kidney transplant recipient"). In CareDX's words:

- "[T]he claims are directed to new processes for detecting [a donor's] []cfDNA." C.A. No. 19-0567, D.I. 68 at 9.
- "The inventors [of the asserted patents] improved on these deficiencies [in the prior art] through the use of innovative, highly precise assays capable of detecting tiny increases in donor-specific cell free DNA . . . ." D.I. 15 at 2; C.A. No. 19-1804, D.I. 15 at 1.
- "[T]he plain language of the claims and the specification of the asserted patents establish that the claims are directed to specific, concrete methods of detecting particular concentrations of donor-specific, cell-free DNA in the bodies of donor recipients . . . ." C.A. No. 19-0567, D.I. 15 at 3.
- "Claim 1 of [the #]497 patent, for example, is directed to 'a method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient.' D.I. 15 at 10.

- "[T]he challenged claims recite a series of specific, non-conventional laboratory techniques for detecting cell-free DNA with a high degree of sensitivity, in a manner that improves upon prior art methods of attempting such detection." D.I. 15 at 13.
- "[T]he claims of the asserted patents are directed to specific, novel processes for detecting donor-specific cell free DNA . . . ." D.I. 15 at 15.

It is undisputed that donor-specific cfDNA and the correlation donor-specific cfDNA has with organ rejection are natural phenomena.[12] Because the asserted claims are directed to the detection of these natural phenomena, the dispositive inquiry under both steps of the *Alice* inquiry is whether the claimed methods of detection are conventional (i.e., standard or routine).

In this case, the written description of the asserted patents makes clear that the claimed detection methods are conventional. It expressly states that

> [t]he practice of the present invention employs, unless otherwise indicated, conventional techniques of immunology, biochemistry, chemistry, molecular biology, microbiology, cell biology, genomics and recombinant DNA, which are within the skill of the art.

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[12] The correlation between donor-specific cfDNA and organ rejection could also be described as a natural law. I need not parse the differences between a natural law and a natural phenomenon since both concepts are patent-ineligible subject matter. For ease of reference, I will refer to both donor-specific cfDNA and the correlation donor-specific cfDNA has with organ rejection as natural phenomena.

#652 patent at 5:36-40. As noted above, nothing in the written description "otherwise indicates" that any of the techniques recited in the claims are nonconventional. To the contrary, as discussed above, there are numerous characterizations of the specific techniques in the written description that confirm their conventionality. *See supra* note 5.

The patentee's unequivocal and binding admission in the written description that the recited detection methods are conventional ends the matter before me. *See Mayo,* 566 U.S. at 79 (affirming summary judgment of invalidity under § 101 of patents directed to natural laws where, "[a]s the patents state, [the claimed] methods for determining metabolite levels were well known in the art"); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.,* 788 F.3d 1371, 1377 (Fed. Cir. 2015) (affirming summary judgment of invalidity under § 101 of patents directed to a natural phenomenon where "[t]he specification of the '540 patent confirms that the preparation and amplification of DNA sequences in plasma or serum were well-understood, routine, conventional activities performed by doctors in 1997"); *Cleveland Clinic,* 859 F.3d at 1360-63 (affirming dismissal pursuant to Rule 12(b)(6) on the grounds that the asserted patents directed to a natural phenomenon were invalid under § 101 where "[t]he specifications of the testing patents confirm that known testing methods could be used to detect MPO, and that there were commercially available testing kits for MPO detection," and "the claims here instruct that MPO levels be detected or determined using any of these known techniques"); *SAP Am., Inc. v. InvestPic, LLC,* 898 F.3d 1161, 1170 (Fed. Cir. 2018) (affirming Rule 12(c) judgment on the pleadings that the asserted patent directed to an abstract idea was invalid under § 101 where the

patent's "invocation" of "generic parallel processing components" "amount[ed] to a recitation of what is well-understood, routine, and conventional" (internal quotation marks and citation omitted)); *see also Mortgage Grader,* 811 F.3d at 1325 (recognizing that "it is also possible, as numerous cases have recognized, that a § 101 analysis may sometimes be undertaken without resolving fact issues," and that "[t]he mere existence in the record of dueling expert testimony does not necessarily raise a genuine issue of material fact"); *Aatrix Software, Inc. v. Green Shades Software, Inc.,* 890 F.3d 1354, 1356 (Fed. Cir. 2018) (Moore, J., concurring in the denial of the petition for rehearing en banc) ("In a situation where the specification admits the additional claim elements are well-understood, routine, and conventional, it will be difficult, if not impossible, for a patentee to show a genuine dispute.").[13]

CareDx argues that "the specification['s] admission] that the claimed techniques are routine and conventional appears verbatim in myriad patents and patent applications covering different technologies that are not limited to DNA sequencing applications," D.I. 176 at 20 n.6; and it insists that "[i]t would be unfair to read this widely repeated passage in biotech patents referencing generic publications about biochemistry basics to be some sort of supposed voluntary confession that there is no inventive concept in the specification," D.I. 176 at 19–20. It should come

[13] The Magistrate Judge did not address in his Report and Recommendation the fact that the written description of the asserted patents expressly characterized the recited detection techniques as conventional.

as no surprise that CareDx cites no case law to support this argument, and I reject it out of hand.

The idea that a patentee is bound by the words it uses in its patent—whether in the claims or elsewhere in the specification—is a fundamental tenet of the patent law.[14] The PTO relies on the patent applicant's representations when it decides whether to issue a patent; and the patentee's words in the claims and written description put the public on notice of the scope of the claimed invention.[15] Accordingly, as the Supreme Court recently noted,

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[14] *See Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.,* 381 F.3d 1111, 1117 (Fed. Cir. 2004) ("[A] patentee who notifies the public that claim terms are to be [understood] beyond their ordinary meaning to one of skill in the art will be bound by that notification, even where it may have been unintended."); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1362 (Fed. Cir. 2007) ("Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness."); *Constant v. Advanced Micro-Devices, Inc.,* 848 F.2d 1560, 1570 (Fed. Cir. 1988) ("A statement in the patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness."); *Sjolund v. Musland,* 847 F.2d 1573, 1577-79 (Fed. Cir. 1988) (the patent specification admitted that certain matter was prior art, and thus "the jury was not free to disregard [that matter]" and "must have accepted [it] as prior art, as a matter of law").

[15] *See McClain v. Ortmayer,* 141 U.S. 419, 423-24 (1891) ("Nothing is better settled in the law of patents than that the patentee may claim the whole or only a part of his invention, and that, if he only describe and claim a part, he is presumed to have abandoned the residue to the public. The object of the patent law in requiring the patentee to 'particularly point out and distinctly claim the part, improvement, or combination which he claims as his invention or discovery' is not only to secure to him all to which he is entitled, but to apprise the public of what is still open to them. The claim is the measure of his right to relief, and, while

> the patent law[] demand[s] . . . honesty from patent applicants. In applying for a patent, the inventor must ordinarily submit an oath—a statement attesting that he is "the original inventor" of the "claimed invention." And the inventor must comply with "a duty of candor and good faith" in the patent process, including "a duty to disclose" to the PTO all information he knows "to be material to patentability."

Minerva Surgical, Inc. v. Hologic, Inc., 141 S. Ct. 2298, 2309 n.3 (2021) (citations omitted). After the patent issues, courts rely on the patentee's representations in the specification when they construe the claims that define the metes and bounds of the monopoly the patent confers on the patentee. Competitors rely on those representations to ascertain and design around infringement. The demand that the patentee be forthright in the application that ultimately takes the form of the issued patent's written description is so fundamental that a patent can be deemed unenforceable if a court determines that the patentee made false representations to the PTO in or during the prosecution of the patent application with a specific intent to mislead. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1287 (Fed. Cir. 2011) (en banc). There is therefore nothing unfair about holding CareDx to its representations in the patent's written description.

It is of no moment that CareDx's representation that the recited techniques are conventional "appears in myriad patents." As a logical matter, the number

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the specification may be referred to to *[sic]* limit the claim, it can never be made available to expand it.")

of times a representation is made has no bearing on its truthfulness. But in any event, there is a reason why patentees frequently represent to the PTO that techniques recited in their patents are conventional. Section 112 of the Patent Act requires that the specification provide sufficient explanation of the claimed invention to enable an artisan of ordinary skill to make and use the invention. To avoid or overcome an objection by the PTO that the requested patent lacks adequate detail to satisfy § 112, patent applicants will often expressly represent that recited techniques are conventional. Having done that here, CareDx cannot now avoid the consequences that flow from its representation. Indeed, it would be unfair to Defendants to let it do so.

In the supplemental brief it filed after the May 2021 evidentiary hearing, CareDx argues that the patents "otherwise indicate[]" that some of the individual techniques are nonconventional. D.I. 176 at 21. But CareDx mischaracterizes the written description. For example, CareDx cites nine lines of the written description as evidence that the patents' "discussion of digital PCR," a sequencing technique recited in the #497 claims, "describes [digital PCR] as an emerging technique" and "expressly directs the reader to inventor Quake's landmark 2006 journal article" "[t]o teach how to use d[igital] PCR with the claimed inventions." D.I. 176 at 21-22 (citing #652 patent at 14:55-64). This assertion by CareDx is simply false. Here is what the cited text actually says:

> In some embodiments, digital PCR or real time PCR to quantitate the presence of specific polymorphisms that have already been identified in the initial genotyping step pre-transplantation. Compared with the

> quantitative PCR techniques used in some of the earlier cited work, digital PCR is a much more accurate and reliable method to quantitate nucleic acid species including rare nucleic acid species, and does not require a specific gender relationship between donor and recipient. (Warren, L., Bryder, D., Weissman, L L., Quake, S. R., Proc Natl Acad Sci, 103,17807-17812 (2006)).

#652 patent at 14:55-64. The fact that digital PCR is more accurate and reliable than earlier PCR techniques does not mean that digital PCR was an emerging technique as of 2009. In fact, the cited text does not characterize digital PCR as "an emerging technique," nor does it direct the reader to the Quake article to learn how to use digital PCR.

CareDx also argues that a "lengthy discussion of next generation sequencing (NGS) in the specification also indicates vividly that this technology is not routine, conventional, or well-understood." D.I. 176 at 22. CareDx claims that this discussion "identifies a series of new NGS systems over several columns and then teaches extensively about them with copious citation to patent *applications* and other contemporaneous literature." D.I. 176 at 22 (emphasis in original). But this "lengthy discussion," does not suggest in any way, let alone "vividly" indicate, that NGS was nonconventional as of 2009. The discussion identifies commercial sequencing machines and gives high-level descriptions of how they work, referring to sensitivity and error rate concepts that CareDx's expert, Dr. Van Ness, admitted were "known and accepted in the art." Tr. of May 17,2021 Hr'g at 264:18265:18; *see also id.* at 249:23-255:6. Dr. Van Ness was correct when he testified at the evidentiary

hearing that the asserted patents' specifications "don't get into the details and describe the individual methods for each of th[e] sequencing platforms that are described in the patent[s]." *Id.* at 225:17-21. He was also correct that no such details are claimed—an important fact since "features that are not claimed are irrelevant as to step 1 or step 2 of the *Mayo / Alice* analysis," *Am. Axle & Mfg., Inc. v. Neapco Holdings LLC,* 939 F.3d 1355,1363 (Fed. Cir. 2019).

CareDx argues, too, that the patents' written description "unambiguously state[s] that the[] [inventors] applied a never-before-used combination of techniques to better measure the correlation and specifically contrast their invention with how the prior art attempted to conquer the very same long-standing problem." D.I. 176 at 20 (citing #652 patent at 7:48-52; 8:45-50). But this assertion is also not true. CareDx cites in support of this assertion nine lines from the patents' written description. Here is what those lines actually say:

> In some embodiments, the invention provides methods, devices, compositions and kits for detection and/or quantitating circulating nucleic acids, either free in plasma or from circulating cells, for the diagnosis, prognosis, detection and/or treatment of a transplant status or outcome.
>
> * * * *
>
> In some embodiments, the 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.

#652 patent at 7:48-52; 8:45-50. There is no suggestion, let alone "unambiguous statement," in these cited excerpts—or anywhere else in the asserted patents—that the claimed methods employ "a never-before-used combination of techniques."

CareDx seems to argue that the novelty of the application of the recited techniques to the detection of donor-specified cfDNA makes the techniques nonconventional. In CareDx's words, "[a]s applied to cfDNA, the claimed techniques were not routine in 2009." D.I. 180 at 8; *see also* D.I. 176 at 2 (describing "the purported invention" of the asserted patents as "the never-before-taught *application of different combinations of particular laboratory techniques to better measure* the correlation" of donor-specific cfDNA and organ rejection (emphasis in the original)). The Supreme Court in *Mayo,* however, "made clear that transformation into a patent-eligible application requires more than simply stat[ing] the law of nature [in this case, cfDNA] while adding the words apply it." *Ariosa,* 788 F.3d at 1377 (internal quotation marks omitted) (quoting *Mayo,* 566 U.S. at 72). And *Alice* step two's requirement of "additional features that must be new and useful" is simply not met in this case because the asserted method claims recite standard detection techniques applied to naturally occurring phenomena. *Roche Molecular Sys., Inc. v. CEPHEID,* 905 F.3d 1363, 1372 (Fed. Cir. 2018).

CareDx also argues that it is the combination of the recited techniques that is nonconventional. D.I. 176 at 2, 28. But the asserted patents do not claim an ordered combination of the recited techniques. The recited techniques, "when viewed as a whole, add

nothing significant beyond the sum of the[] [techniques] taken separately[,]" and therefore the recited techniques are "not sufficient to transform unpatentable natural correlations into patentable applications of those regularities." *Mayo,* 566 U.S. at 80; *see also Alice,* 573 U.S. at 217 ("[W]e consider the elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." (quoting *Mayo,* 566 U.S. at 78-79)).

Finally, CareDx argues that extrinsic evidence establishes that the recited detection techniques were not conventional. *See* D.I. 176 at 25-28. CareDx cites no case in which a court allowed a patentee to avoid a declaration of a patent's invalidity by offering extrinsic evidence that contradicted an unambiguous admission in an asserted patent's written description. I can't imagine CareDx could find such a case. Permitting CareDx to now nullify with extrinsic evidence an unambiguous representation it made to the PTO to secure its patents and exclude competitors like Defendants from making or using the claimed invention would be fundamentally at odds with the basic principles underlying our patent system.

In *Vitronics Corp. v. Conceptronic, Inc.,* 90 F.3d 1576,1583 (Fed. Cir. 1996), the Federal Circuit held that when construing the claims of a patent

> where the public record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper. The claims, specification, and file history, rather than extrinsic evidence, constitute the public record of the patentee's claim, a record on which the public is entitled

> to rely. In other words, competitors are entitled to review the public record, apply the established rules of claim construction, ascertain the scope of the patentee's claimed invention and, thus, design around the claimed invention. *See Markman,* 52 F.3d at 978-79, 34 USPQ2d at 1329. Allowing the public record to be altered or changed by extrinsic evidence introduced at trial, such as expert testimony, would make this right meaningless. *See Southwall,* 54 F.3d at 1578, 34 USPQ2d at 1678 ("A patentee may not proffer an interpretation for the purposes of litigation that would alter the indisputable public record consisting of the claims, the specification and the prosecution history, and treat the claims as a 'nose of wax.'" (quoting *Senmed, Inc. v. Richard-Allan Med. Indus., Inc.,* 888 F.2d 815, 819 n.8, 12 USPQ2d 1508, 1512 n.8 (Fed.Cir.1989))).

I see no reason why the holding of *Vitronics* should be limited to claim construction and not apply here. Allowing CareDx to alter by extrinsic evidence the unambiguous public record it established with the claims and written description of the asserted patents would make Defendants' right to design around meaningless. It would also reward CareDx for being dishonest—either when it told the PTO that the recited techniques were conventional or when it insisted before this Court that they were not.[16]

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[16] Ironically, the testimony of CareDx's expert that I found most credible and compelling at the evidentiary hearing confirms the conventionality of the recited techniques in the asserted method claims:

V. CONCLUSION

For the reasons discussed above, I find that the claims of the asserted patents are invalid as a matter of law under § 101 for claiming patent-ineligible subject matter. Accordingly, pursuant to Federal Rule of Civil Procedure 56(0(3), I will enter summary judgments in Defendants' favor.

The Court will issue Orders consistent with this Memorandum Opinion

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> THE COURT: [Y]ou would agree that every disclosed technique is routine and conventional in some application. Your point is, it's just not the application of this patent?
>
> THE WITNESS: I think that's an accurate statement.
>
> * * * *
>
> THE COURT: So the application to what? What am I applying the disclosed techniques to?
>
> THE WITNESS: Applying it to the detection of donor-derived DNA in a recipient receiving an organ transplant . . . .

Tr. of May 17,2021 Hr'g at 261:12-17; 263:11-15.

APPENDIX C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civil Action No. 19-0567-CFC-CJB
CONSOLIDATED

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs,

v.

NATERA, INC.,

Defendant.

ORDER

At Wilmington on this Twenty-eighth day of September in 2021:

Pursuant to Federal Rule of Civil Procedure 56(f) and for the reasons set forth in the Memorandum Opinion issued this day, IT IS HEREBY ORDERED that summary judgment of invalidity under 35 U.S.C. § 101 is GRANTED in Defendant Natera Inc.'s favor and all claims of U.S. Patent No. 8,703,652, all claims of U.S. Patent No. 9,845,497, and all claims of U.S. Patent No. 10,329,607 are INVALID.

/s/ Colm F. Connolly
United States Chief District Judge

APPENDIX D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civil Action No. 19-1804-CFC-CJB

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs,

v.

EUROFINS VIRACOR, INC.,

Defendant.

ORDER

At Wilmington this Twenty-eighth day of September in 2021:

Pursuant to Federal Rule of Civil Procedure 56(f) and for the reasons set forth in the Memorandum Opinion issued this day, IT IS HEREBY ORDERED that summary judgment of invalidity under 35 U.S.C. § 101 is GRANTED in Defendant Eurofins Viracor Inc.'s favor and all claims of U.S. Patent No. 8,703,652 are INVALID.

/s/ Colm F. Connolly
United States Chief District Judge

APPENDIX E

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civil Action No. 19-567-CFC-CJB

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs,

v.

NATERA, INC.,

Defendant.

MEMORANDUM ORDER

Pending before me is Defendant Natera, Inc.'s Motion for Summary Judgment of Invalidity Under 35 U.S.C. § 101 (D.I. 100). In its Concise Statement of Facts in Support of Its Motion for Summary Judgment of Invalidity Under 35 U.S.C. § 101, Natera states that "[n]either the written description nor the claims of the Patents disclose nonconventional techniques for performing genotyping and/or multiplex/high-throughput sequencing, individually or in combination." D.I. 102 ¶ 23. In support of this statement of fact, Natera relies on the written description of the asserted patents[1] and the declaration of its expert, Dr. John Quackenbush. D.I. 102 ¶ 23 and cited exhibits.

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[1] The patents share a written description. *See* Tr. of Apr. 30,2020 Hr'g at 19:18-21.

Plaintiffs deny this factual assertion. They state that some of the techniques disclosed in the asserted patents were nonconventional. And they cite in support of that position, among other things, six scientific articles that discuss the limitations and nascent nature of some of the specifically disclosed techniques as well as the declaration of their expert, Dr. Brian Van Ness. D.I. 104 ¶ 23 and cited exhibits; *see also, e.g.,* D.I. 102-3 at B0325-26, B0331 (a 2008 scientific article describing some of the disclosed high-throughput techniques as "new technologies" that are "poised to emerge as the dominant genomics technolog[ies]" but cautioning that "method development is still in its infancy" and that "[e]fficient data analysis pipelines are required for many applications *before they become routine"* (emphasis added)); D.I. 102-3 at B0237-39 (a 2009 scientific article describing the transition of the disclosed techniques from basic-research to clinical diagnostics as being in the "early stages of development," but noting that the issues of "complexity of technical procedures, robustness, accuracy, and cost" are barriers to that transition); D.I. 104-1 at C0524 (a 2020 scientific article stating that "standard targeted [multiplex or high-throughput sequencing] is significantly limited by its cost, turnaround time[], and level of sensitivity imposed by background noise"); D.I. 104-1 at C0601 (a 2008 scientific article expressing skepticism that a sequencing technique disclosed in the patents would gain regulatory approval for diagnostic purposes).

Because there is a disputed fact that Natera has said is material to its summary judgment motion, I will deny the motion. See *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 248 (1986) (holding that summary judgment will not lie if there is a genuine dispute about a material fact).

NOW THEREFORE, at Wilmington this First day of December in 2020, IT IS HEREBY ORDERED that Defendant Natera, Inc.'s Motion for Summary Judgment of Invalidity Under 35 U.S.C. § 101 (D.I. 100) is DENIED.

/s/ Colm F. Connolly
United States District Judge

Filed: December 1, 2020

APPENDIX F

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civil Action No. 19-1804-CFC-CJB

CAREDX, INC.,

Plaintiffs

v.

EUROFINS VIRACOR, INC.,

Defendant,

and

THE BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY

Nominal Defendant.

MEMORANDUM ORDER

Pending before me is Defendant Eurofms Viracor Inc.'s Motion for Summary Judgment that the Asserted Claims of U.S. Patent No. 8,703,652 are Invalid Under 35 U.S.C. § 101 (D.I. 61). In its Concise Statement of Facts in Support of Its Motion for Summary Judgment that the Asserted Claims of U.S. Patent No. 8,703,652 are Invalid Under 35 U.S.C. § 101, Eurofins states that "[n]either the written description nor the claims of the Patent[] disclose nonconventional techniques for performing genotyping and/or multiplex/high-throughput sequencing, individually or in combination." D.I. 63 ¶ 23. In support of this statement of fact, Eurofins relies on the written description of the asserted patent, the written descriptions of two non-

asserted patents (which both share a written description with the asserted patent) and the declaration of its expert, Dr. John Quackenbush. D.I. 63 ¶ 23 and cited exhibits.

Plaintiff denies this factual assertion. It states that some of the techniques disclosed in the asserted patent were nonconventional. And it cites in support of that position, among other things, six scientific articles that discuss the limitations and nascent nature of some of the specifically disclosed techniques as well as the declaration of its expert, Dr. Brian Van Ness. D.I. 65 ¶ 23 and cited exhibits; *see also, e.g.,* D.I. 63-30 at B0325-26, B0331 (a 2008 scientific article describing some of the disclosed high-throughput techniques as "new technologies" that are "poised to emerge as the dominant genomics technolog[ies]" but cautioning that "method development is still in its infancy" and that "[e]fficient data analysis pipelines are required for many applications *before they become routine"* (emphasis added)); D.I. 63-18 at B0237-39 (a 2009 scientific article describing the transition of the disclosed techniques from basic-research to clinical diagnostics as being in the "early stages of development," but noting that the issues of "complexity of technical procedures, robustness, accuracy, and cost" are barriers to that transition); D.I. 65-1 at C0524 (a 2020 scientific article stating that "standard targeted [multiplex or high-throughput sequencing] is significantly limited by its cost, turnaround time[], and level of sensitivity imposed by background noise"); D.I. 65-1 at C0601 (a 2008 scientific article expressing skepticism that a sequencing technique disclosed in the patents would gain regulatory approval for diagnostic purposes).

Because there is a disputed fact that Eurofins has said is material to its summary judgment motion, I will deny the motion. See *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 248 (1986) (holding that summary judgment will not lie if there is a genuine dispute about a material fact).

NOW THEREFORE, at Wilmington this First day of December in 2020, IT IS HEREBY ORDERED that Defendant Eurofins Viracor Inc.'s Motion for Summary Judgment that the Asserted Claims of U.S. Patent No. 8,703,652 are Invalid Under 35 U.S.C. § 101 (D.I. 61) is DENIED.

/s/ Colm F. Connolly
United States District Judge

Filed: December 1, 2020

APPENDIX G

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civ. No. 19-1804-CFC-CJB

CAREDX, INC.,

Plaintiff,

v.

EUROFINS VIRACOR, INC.,

Defendant,

and

THE BOARD OF TRUSTEES OF THE
LELAND STAFORD JUNIOR UNIVERSITY,

Nominal Defendant.,

MEMORANDUM ORDER

Pending before me are Defendant Eurofin Viracor, Inc.'s objections (D.I. 37) to the Magistrate Judge's Report and Recommendation issued on February 10, 2020 (D.I. 30). The Magistrate Judge recommended in his Report and Recommendation that I deny Eurofin's motion to dismiss the Complaint filed by Plaintiff CareDx, Inc (D.I. 6). I have reviewed the Report and Recommendation, the objections, CareDx's response to the objections (D.I. 41), the parties' briefing filed in connection with the motion to dismiss (D.I. 7; D.I. 15; D.I. 16), and the transcript of the oral argument before the Magistrate Judge.

Eurofin argued in support of its motion to dismiss that the claims of the asserted patent (U.S. Patent No. 8,703,652) are directed to a natural phenomenon (i.e., the correlation between transplant rejection and the presence of naturally occurring cfDNA) and therefore are not eligible for patenting under 35 U.S.C. § 101. The Magistrate Judge disagreed, concluding that the claims are directed to a "purportedly new, unconventional combination of steps" to detect that natural phenomenon. D.I. 30 at 9. Although language in the written descriptions of the two asserted patents suggests that the patented steps are neither new nor unconventional, *see generally Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC,* 915 F.3d 743, 757 (Fed. Cir. 2019) (claims that "recite only a natural law together with conventional steps to detect that law, . . . are ineligible under § 101"), I agree with the Magistrate Judge that it would be premature to make at this time a definitive ruling on whether the claims recite patent eligible subject matter. Accordingly, I will adopt the recommendation of the Magistrate Judge and deny Eurofin's motion to dismiss.

Because the patents' specifications raise doubts about the patents' validity, and mindful of my obligation to facilitate the "just, speedy, and inexpensive determination of every action and proceeding," Fed. R. Civ. P. 1, I will entertain in this case early dispositive motion practice and, to that end, will convene a teleconference with the parties to discuss scheduling.

WHEREFORE, on this 21st day of April in 2020, IT IS HEREBY ORDERED that:

1. Defendant's Objections to the Magistrate Judge's Report and Recommendation (D.I. 37) are OVERRULED;

2. The Report and Recommendation (D.I. 30) is ADOPTED;

3. Defendant's motion to dismiss (D.I. 6) is DENIED; and

4. A scheduling teleconference will be held on April 30, 2020 at 10:00 a.m. Defendant's counsel shall make the necessary arrangements for the teleconference.

/s/ Colm F. Connolly
United States District Judge

Filed: April 21, 2020

APPENDIX H

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civil Action No. 19-567-CFC-CJB
(CONSOLIDATED)

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs,

v.

NATERA, INC.,

Defendant.

Civil Action No. 19-1804-CFC-CJB

CAREDX, INC.,

Plaintiff,

v.

EUROFINS VIRACOR, INC.,

Defendant,

and

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Nominal Defendant.

REPORT AND RECOMMENDATION

1. Presently pending before the Court in these patent infringement cases are motions filed by Defend-

ant 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 prem-

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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. 19567-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. 191804-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).

ised 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 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]

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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

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. 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

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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.

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

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

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 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.

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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)

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 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

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[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 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.

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 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

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[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. l9-1804-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 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)

"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 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

/s/ Christopher J. Burke
Christopher J. Burke
UNITED STATES MAGISTRATE JUDGE

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[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)

APPENDIX I

NOTE: This order is nonprecedential.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

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2022-1027

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CAREDX, INC., THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs-Appellants

v.

NATERA, INC.,

Defendant-Appellee

———

Appeal from the United States District Court for the District of Delaware in Nos. 1:19-cv-00567-CFC-CJB, 1:20-cv-00038-CFC-CJB, Chief Judge Colm F. Connolly.

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2022-1028

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CAREDX, INC., THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs-Appellants

v.

EUROFINS VIRACOR, INC.,

Defendant-Appellee

———

Appeal from the United States District Court for the District of Delaware in No. 1:19-cv-01804-CFC-CJB, Chief Judge Colm F. Connolly.

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before NEWMAN, LOURIE, BRYSON[1], DYK, PROST, REYNA, TARANTO, CHEN, HUGHES, STOLL, and CUNNINGHAM, *Circuit Judges*.[2]

PER CURIAM.

ORDER

CareDx, Inc. and the Board of Trustees of the Leland Stanford Junior University filed a combined petition for panel rehearing and rehearing en banc. Responses to the petition were invited by the court and filed by Eurofins Viracor, Inc. and Natera, Inc. Paul R. Michel requested leave to file a brief as amicus curiae which the court granted. The petition was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

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[1] Circuit Judge Bryson participated only in the decision on the petition for panel rehearing.

[2] Chief Judge Moore and Circuit Judge Stark did not participate.

The mandate of the court will issue December 9, 2022.

December 2, 2022
Date

FOR THE COURT

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court