**Appeal Nos. 2022-1027, 2022-1028**

# In the United States Court of Appeals for the Federal Circuit

**CAREDX, INC., THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,**
*Plaintiffs-Appellants*
*v.*
**NATERA, INC.,**
*Defendant-Appellee*

2022-1027

Appeal from the United States District Court for the District of Delaware in No. 1:19-cv-00567-CFC-CJB, 1:20-cv-00038-CFC-CJB, Judge Colm F. Connolly.

**CAREDX, INC., THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,**
*Plaintiffs-Appellants*
*v.*
**EUROFINS VIRACOR, INC.,**
*Defendant-Appellee*

2022-1028

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

## APPELLANTS' COMBINED PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Zachary D. Tripp
WEIL, GOTSHAL & MANGES LLP
2001 M Street NW, Suite 600
Washington, DC 20036
(202) 682-7220
zack.tripp@weil.com

Edward R. Reines
Derek C. Walter
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
(650) 802-3000
edward.reines@weil.com
derek.walter@weil.com

*Counsel for Plaintiffs-Appellants*

September 16, 2022

# CERTIFICATE OF INTEREST

As required by Federal Circuit Rule 47.4, I certify the following:

1. Represented Entities. Fed. Cir. R. 47.4(a)(1). Provide the full names of all entities represented by undersigned counsel in this case.

   CareDx, Inc., The Board of Trustees of the Leland Stanford Junior University

2. Real Party in Interest. Fed. Cir. R. 47.4(a)(2). Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.

   Not applicable.

3. Parent Corporations and Stockholders. Fed. Cir. R. 47.4(a)(3). Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.

   None.

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

   STEPHEN BOSCO
   FORMERLY OF
   WEIL, GOTSHAL & MANGES LLP
   2001 M STREET NW, SUITE 600
   WASHINGTON, DC 20036

   ANNA E. DWYER
   FORMERLY OF
   WEIL, GOTSHAL & MANGES LLP
   767 FIFTH AVE
   NEW YORK, NY 10153

BRIAN E. FARNAN
MICHAEL J. FARNAN
FARNAN LLP
919 N. MARKET STREET, 12TH FLOOR
WILMINGTON, DELAWARE 19801

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

Not Applicable.

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

Not applicable.

Dated: September 16, 2022

Respectfully submitted,

*/s/ Edward R. Reines*

Edward R. Reines
*Principal Attorney*
WEIL GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
Telephone: (650) 802-3000
edward.reines@weil.com

*Counsel for Appellants*

# TABLE OF CONTENTS

**Page**

# TABLE OF AUTHORITIES

**Page(s)**

**CASES**



**STATUTES AND REGULATIONS**

## STATEMENT OF COUNSEL

Based on my professional judgment, I believe the panel decision is contrary to the following decisions: *Diamond v. Diehr*, 450 U.S. 175, 187 (1981); *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012); *CosmoKey Solutions GmbH & Co. v. Duo Security LLC*, 15 F.4th 1091 (Fed. Cir. Oct. 4, 2021).

Based on my professional judgment, I believe this appeal requires an answer to the following precedent-setting questions of exceptional importance:

1. Whether an improvement on a human-made method is patent eligible at *Alice* step one, when the claimed advance is also human-made?

2. Whether an improvement upon a human-made method is patent eligible at *Alice* step two, when the method includes an innovative application of existing tools.

In addition, the panel opinion overlooked or misapprehended:

1. That the claimed advance frames the *Alice* step one inquiry and here is a patent-eligible improvement on existing measurement methods (which are human-made), not discovery of the underlying phenomenon itself (which is not).

2. That a patent that claims an improved method for measuring a long-known natural phenomenon is patent-eligible at *Alice* step two when it departs from conventional methods for measuring that phenomenon and instead applies existing laboratory tools in a new context that evaded the prior art.

Dated: September 16, 2022 /s/ *Edward R. Reines*
*Attorney of Record for Appellants*

## I. INTRODUCTION

Section 101 protects "improvement[s]" upon existing methods and Congress intended Section 101 to reach "anything under the sun that is made by man," with exclusion from that broad protection driven by "pre-emption" concerns. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980); *Alice Corp. Pty. Ltd. v. CLS Bank Intern*. 573 U.S. 208, 216 (2014).

The panel opinion here nonetheless invalidated patents covering improved methods for measuring a long-known natural phenomenon, using human-made techniques, and where no concern of pre-emption has ever been raised. In so doing, the panel opinion improperly extended *Athena*, causing even more damage to innovation in medical diagnostics and further confusing an already fraught area of the law. And unlike the en banc majority view expressed in *Athena*, the outcome here is not required by *Mayo*, but rather contravened it.

Supreme Court precedent and the text of §101 confirm the patent eligibility of improved laboratory measurement methods. This Court should grant rehearing en banc, or at least panel rehearing, to confirm that improved laboratory measurement methods are patent eligible, and protect the incentive for scientists to improve such measurements.

Based on the work of pioneering researchers at Stanford University, the patents claim an improved method for measuring a long-known natural

phenomenon: when a transplant recipient begins undergoing organ rejection, the proportion of the donor's cell-free DNA in the recipient's blood increases. The patents explain, with copious prior art citation, that the natural correlation was known for a decade, but that many motivated prior artists were unable to arrive at a good way to measure it. The conventional methods were inaccurate and worked only for a subset of patients. The patents instead claim a new and better way to measure that phenomenon, by using human-made tools (next-generating sequencing and digital PCR) in particular ways, to identify "single nucleotide polymorphisms" that uniquely correspond to the donor or the recipient. That improved method works for all patients and is far more accurate, and thus a dramatic and life-saving improvement.

The panel opinion nonetheless invalidated the patents by concluding that, because those tools already existed, the Stanford inventions are directed to a natural phenomenon and used merely "conventional" tools. That analysis is fundamentally flawed and conflicts with precedent from the Supreme Court and this Court.

En banc review is warranted to restore critical legal safeguards that prevent the exceptions to §101 from contravening the purposes of the Patent Act.

First, review is needed to address whether a patent in which the claimed advance is a new and improved laboratory measurement method is patent-eligible at step one. This Court's precedent requires that the *Alice* step one analysis consider

the "claimed advance." *See, e.g., CosmoKey Solutions GmbH & Co. v. Duo Security LLC,* 15 F.4th 1091 (Fed. Cir. Oct. 4, 2021) ("Under *Alice* step one, we consider what the patent asserts to be the focus of the claimed advance over the prior art."). The Stanford Patents establish that the claimed advance is new, different, and better ways to measure a natural correlation that had eluded the prior art for a decade. Improved measurement methods are eligible for patent protection because they are human-made and §101 expressly protects "improvement[s]."

The panel decision conflicts with this Court's precedent by failing to consider the claimed advance in determining what an improved method is "directed to." Here, it is not directed to the underlying phenomenon. It is directed to improving human-made methods to measure that phenomenon. For this reason, in this case there has never been a concern raised about preemption of the underlying natural correlation.

The panel opinion improperly displaced the "claimed advance" analysis of step one with a "conventionality" analysis that duplicates step two, thus effectively emptying step one of independent meaning. En banc reconsideration is warranted to restore the importance and necessity of the "claimed advance" inquiry, and render improved measurement methods patent-eligible at step one.

Second, review is needed to address the panel opinion's "conventionality" analysis at step two because it wrongly excludes human-made improvements when they employ existing tools. The patents identify a series of conventional methods

for measuring the phenomenon at issue, explain their shortcomings, and explain how the claimed methods are new, different, and better than those conventional methods. If the patented measurement methods were conventional, the prior art would not have missed them for a decade. That is proof positive that the claimed improvement was not conventional, well-known, or routine.

The panel opinion nonetheless invalidated the patents as "conventional" because, in the panel opinion's view, the specification admits that each of the underlying steps in the new method was itself previously known. But that conflicts with basic Supreme Court law. It is "commonplace that an 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 (1981); *Bilski v. Kappos*, 561 U.S. 593 (2010) (same); *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012) (same). By dissecting the claim elements instead of valuing the innovation of their application as a whole to the problem of measuring the particular phenomenon here, the panel opinion departed from the Supreme Court's direction that a court must not "dissect the claims" and instead "must" consider the "claim as a whole." *Diehr*, 450 U.S. at 188.

The combination of these two errors creates a deeply damaging decision. It adds further confusion to an already challenging area of law and undermines innovation in the field of medical diagnostics. This Court should grant the petition

to restore the appropriate boundaries on the §101 analysis, and to protect improvements upon human-made methods.

## II. THE STANFORD PATENTS

### A. The Problem Solved

The Stanford Patents thoroughly explain the measurement problem they solve. Specifically, organ rejection is a life-threatening complication of a transplant, so doctors have long sought to identify advance signs of rejection. By the 1990s, scientists recognized that the amount of cell-free DNA released from the donated organ in the recipient's blood stream increases during organ rejection. Appx120 at 6:57-58; Appx1491-Appx1492. Thus, the medical community has long known that an increase in the donor's cf-DNA from a transplanted organ undergoing rejection correlates with organ rejection. *Id.* By 1998, scientists had proposed in a Lancet article that measuring the donor cf-DNA in an organ transplant patient's bloodstream could allow inexpensive and early identification of rejection because of that known correlation. *Id.*

For a decade, however, researchers struggled to develop good methods for measuring that correlation. Appx121 at 7:47-8:55. The leading conventional measurement method focused on Y-chromosomal cf-DNA that is unique to males. *Id*. This approach only works when the donor is male and the recipient female, so that the donor's DNA can be differentiated from the recipient's. It was therefore not

universally applicable to all transplant patients. It also suffered from inaccuracy, particularly if the female recipient had previously been pregnant with a male. The patents also explain that prior artists attempting to solve the measurement problem tried to use human leukocyte antigen (HLA) alleles in cf-DNA. Appx121 at 8:34-44. But that conventional approach also had disadvantages. *Id*. at 8:39-44.

Only a year before the inventions, scientists believed that it would be altogether impractical to measure the donor cf-DNA correlation to reliably identify organ rejection. In an article cited in the Stanford Patents, a large team lead by Dr. Vymetalova concluded that, "the use of plasma free DNA [cf-DNA] for the detection of organ rejection is ***difficult and impractical***." *Id*. at 8:22-34; Appx2387; Appx2389 ("It would be difficult to differentiate the origin of cell free DNA in the plasma of heart transplant patients, making the use of plasma free DNA ***impractical*** for detection of organ rejection") (emphases supplied). As defendants' expert conceded, cf-DNA was believed to be "more challenging" than other forms of DNA to measure because cf-DNA is smaller, not random, typically present in low concentrations, and because the "detection analysis is difficult with techniques prior to 2009." Appx273 at 138:11-139:14.

### B. The Stanford Inventions

In 2008 the Stanford inventors developed an improved method that solved the problems that had plagued the conventional measurement methods for a decade. As the Stanford Patents explain, the new methods employ a "universal approach to noninvasive detection of graft rejection in transplant patients" that applies to all genders and are "sensitive, rapid, and inexpensive." Appx118 at 1:23-25, Appx121 at 8:45-54[1].

The Stanford inventors applied next generation sequencing (NGS) tools and digital PCR tools to measure and quantify single nucleotide polymorphisms (SNPs) from donor cf-DNA, which could be differentiated from SNPs of the recipient in particular ways. At the time of the invention, the literature described NGS as in its "infancy" and identified numerous perceived problems that limited its application. Only a year before the inventions, Natera's own scientists published an article describing the advent of digital PCR tools, noting that using such tools was a "major challenge" that was not possible in SNP-based applications, the very application described and claimed in the Stanford Patents. Appx2781. Despite the nascent stage of NGS and digital PCR and their well-documented limitations, the Stanford Patents nevertheless explain that these techniques in fact can be used, as claimed, to measure

[1] The patents-in-suit are U.S. Patent Nos. 8,703,652 ("the '652 Patent"), 9,845,497 ("the '497 Patent"), and 10,329,607 ("the '607 Patent") and they share a common specification.

SNPs from donor cf-DNA such that organ rejection can be detected. The Stanford Patents identify detailed near-contemporaneous patent applications and publications disclosing these techniques.

### C. CareDx Brings The Stanford Inventions To Transplant Patients

Recognizing the breakthrough and its extraordinary impact on the lives of transplant recipients, CareDx decided to partner with Stanford. In 2016, CareDx commercialized AlloSure® - the first organ transplant blood test using donor cf-DNA for early surveillance of organ rejection. CareDx made those investments in reliance on the protection of the Stanford Patents. CareDx committed massive capital by (1) sponsoring a major prospective clinical study to establish the test's efficacy, (2) funding on an on-going campaign to persuade clinicians of the benefits of this revolutionary new approach, and (3) obtaining Medicare approval to ensure insurance coverage for patients.

## III. PROCEDURAL HISTORY

After CareDx successfully introduced its organ rejection test, defendants Natera and Eurofins began marketing copycat tests for organ rejection using the Stanford Patents. Plaintiffs sued each for infringement and Defendants moved to dismiss based on an alleged violation of §101.

### A. The Magistrate Judge Correctly Concluded That The Stanford Patents Claimed Patent Eligible Subject Matter

Magistrate Judge Burke issued a Report and Recommendation denying defendants' §101 challenge, determining that "the motions [to dismiss] can be resolved at *Alice's* step one." Appx8-Appx10. He zeroed in on the claimed advance, explaining, "[h]ow could it be the case that the 'basic thrust' or 'character as a whole' or 'focus' 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?" Appx10. He further explained that the "patent is saying that what the inventors were focused on here was how to develop a new, more accurate and useful analytic method," which is protectable human innovation. *Id.*

The district court adopted this recommendation, but stated that the court was agreeing only with the conclusion that the challenge was premature – a conclusion the magistrate judge had not made. Appx8-Appx13.

### B. The District Court Denies Summary Judgment

The district court initiated early summary judgment proceedings and originally found that there was material evidence establishing the claimed techniques were "***non-conventional***." Appx63-Appx64; Appx66-Appx67 (emphasis supplied). The court's opinion credited and quoted the scientific literature as establishing that the techniques used in the claimed measurement methods were "nascent," still in

their "infancy," "new," and that they had known issues with the "complexity of technical procedures, robustness, accuracy, and cost." *Id*.

### C. The District Court Sua Sponte Reconsidered Summary Judgment After It Initiated A §101 Evidentiary Hearing

The district court thereafter initiated an evidentiary hearing on §101 and reconsidered its original decision denying summary judgment, instead issuing a decision invalidating the Stanford Patents. The court concluded that both step one and step two collapse into the "exact same" analysis: "the dispositive inquiry under both steps of the *Alice* inquiry is whether the asserted method uses more than standard or conventional techniques of detection." Appx93-Appx94.

The district court concluded that the entire claim was "conventional" because of a supposed "disclaimer" in the specification admitting that each step in the claimed method alone was preexisting – notwithstanding the extensive description in the patents explaining how the combination and use of the claimed methods in this context was novel and improved on a decade of prior art failures. Appx96.

### D. The Panel Decision

A panel affirmed. At step one, the panel opinion did not seek to identify the claimed advance, and did not address the specification's unequivocal statements that the claim improved upon the prior art measurement methods. The panel opinion instead found that the claims were for a "diagnostic method," which the panel opinion found "indistinguishable" from those at issue in *Athena* and its progeny. Op.

at 12.

At step two, the panel opinion found that the claims use "conventional measurement techniques to detect a natural phenomenon." The panel opinion found it sufficient that the new and improved method used a combination of existing laboratory tools that the specification supposedly admitted were each conventional. Op. at 17. The panel opinion failed to address the innovation in applying the existing tools to a new context and failed to explain why, if the patented inventions were conventional, a decade of unsuccessful prior art attempts had missed them.

## IV. ARGUMENT

This Court should grant en banc or panel rehearing because the panel opinion erred in holding that (1) an improved method of measuring a natural phenomenon is directed to the phenomenon itself, rather than directed to improving the human-made methods for measuring it; and (2) an improved method is "conventional" if it uses existing tools, notwithstanding that combining those steps and applying them in this way departed sharply from the conventional methods for detecting the very phenomenon at issue. At each step, the panel opinion's analysis conflicts with decisions of this Court and the Supreme Court. And together, the holdings further confuse this difficult area of law and magnify the harmful impact of *Athena* by undermining incentives for inventing improved diagnostic methods.

### A. An Improved Method Of Measuring A Known Phenomenon Is Patent-Eligible At Step One

Step one asks whether the claims of the patent are directed to ineligible subject matter. This Court has consistently held that to determine whether the claim is directed to such subject matter the "claimed advance" must first be identified. "Under Alice step one, we consider what the patent asserts to be the focus of the claimed advance over the prior art." *CosmoKey*, 15 F.4th at 1097 (citations and quotations omitted); *see, e.g., Trading Tech v. IBG LLC*, 921 F.3d 1378 (Fed. Cir. 2019); *Solutran, Inc. v. Elavon, Inc.*, 931 F.3d 1161, 1168 (Fed. Cir. 2019).

When a patent claims an improved method for measuring a known phenomenon, that analysis is straightforward: the claimed advance over the prior art is a new measurement method that is better than prior methods. The claim is thus directed to an improvement on those prior art methods (which are human-made), and is not directed to the natural phenomenon itself. The claimed advance approach fulfills the aims of the *Alice* inquiry because preemption concerns are absent when a claim is for an improvement upon previous methods. The claim cannot preempt usage of the natural phenomenon, or even measuring of the phenomenon, because those previous methods by definition must remain unclaimed.

The panel opinion acknowledged CareDx and Stanford's argument that "the claimed advance is improved measurement methods spelled out in the claims as superior to the inadequate prior art measurement techniques." Op. at 11. But in

conflict with this Court's precedent, *e.g.*, *CosmoKey*, 15 F.4th at 1097, it never identified the claimed advance. Instead, the panel opinion observed that the claims involve detection of a natural phenomenon, and repeated its "conventionality" analysis from step two. Op. at 17 (erroneously finding step one satisfied because "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.").

That analysis is fundamentally misplaced. The purpose of a §101 analysis is to determine whether a claim is, in reality, a claim on a natural phenomenon or instead a claim on something human-made. The "claimed advance" inquiry frames that question and protects against undue expansion of the exception to patent eligibility. Here, the claimed advance confirms the claims are directed to an improvement upon prior art measurement methods. The specification discloses the prior art methods, explains that they were limited, and discloses a new and different method that works better. Appx121 at 7:47-8:55. Both the prior conventional measurement methods and the "improvement" that is claimed are human-made. Defendants have never even suggested that the Stanford Patents might preempt the natural correlation. As Magistrate Judge Burke explained, this should end the §101

inquiry. Appx8-Appx10. Whether the asserted advance is truly worthy of a patent is a question of obviousness and other doctrines, not §101. *Id*.

### B. An Improved Measurement Method Is Not "Conventional" Merely Because It Involves Application Of Available Tools From Other Contexts To Make The Novel Improvement

The panel opinion compounded its error, and increased the need for rehearing, at step two. The Supreme Court has squarely established that "an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection."); *Bilski*, 561 U.S. at 611 (same); *Mayo*, 566 U.S. at 71 (same). This is because patent eligibility is measured by the "claim as a whole." *Diehr*, 450 U.S. at 188. "It is inappropriate to dissect the claims" because "claims must be considered as a whole" in determining patent eligibility. *Id.* Inventiveness accordingly can surely reside in the idea to apply existing tools to a different context to arrive at a new solution to a problem that had eluded determined prior artists.

The panel's decision conflicts with *Diehr*, however, in holding that an improved measurement method is ineligible for patent protection when it uses a combination of tools, each of which itself already exists. In particular, the panel opinion emphasized that "the specification admits that the laboratory techniques disclosed in the claims require only conventional techniques and off-the-shelf technology." Op. at 17. CareDx strongly disagrees with that statement factually, but the panel opinion's deeper error is legal: Even if the NGS and dPCR tools were

"conventional" and "off-the-shelf," that would not address whether the ***application*** of those general tools to the unique problem of measuring donor cf-DNA using SNPs found amidst the recipient's cf-DNA is "conventional."

Again, the answer to the conventionality question should be straightforward when a claim is for an improved method for measuring a known phenomenon, and is particularly clear here. The Stanford Patents explain that the relevant "conventional" methods are ***the prior art methods for measuring that same phenomenon*** that the patented methods improve upon. Appx121 at 7:47-8:55. The Stanford Patents disclose that a decade of motivated workers had arrived at a series of conventional tools for measuring the phenomenon at issue, including the use of a Y chromosome as a biomarker and the use of HLA alleles. *Id.* And the Stanford Patents plainly depart from those methods, because they disclose their existence and instead claim new and different methods that are more effective and that the prior art missed. Moreover, the district court *denied* summary judgment on the inventiveness of the claimed combination of steps, thus confirming that the improved method could not be dismissed as merely "conventional" overall.

The panel's ruling also cannot be cabined as merely a fact-bound determination that the Stanford Patents supposedly "disclaimed" the inventiveness of the patented methods. The specification contains no language to that effect and the panel opinion cited none. Indeed, it is anomalous to interpret a patent on a new

and improved measurement method as somehow disclaiming the claimed advance as entirely conventional. But more fundamentally, in any patent where each underlying step is preexisting (but the combination is not), the defendant will be able to prove that each underlying step is preexisting and thus not itself inventive. If that were a sufficient basis to defeat the eligibility of an improved method that combines preexisting tools and puts them to use in a new way, then improved methods face a uniquely demanding eligibility test that has no basis in the statutory text, precedent, or logic.

### C. The Same Patent Ineligibility Rules Should Apply to Diagnostic Claims As Apply To All Other Claims

The combination of the errors above not only further convolutes this fraught area of the law, but is particularly damaging to innovation in medical diagnostics. The panel opinion's step one analysis largely depended upon its labelling of the claims as "diagnostic" claims rather than "a new measurement technique." Op. at 12-13. In particular, the panel opinion found this case "indistinguishable" from the diagnostic claims invalidated in *Mayo* and *Ariosa*. *Id*. at 15. But the claims in those cases were fundamentally different, as the "claimed advance" inquiry illuminates. In *Mayo* and *Ariosa*, the only claimed advance was the discovery of the natural phenomenon. In neither case did the patent owner allege that anything about the measurement method was itself inventive or that skilled artisans had difficulty in the prior art inventing an effective method. Likewise in *Athena* and *Cleveland* the

patents said nothing about the inventiveness of the measurement method, instead depending on the original discovery of the natural phenomenon to establish inventiveness.

By contrast, the inventors here did not purport to discover the natural phenomenon. Rather, the Stanford patents explain that the invention lies in the development of improved measurement methods that had long eluded the prior art. Appx121 at 7:47-8:55.

Those cases are also distinguishable at step two. The invention here lies in using a new and non-conventional method that works better than those preexisting methods, and which had never before been used in this context. And although each individual component of the new method may have existed, that is immaterial because a court must consider the "claim as a whole," *Diehr*, 450 U.S. at 188, and it was groundbreaking to use that combination of steps to solve this particular problem.

### D. The Panel Should Reconsider Its Ruling

The panel's ruling warrants review because it improperly extended *Athena* to the new and different context of improved measurement methods. Under the panel opinion, any such method will be addressed at step two of the *Alice* inquiry (because it will be deemed to be directed to the natural phenomenon, even when it is actually directed to improving a human-made method). Then at step two, it will fail for conventionality so long as each underlying step in the claim involves use of a tool

that is deemed "conventional" and "off-the-shelf"—even if the combination of steps had never before been used to measure the phenomenon at issue.

## V. CONCLUSION

For the reasons set forth above, the court should grant rehearing en banc or, at a minimum, panel rehearing.

Respectfully submitted,

Dated: September 16, 2022

*/s/ Edward R. Reines*

Edward R. Reines
Derek C. Walter
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
(650) 802-3000
edward.reines@weil.com
derek.walter@weil.com

Zachary D. Tripp
WEIL, GOTSHAL & MANGES LLP
2001 M Street NW, Suite 600
Washington, DC 20036
(202) 682-7220
zack.tripp@weil.com

*Counsel for Appellants*

# ADDENDUM

# United States Court of Appeals for the Federal Circuit

---

**CAREDX, INC., THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,**
*Plaintiffs-Appellants*

**v.**

**NATERA, INC.,**
*Defendant-Appellee*

---

2022-1027

---

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.

---

**CAREDX, INC., THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,**
*Plaintiffs-Appellants*

**v.**

**EUROFINS VIRACOR, INC.,**
*Defendant-Appellee*

---

2022-1028

---

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 quantifying 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,

---

[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 PCR-based 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 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

CareDx's 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.

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

---

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").

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 combination 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**

## CERTIFICATE OF COMPLIANCE

1. The undersigned certifies that this brief complies with the type-volume limitation of Federal Circuit Rule 32(a) or Federal Rule of Federal Circuit Rule 28.1. This brief contains 3,880 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f).

2. The undersigned further certifies that this brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) or Federal Rule of Federal Circuit Rule 28.1 and the type style requirements of Federal Rule of Appellate Procedure 32(a)(5) or Federal Rule of Federal Circuit Rule 28.1 and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6).

This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14 point font.

Dated: September 16, 2022

/s/ *Edward R. Reines*

Edward R. Reines
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
(650) 802-3000
edward.reines@weil.com

## CERTIFICATE OF SERVICE

I hereby certify that on September 16, 2022, I filed or caused to be filed copies of the foregoing with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system and served or caused to be served a copy on all counsel of record by U.S. Mail and E-mail.

Dated: September 16, 2022

/s/ *Edward R. Reines*

Edward R. Reines
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
(650) 802-3000
edward.reines@weil.com