NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

CLEVELAND CLINIC FOUNDATION, CLEVELAND HEARTLAB, INC.,
Plaintiffs-Appellants

v.

TRUE HEALTH DIAGNOSTICS LLC,
Defendant-Appellee

2018-1218

Appeal from the United States District Court for the Eastern District of Virginia in No. 1:17-cv-00198-LMB-IDD, Judge Leonie M. Brinkema.

Decided: April 1, 2019

LAWRENCE D. ROSENBERG, Jones Day, Washington, DC, argued for plaintiffs-appellants. Also represented by SUSAN M. GERBER, CALVIN GRIFFITH, Cleveland, OH.

ADAM LOUIS MARCHUK, Perkins Coie LLP, Chicago, IL, argued for defendant-appellee. Also represented by MARK T. SMITH; DAN L. BAGATELL, Hanover, NH.

DAVID MOVIUS, McDonald Hopkins LLC, Cleveland,

OH, for amicus curiae Raymond A. Mercado.

SCOTT A. M. CHAMBERS, Porzio, Bromberg & Newman, PC, Washington, DC, for amici curiae Walter Matystik, Adam Mossoff, Kristen J. Osenga, Michael Risch, Ted M. Sichelman, David O. Taylor. Also represented by MATTHEW ZAPADKA, Bass, Berry & Sims, PLC, Washington, DC.

Before LOURIE, MOORE, and WALLACH, *Circuit Judges.*

LOURIE, *Circuit Judge.*

The Cleveland Clinic Foundation and Cleveland HeartLab, Inc., (collectively, "Cleveland Clinic") appeal from a decision of the United States District Court for the Eastern District of Virginia, dismissing their complaint for patent infringement under Rule 12(b)(6) and holding claim 1 of U.S. Patent 9,575,065 (the "'065 patent") and claims 1 and 2 of U.S. Patent 9,581,597 (the "'597 patent") invalid under 35 U.S.C. § 101 as directed to an ineligible natural law. *Cleveland Clinic Foundation v. True Health Diagnostics LLC*, No. 1:17-cv-00198-LMB-IDD, 2017 WL 3381976 (E.D. Va. Aug. 4, 2017) ("*Decision*"). Because the district court correctly concluded that the claims are directed to a natural law and recite no other inventive concept, we *affirm*.

BACKGROUND

The patents at issue[1] disclose "diagnostic test[s] which can be used to determine whether an individual . . . is at a

---

[1] The patents each claim priority from an application which issued as U.S. Patent 7,223,552 and contain materially identical specifications. For consistency, our citations of their common specification refer to the '065 patent.

lower risk or higher risk of developing or having cardiovascular disease." '065 patent col. 1 ll. 21–25. These diagnostic tests are "based on the discovery that patients with coronary artery disease (CAD) have significantly greater levels of leukocyte and blood myeloperoxidase (MPO) levels." *Id*. col. 2 ll. 36–39.

At the time of the invention, cardiovascular disease ("CVD") was understood to be multifactorial, '065 patent col. 1 l. 51–col. 2 l. 26, and scientists and physicians were developing predictive algorithms based on genetic, environmental, and lifestyle factors. *Id.* col. 1 l. 53–60. However, these factors alone did not fully predict an individual's risk of developing CVD; in particular, "a large number of cardiovascular disorders occur[red] in individuals with apparently low to moderate risk profiles." Appellant Br. 6 (citation omitted). Thus, the patents disclose a need in the art for "[d]iagnostic tests which employ risk factors that are independent of traditional CVD risk factors such as LDL levels." '065 patent col. 2 ll. 24–26.

Myeloperoxidase ("MPO") is a naturally-occurring heme protein associated with some types of white blood cells. '065 patent col. 6 ll. 60–65. It functions as an oxidant, converting inert substrates to reactive oxygen species toxic to pathogens, to aid in phagocytosis, an important process in the body's immune system. *Id.* col. 7 ll. 4–22. Atherosclerosis (the major cause of coronary artery disease) was known to be "a chronic inflammatory disorder," and high blood levels of other metabolites had been correlated to CVD. *Id.* col. 2 ll. 12–21 (disclosing the then-recent discovery that plasma concentrations of C-reactive protein could predict an individual's risk of developing some types of CVD). But these metabolites are imperfect markers of CVD because they are not specific to cardiovascular inflammation. While MPO had been found to be present at elevated levels in atherosclerotic lesions, it had not been shown that MPO was present at elevated levels in blood

samples from patients with atherosclerotic CVD. *Id.* col. 6 l. 66–col. 7 l. 3.

The patents disclose several methods of measuring a patient's blood MPO level. *See, e.g.*, '065 patent col. 8 ll. 35–36 ("Myeloperoxidase activity may be determined by any of a variety of standard methods known in the art."). As is relevant to the claims, the patents disclose use of an enzyme-linked immunosorbent assay ("ELISA"), a well-known technique that quantifies the level of an antigen in a bodily sample by detecting its binding to a biochemically compatible antibody. *Id.* col. 9 ll. 33–35 ("The mass of myeloperoxidase in a given sample is readily determined by an immunological method, e.g.[,] ELISA. Commercial kits for MPO quantification by ELISA are available.").

Example 1 discloses the results of a study of 326 patients and concludes that blood MPO levels strongly correlate with risk of coronary artery disease but not with traditional risk factors for coronary artery disease. '065 patent col. 27 ll. 9–59. In the study, MPO mass was quantified with ELISA, specifically by using a commercially-available antibody modified to bind to MPO. *Id.* col. 24 ll. 11-13. Examples 3–6 disclose experimental results, using other methods, showing that common oxidation products of MPO were present in significantly higher levels in blood samples from patients with coronary artery disease as compared to a control group. *Id.* col. 28 l. 45–col. 30 l. 30.

We previously addressed the subject matter eligibility of a parent patent, U.S. Patent 7,223,552, in *Cleveland Clinic Foundation v. True Health Diagnostics LLC*, 859 F.3d 1352 (Fed. Cir. 2017), *cert. denied*, 138 S. Ct. 2621, (2018) ("*Cleveland Clinic I*"). Claim 11 of the '552 patent was exemplary:

> 11. A method of assessing a test subject's risk of having atherosclerotic cardiovascular disease, comprising

> comparing levels of myeloperoxidase in a bodily sample from the test subject with levels of myeloperoxidase in comparable bodily samples from control subjects diagnosed as not having the disease, said bodily sample being blood, serum, plasma, blood leukocytes selected from the group consisting of neutrophils, monocytes, sub-populations of neutrophils, and sub-populations of monocytes, or any combination thereo[f];
>
> wherein the levels of myeloperoxidase in the bodily [samples] from the test subject relative to the levels of [m]yeloperoxidase in the comparable bodily samples from control subjects is indicative of the extent of the test subject's risk of having atherosclerotic cardiovascular disease.

'552 patent col. 30 ll. 47–62.

In *Cleveland Clinic I*, we held these methods invalid under § 101 as directed to the ineligible natural law that blood MPO levels correlate with atherosclerotic CVD. *Id.* at 1360–61 (holding that the claimed method "starts and ends" with observation of "naturally occurring phenomena," as in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015)). We further held that, because the patent did not purport to have invented any of the biological techniques used to detect MPO or the statistical methods used to compare a patient's MPO levels to the control group, the claims recited no further inventive concept sufficient to transform the nature of the claims into a patent-eligible application of the natural law. *Id.* at 1361–62 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 78 (2012)).

Meanwhile, Cleveland Clinic was issued the patents in suit from continuation applications ultimately claiming

priority from the '552 patent. Claim 1 of the '597 patent is illustrative:

> 1. A method for identifying an elevated myeloperoxidase (MPO) concentration in a plasma sample from a human subject with atherosclerotic cardiovascular disease comprising:
>
> a) contacting a sample with an anti-MPO antibody, wherein said sample is a plasma sample from a human subject having atherosclerotic cardiovascular disease;
>
> b) spectrophotometrically detecting MPO levels in said plasma sample;
>
> c) comparing said MPO levels in said plasma sample to a standard curve generated with known amounts of MPO to determine the MPO concentration in said sample; and
>
> d) comparing said MPO concentration in said plasma sample from said human subject to a control MPO concentration from apparently healthy human subjects, and identifying said MPO concentration in said plasma sample from said human subject as being elevated compared to said control MPO concentration.

Claim 2 further requires collecting the plasma sample by "centrifuging an anti-coagulated blood sample from said human subject." Claim 1 of the '065 patent is directed to:

> 1. A method of detecting elevated MPO mass in a patient sample comprising:
>
> a) obtaining a plasma sample from a human patient having atherosclerotic cardiovascular disease (CVD); and

> b) detecting elevated MPO mass in said plasma sample, as compared to a control MPO mass level from the general population or apparently healthy subjects, by contacting said plasma sample with anti-MPO antibodies and detecting binding between MPO in said plasma sample and said anti-MPO antibodies.

These claims recite methods of identifying and detecting MPO, in contrast to the '552 patent's claimed method of assessing atherosclerotic CVD risk from blood MPO levels.

In February 2017, Cleveland Clinic filed a complaint against True Health Diagnostics LLC ("True Health") for patent infringement in the Eastern District of Virginia. True Health moved to dismiss the counts of infringement of the asserted patents under Rule 12(b)(6). After our decision in *Cleveland Clinic I* issued, the district court held the asserted claims ineligible as directed to a natural law under § 101 and dismissed Cleveland Clinic's complaint for failure to state a claim. Cleveland Clinic appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review a district court's order of dismissal under Rule 12 according to the law of the regional circuit. *BASCOM Glob. Internet Servs., Inc. v. AT&T Mobility LLC*, 827 F.3d 1341, 1347 (Fed. Cir. 2016) (citing *In re Bill of Lading Transmission & Processing Sys. Patent Litig.*, 681 F.3d 1323, 1331 (Fed. Cir. 2012)). In the Fourth Circuit, Rule 12 dismissal is reviewed *de novo* and is appropriate when, assuming all well-pleaded facts are true and drawing all reasonable inferences in favor of the plaintiff, the complaint fails to allege "sufficient facts to state a claim that is 'plausible on its face.'" *E.I. du Pont de Nemours & Co. v. Kolon Indus., Inc.*, 637 F.3d 435, 440 (4th Cir. 2011)

(quoting *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007)).

Section 101 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." 35 U.S.C. § 101. But the Supreme Court has long interpreted these categories as excluding "laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981); *see also Le Roy v. Tatham*, 55 U.S. 156, 175 (1852) ("[A] principle is not patentable. A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right."). A claim to otherwise statutory subject matter does not become ineligible simply because it recites a natural law. *See Parker v. Flook*, 437 U.S. 584, 590 (1978). But the Supreme Court has held that a claim directed to a natural law may nevertheless be patent-eligible if it "contain[s] other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Mayo*, 566 U.S. at 72–73 (citing *Flook*, 437 U.S. at 594).

Patent eligibility under § 101 is a question of law that can include subsidiary questions of fact. *See Aatrix Software, Inc. v. Green Shades Software, Inc.*, 882 F.3d 1121, 1128 (Fed. Cir. 2018). Such factual issues may be resolved on the pleadings "based on the sources properly considered on a motion to dismiss, such as the complaint, the patent, and materials subject to judicial notice." *Id.*; *see Data Engine Techs. LLC v. Google LLC*, 906 F.3d 999, 1008 n.2 (holding that relevant prosecution histories are "public records" properly considered at the pleadings stage) (citing *Hockerson-Halberstadt, Inc. v. Avia Grp. Int'l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000)); *cf. Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1349 (Fed. Cir. 2004) ("[A

patentee's] statement made during prosecution of [a continuation] patent is relevant to an understanding of the common disclosure in the sibling . . . patents.").

Cleveland Clinic argues that the claims are not directed to a natural law, but to the technique of using an immunoassay to measure the blood MPO levels of patients with atherosclerotic CVD. Cleveland Clinic further asserts that, in any case, the correlation between blood MPO levels and atherosclerotic CVD is not a natural law because it can only be detected using certain techniques. According to Cleveland Clinic, prior art techniques were either too invasive (*e.g.*, detecting MPO in samples of excised atherosclerotic lesions) or failed to predict CVD risk (*e.g.*, a flow cytometry-based method called MPXI and an older technique for measuring MPO in white blood cells by staining). Cleveland Clinic also argues that, while performing an immunoassay on blood samples was known, using the immunoassay to detect the correlation between blood MPO levels and atherosclerotic CVD supplies an inventive concept sufficient to transform the claims into patent-eligible subject matter.

True Health responds that the correlation between atherosclerotic CVD and blood MPO levels is a natural law because it exists in nature apart from human intervention, regardless of the technique used to observe it. True Health further argues that using known techniques in a standard way to observe the natural law neither renders the claims directed to something other than this natural law nor supplies an additional inventive concept.

We agree with True Health and conclude, as we did in *Cleveland Clinic I*, that the claims are directed to the natural law that blood MPO levels correlate with atherosclerotic CVD. Cleveland Clinic's primary argument to the contrary is that, unlike the '552 patent claims, the claims at issue are not directed to "assessing a test subject's risk of having atherosclerotic [CVD]" by comparing the subject's

MPO levels to a control group, '552 patent col. 30 ll. 47–62, but rather to "techniques for detecting elevated levels of MPO in the blood of patients having CVD." Appellant Br. 3.

We find, however, as the district court did, that this distinction is "overly superficial." *Decision*, 2017 WL 3381976, at *8. The claims are not directed to new techniques for performing an immunoassay to detect a patient's blood MPO levels. They only recite applying known methods to detect MPO levels in plasma, comparing them to standard MPO levels, and reaching a conclusion: that the patient's blood MPO levels are *elevated* in comparison to a control group. This conclusion is simply another articulation of the natural law that blood MPO levels correlate with atherosclerotic CVD. Thus, as we held in *Cleveland Clinic I*, the claims are directed to the patent-ineligible natural law that blood MPO levels correlate with risk of atherosclerotic CVD. *Cf. Flook*, 437 U.S. at 593 (stating that patent eligibility does not turn "on the draftsman's art"). The rephrasing of the claims does not make them less directed to a natural law.

Nor is the fact that blood MPO levels correlate with atherosclerotic CVD any less a natural law because it can only be observed by use of certain techniques. Many scientific techniques will not reveal a correlation between blood MPO levels and atherosclerotic CVD. But the same is true of the natural laws at issue in our previous cases. *See Ariosa*, 788 F.3d at 1376 (that paternally inherited cffDNA is present in maternal blood plasma); *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 747 (Fed. Cir. 2019) (that some *Myasthenia gravis* patients "generate autoantibodies to a membrane protein called MuSK"). These laws of nature exist regardless of the methods used by humans to observe them. Inadequate measures of detection do not render a natural law any less natural. Thus, we held the claims at issue in those cases directed to a natural law, and we do so again here.

Furthermore, the claims contain no additional inventive concept. Cleveland Clinic's argument to the contrary—that using a known technique in a standard way to observe a natural law can confer an inventive concept—has been consistently rejected by this court in circumstances nearly identical to this case. *Athena*, 915 F.3d at 753–54 (holding that there is no inventive concept in "applying standard techniques in a standard way to observe a natural law"); *see also Ariosa*, 788 F.3d at 1377 ("For process claims that encompass natural phenomenon, the process steps are the additional features that must be new and useful." (quoting *Flook*, 437 U.S. at 591)).

Neither the specification nor the record discloses any technical impediment to using an immunoassay in a standard way to measure MPO levels in blood. The patents disclose that an immunoassay was a known technique for measuring protein mass and never suggest that any significant adjustments needed to be made to accommodate its use for measuring blood MPO levels. '065 patent col. 9 ll. 33–35. Furthermore, the specification and prosecution history plainly concede that each of the process steps was well-known in the art. *See, e.g.*, *id.* col. 21 ll. 1–30 (comparing patient's blood MPO levels to control sample was known); *id.* col. 8 ll. 35–36, col. 9 ll. 33–35, col. 11 ll. 17–19 (detecting blood MPO levels using an ELISA was known); *id.* col. 24 ll. 16–20 (determining MPO concentration from sample data using a standard curve was known). Furthermore, Cleveland Clinic quoted in its complaint statements from the '597 patent application's Notice of Allowability, that collecting a plasma sample, contacting the sample with an anti-MPO antibody, and spectrophotometrically detecting MPO binding to an anti-MPO antibody were known. J.A. 1140.

Cleveland Clinic also argues that remand is warranted because the district court improperly resolved factual disputes against it at the pleadings stage. In view of our conclusion that the specification and prosecution history are

clear that the claimed method uses a known technique in a standard way to observe a natural law, we decline to do so. There is no reason to task the district court with finding an inventive concept that the specification and prosecution history concede does not exist. *See Secured Mail Sols. LLC v. Universal Wilde, Inc.*, 873 F.3d 905, 913 (Fed. Cir. 2017) (holding that a court "need not 'accept as true allegations that contradict matters properly subject to judicial notice'" (quoting *Anderson v. Kimberly-Clark Corp.*, 570 F. App'x 927, 931 (Fed. Cir. 2014))).

Finally, Cleveland Clinic argues that the district court failed to give the appropriate deference to subject matter eligibility guidance published by the PTO[2], as required by *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944). *Skidmore* "requires courts to give some deference to informal agency interpretations of ambiguous statutory dictates, with the degree of deference depending on the circumstances." *See Stephenson v. Office of Pers. Mgmt.*, 705 F.3d 1323, 1330 (Fed. Cir. 2013) (quoting *Cathedral Candle Co. v. U.S. Int'l Trade Comm'n*, 400 F.3d 1352, 1365 (Fed. Cir. 2005)). These circumstances include "the agency's care, its consistency, formality, and relative expertness, [and] the persuasiveness of the agency's position." *United States v. Mead Corp.*, 533 U.S. 218, 228 (2001) (citations omitted). Cleveland Clinic further contends that the district court erred by not granting *Skidmore* deference to the examiner's decision to allow the patents' applications to issue in light of the guidance, specifically Example 29–Claim 1.

True Health responds that the guidance is neither persuasive nor relevant to the eligibility of the claims at issue and the district court correctly found that the example claim is directed to a method of detecting a protein in a

---

[2] Example 29, the disputed portion of the guidance, was published by the PTO on May 4, 2016. J.A. 1151.

plasma sample without linking the results to a disease or other natural phenomenon.

Example 29 sets forth a hypothetical protein, "JUL-1," which naturally occurs in people with an autoimmune disease, "julitis," but not in others. J.A. 1161–63. The applicant discloses "routine and conventional" techniques, including an immunoassay and spectroscopy, to detect the presence of the protein in a patient's plasma sample. J.A. 1161. The example claim is reproduced below:

Example 29–Claim 1

> 1. A method of detecting JUL-1 in a patient, said method comprising:
>
> a. obtaining a plasma sample from a human patient; and
>
> b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody.

J.A. 1162.

In its guidance, the PTO advised that, because the claim does not "recite or describe any [ineligible concept]," it is not directed to a natural law and is eligible under § 101. J.A. 1163.

We agree with True Health that the district court did not err in finding the instant claims ineligible. While we greatly respect the PTO's expertise on all matters relating to patentability, including patent eligibility, we are not bound by its guidance. And, especially regarding the issue of patent eligibility and the efforts of the courts to determine the distinction between claims directed to natural laws and those directed to patent-eligible applications of those laws, we are mindful of the need for consistent application of our case law.

Example 29–Claim 1 is strikingly similar to claim 1 of U.S. Patent 6,258,540 at issue in *Ariosa*:

> 1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
>
> > amplifying a paternally inherited nucleic acid from the serum or plasma sample and
> >
> > detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.

Ariosa, 788 F.3d at 1373–74.

In *Ariosa*, we held this claim ineligible because it was directed to the discovery that paternally inherited cffDNA exists in maternal blood plasma, *id.* at 1376, and the amplification and detection techniques were concededly known in the art. *Id.* at 1377–78. Likewise, Example 29 stipulates that the techniques used to detect JUL-1 were conventionally applied to detect any protein of interest. The only remaining non-conventional element of each claim is the discovery that the protein is present in the bodily sample, and the discovery of a natural law cannot by itself provide the requisite inventive concept. *Id.* at 1377; *see also Flook*, 437 U.S. at 593 n.15 (holding that discovery of a natural phenomenon is not patentably novel because the phenomenon has always existed).

We have considered Example 29 and the arguments relating to it, but to the extent that Example 29–Claim 1 is analogous to the claims at issue, *Ariosa* must control. Accordingly, we decline to follow the PTO's Example 29–Claim 1 and conclude that the district court did not err in its consideration of the PTO's subject matter eligibility guidance.

Finally, to the extent Cleveland Clinic argues that the district court should have deferred to the examiner's decision to allow the asserted claims, we have consistently held that any such deference is incorporated into the presumption of patent validity under 35 U.S.C. § 282, *see Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1357 (Fed. Cir. 2013), which the district court recognized.

CONCLUSION

We have considered the rest of the parties' arguments but find them unpersuasive. For the foregoing reasons, we *affirm* the decision of the district court.

AFFIRMED