2017-2508

United States Court Of Appeals for the Federal Circuit

ATHENA DIAGNOSTICS, INC.; OXFORD UNIVERSITY INNOVATION LTD.; MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.,

Plaintiffs/Appellants,

v.

MAYO COLLABORATIVE SERVICES, LLC, d/b/a Mayo Medical Laboratories; MAYO CLINIC,

Defendants/Appellees,

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS, CASE NO. 1:15-CV-40075-IT. THE HONORABLE INDIRA TALWANI, JUDGE PRESIDING

DEFENDANTS-APPELLEES' RESPONSE TO PETITION FOR REHEARING *EN BANC*

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May 7, 2019

CERTIFICATE OF INTEREST

Counsel for Appellees, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories and Mayo Clinic, certifies the following:

1. The full name of every party represented by me is: Mayo Collaborative Services LLC d/b/a Mayo Medical Laboratories and Mayo Clinic

2. The name of the real party in interest (please only include any real party in interest NOT identified in Question 3) represented by me is: Mayo Collaborative Services, LLC

3. Parent corporations and publicly held companies that own 10% or more of the stock in the party: N/A

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (**and who have not or will not enter an appearance in this case**) are:

Fish & Richardson, P.C.: Adam J. Kessel, Kelly Allenspach Del Dotto

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed.

Cir. R. 47.4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary). None.

Dated: May 7, 2019

/s/ *Jonathan E. Singer*

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INTRODUCTION

Appellants' petition for rehearing *en banc* should be denied because the panel's decision invalidating the asserted claims as ineligible faithfully followed *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012) and this Court's applications of it.

The panel majority correctly concluded that the claims "recite only a natural law together with conventional steps to detect the law, [so] they are ineligible under § 101." (Majority at 22.) In so doing, the majority recognized the claims for what they are—a method of diagnosing disease by observing a law of nature using admittedly routine and conventional techniques, and not what Appellants wish them to be—new laboratory techniques or man-made compositions of matter. That is consistent with the '820 patent-in-suit's disclosure. The patent sets out the inventors' discovery of a newfound correlation between certain autoantibodies and disease, and describes as "standard techniques in the art" the exact directives in the claims for observing that correlation in a method of diagnosis. (*Id.* at 4-6.)

The majority's decision invalidating the claims as ineligible properly flows from these undisputed facts, and there is no reason to revisit it *en banc*. The decision did not hold diagnostic methods *per se* ineligible. Nor did it eschew the requirement of considering the challenged claims "as a whole" in the eligibility analysis. And, in fact, another panel of this Court has since cited the majority's decision with approval to invalidate similar claims. *Cleveland Clinic Found. v. True Health Diagnostics, LLC*, No.

2018-1218, 2019 U.S. App. LEXIS 9451, at *12-13, --- F. App'x ---- (Fed. Cir. Apr. 1, 2019) ("*Cleveland Clinic II*"). The majority's decision was correct and Appellants' petition should be denied.

BACKGROUND

Both the '820 patent and the asserted claims describe the inventors' discovery of a natural law and standard methods for observing it.

Myasthenia gravis, or MG, is a neuromuscular disorder characterized by the weakness and rapid fatigue of skeletal muscles. (Majority at 3.) The '820 patent discloses a previously unknown reason why some patients suffer from MG—they generate autoantibodies to a protein called MuSK. (*Id.* at 4.) Having discovered the correlation between those autoantibodies and MG, the inventors teach in the patent and claim diagnosing MG by detecting autoantibodies to MuSK in bodily fluid samples using undisputedly known techniques. (*Id.* at 4-6.)

Claim 9, for example, covers a method for diagnosing disease by performing a standard radioimmunoassay:

> (1) contacting MuSK or an epitope thereof having a ^{125}I[1] label, with bodily fluid;
>
> (2) immunoprecipitating any antibody/MuSK complex; and
>
> (3) monitoring for the label on the complex, wherein the presence of the label indicates the presence of a MuSK-related disorder.

[1] I is the symbol for the element iodine.

(*Id.* at 4-5; *see also id.* at 12.) The specification admits that "'[i]odination and immunoprecipitation are standard techniques in the art.'" (*Id.* at 6 (quoting patent).) It also "states that '[t]he actual steps of detecting autoantibodies in a sample of bodily fluids may be performed in accordance with immunological assay techniques known per se in the art,' such as radioimmunoassays." (*Id.* at 6 (quoting patent).)

The district court granted Mayo's motion to dismiss Appellants' complaint because the asserted claims are ineligible under Section 101. (*Id.* at 7.) The district court found the claims directed to a natural law and only recited steps involving "standard techniques in the art." (*Id.*)

A majority of the panel affirmed the district court. The majority found the claims directed to a natural law, in this case the "correlation between the presence of naturally-occurring MuSK autoantibodies in bodily fluid and MuSK-related neurological diseases like MG." (*Id.* at 9-10; *see also id.* at 9-15.) It also found the claims lacked an inventive concept, including because the steps of the claim, when viewed individually or as an ordered combination, "only require standard techniques to be applied in a standard way." (*Id.* at 16; *see also id.* at 16-18.) Judge Newman dissented from the panel's ruling.

REASONS FOR DENYING THE PETITION

The panel's ineligibility determination and conclusions reached at *Alice* steps one and two square with *Mayo* and this Court's precedent, including *Cleveland Clinic*, *Ariosa*, and *CellzDirect*. The claims cover methods of diagnosis by observing the

natural-law relationship between autoantibodies to MuSK and MuSK-related disorders like MG using undisputedly standard techniques. The claims do not apply the natural law underlying them in an eligible way. They are the exact type of claims that precedent directs are ineligible.

Appellants' contention that the majority erred in finding the claims ineligible raises arguments this Court and the Supreme Court have repeatedly rejected and should do so again here. It is not enough that the inventors were the first to claim a way of diagnosing disease based on a newfound underlying natural cause, or that such a diagnosis can help people. It is not enough that the asserted claims recite a process, or enumerate well-known, concrete steps as opposed to abstract steps. It is not enough that the claimed methods employ a man-made substance. Something more is required, and the asserted claims here offer nothing in that regard.

Appellants have not demonstrated that the majority erred or misapplied controlling precedent of the Supreme Court or this Court. The petition should be denied.

I. The Panel's Step One Analysis Is Sound

A. The Panel Correctly Found the Claims "Directed To" A Natural Law After Considering Them as a Whole

As *Mayo* instructs, the panel was tasked with "determin[ing] whether the claimed processes have transformed the [recited] unpatentable natural laws into

patent-eligible applications of those laws." *Mayo*, 566 U.S. at 72. At *Alice* step one the majority undertook that analysis and correctly determined they did not.

The majority considered the asserted claims as a whole in concluding that they are directed to ineligible subject matter. (Majority at 10 ("The step one 'directed to' inquiry focuses on the claims as a whole.").) First, the majority defined the natural law that undisputedly permeates the claims as the correlation between autoantibodies and disease. (*See* Majority at 9-10.) Next, the majority considered "whether the claimed advance improves upon a technological process or merely an ineligible concept, based on both the written description and the claims." (*Id.* at 10.) The majority acknowledged that the claims "involve both the discovery of a natural law and certain concrete steps to observe its operation." (*Id.* at 12.) After considering those steps, the majority concluded that the claims "are directed to a natural law because the claimed advance was only in the discovery of the natural law," and "the additional recited steps only apply conventional techniques to detect that natural law." (*Id.*)

The majority's conclusion rested foremost on the words of the claims, including the steps recited therein, which it went over in its analysis. (*Id.*) The majority also consulted the specification to confirm the only thing arguably innovative in the claimed methods was the discovery of the underlying natural law. (*Id.* at 12-13.) That was an easy task, given that the specification concedes that the claimed assay techniques were "standard" and "known" in the art. (*Id.* at 12.)

The majority's analysis thus makes clear that it gave proper weight to the claims as a whole at *Alice* step one. Its consultation of the specification as part of the analysis is grounded in this Court's precedent. (*Id.* at 10-11 (collecting cases).) Accordingly, Appellants' complaint that the majority either ignored or glossed over the details in and steps of the claims is unfounded. (*See generally* Petition at 8-13.)

B. The Panel's Step One Conclusion Is Consistent with Supreme Court Precedent and This Court's § 101 Decisions

Section 101 precedent from both the Supreme Court and this Court compels the conclusion that the asserted claims are directed to a law of nature, just as the majority decided.

In *Mayo*, the Supreme Court concluded that claims directed to "relationships between concentrations of certain metabolites [of a thiopurine drug] in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm" were based on "entirely natural processes" and were therefore drawn to a law of nature. *Mayo*, 566 U.S. at 77. This was so even though the claims required the additional action of determining metabolite blood levels, which was "well known in the art." *Id.* at 79. Likewise, the asserted claims here set out the correlation between the presence of a MuSK-related disease and the existence of the naturally occurring MuSK autoantibodies, and recite admittedly known methods to observe that correlation.

This Court's precedent in *Cleveland Clinic* and *Ariosa* illustrate the same principle—when the claim is reciting the observation of a correlation or relationship that is naturally occurring, only uses routine techniques to do so, and does not make any use of that correlation or relationship other than to observe it, then the claim fails step one of the *Alice* analysis. (*See* Majority at 11.) *Cleveland Clinic II*, 2019 U.S. App. LEXIS 9451 at *11-13; *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1361-62 (Fed. Cir. 2017); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376-78 (Fed. Cir. 2015).

In contrast, claims that use a natural relationship to achieve a specific outcome, like the treatment of a disease, or a new laboratory test method, are not simply directed to the natural law and are thus eligible under step one. This has been the case since *Diamond v. Diehr*, 450 U.S. 175 (1981). There, the Supreme Court found eligible claims to a detailed step-by-step method that used the Arrhenius equation to solve a significant industrial problem. The claimed method required continuously monitoring temperature inside a mold and using that data to open the mold only when the rubber was perfectly cured, which amounted to "a result heretofore unknown in the art." *Id.* at 177-79, 184, 193 n.15. The method narrowly confined use of the Arrhenius equation in a "process which, when considered as a whole, is performing a function which the patent laws were designed to protect"—transforming raw rubber into precision molded products. *Id.* at 184, 192.

Put another way, the *Diehr* claims used a natural law to achieve a specific outcome; they were not simply directed to the equation itself. Not so for the asserted claims, whose end result is merely observation of the natural correlation between antibodies to MuSK and disease and not a truly new outcome or application of the correlation.

In this regard, the asserted claims are also unlike those held eligible in *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016). The *CellzDirect* claims recited "[a] method of producing a desired preparation of multi-cryopreserved hepatocytes" and set out steps required to produce such a preparation. *Id.* at 1046. Though the *CellzDirect* claims included a newfound natural law, cells' capability of surviving multiple freeze-thaw cycles, the "end result" of the claims was not observing or detecting that natural law, but rather using it in a "new and improved way of preserving hepatocyte cells for later use." *Id.* at 1047-48. Appellants' claims do not recite a comparable outcome or result.

This Court's recent decision in *Vanda* also illustrates the difference between ineligible claims like those in this case, which ***do not apply*** the natural law, and eligible claims that ***apply*** the natural law. *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018). The claims in *Vanda* were directed to treatment of schizophrenia through administration of particular ranges of a drug (iloperidone) that were determined based on a natural relationship (metabolism of iloperidone by the CYP2D6 enzyme), so as to reduce the risk of a potential heart issue (QTc

prolongation) based on the dose administered. *Id.* at 1121. The Court found the claims eligible because, although they involved the "relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation," they "claimed an ***application*** of that relationship" by reciting a treatment method with particular requirements as to dosing based on the results of an assay. *Id.* at 1135 (emphasis added).

The *Vanda* claims did not remain open ended as to the application of the relationship, as the claims in this case do, and the claims in *Mayo* did. Rather, they applied it to require specific dosing of the drug, creating "'a new way of using an existing drug' that is safer for patients because it reduces the risk of QTc prolongation." *Id.* at 1135 (quoting *Mayo*, 566 U.S. at 87).

Similarly, in *Endo*, the claims were not directed to an ineligible concept because they applied a natural law to claim a method of treating a particular condition using particular drug doses. *Endo Pharms. Inc. v. Teva Pharms. USA, Inc.*, --- F.3d ---, No. 2017-1420, 2019 U.S. App. LEXIS 9189 (Fed. Cir. Mar. 28, 2019). Like *CellzDirect*, and unlike here, the end result of the *Endo* claims was not simply an observation or detection of a natural law. *See id.* at *10-15; *see also Nat. Alts. Int'l ,Inc. v. Creative Compounds, LLC*, 918 F.3d 1338, 1345-47 (Fed. Cir. 2019) (finding at the 12(c) stage claims directed to a treatment method with an effective and unnatural amount of a natural substance were more than an observation of a natural law and there was no admission in the specification that the recited method steps were conventional).

Finally, *Cleveland Clinic II* demonstrates the panel's step one analysis is correct. There, as here, a panel invalidated methods for identifying in a patient's bodily sample a naturally occurring substance that correlated to disease state by using a routine immunoassay. *Cleveland Clinic II*, 2019 U.S. App. LEXIS 9451, at *6-7, 11-12. That panel also rejected as "overly superficial" the patentee's attempt to recast its claims as directed to new lab techniques and not a natural law, just as the panel did here. *Id. at* *11-12. (*See* Majority at 9, 13.)

This Court has recognized that, "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," it must be "mindful of the need for consistent application of our case law." *Cleveland Clinic II*, 2019 U.S. App. LEXIS 9451, at *16-17. The cases above do just that, and set out the key dividing lines for what is eligible and what is not. The majority's decision here is yet another consistent application of the Section 101 case law to Appellants' claims.[2]

[2] Amici's professed concern regarding standards for applying the *Mayo/Alice* step one analysis is not relevant to this case. There can be no reasonable dispute in this case that the claims are designed to observe or detect the association between the naturally occurring autoantibodies to MuSK and the MuSK-related disease. That is a natural relationship. While a future case may present itself to elucidate further the standard for *Mayo/Alice* step one in the area of diagnostics, this case does not require such elaboration.

C. The Majority Correctly Rejected Appellants' Plea for Eligibility Based on the Claims' Recitation of Man-Made Reagents and Lack of Complete Preemption

As the above precedent shows, the mere fact that claims are written as covering methods or processes does not make them *per se* eligible. The same is true for claims that recite the use of man-made materials, including the claims at issue here. And that has long been the case. (Majority at 14 ("We thus reaffirm that use of a man-made molecule in a method claim employing standard techniques to detect or observe a natural law may still leave the claim directed to a natural law.").)

Indeed, the methods recited in *Mayo* involved the administration of man-made drugs, and that did not make those methods eligible. *Mayo*, 566 U.S. at 74-75. Nor did the use of man-made, synthetic DNA probes make the methods claimed in *BRCA1* or *Ariosa* patent eligible. *See In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 765 (Fed. Cir. 2014) (claims to methods involving hybridizing a synthetic DNA probe not eligible); *Ariosa*, 788 F.3d at 1373-74, 1378 (claim involving use of a man-made probe to detect a naturally-occurring substance not eligible). Thus, the fact that the asserted claims here involve the use of certain man-made compounds—*i.e.*, labeled MuSK—does not automatically render them patent eligible, as the panel properly found. (Majority at 14.)

Appellants attempt to distinguish these cases by relying on the alleged "novel" nature of labeled MuSK, but this argument is belied by the admission in the specification that iodination (adding an Iodine label like 125I) is a "standard"

technique. (Majority at 5, 6.) Appending a label to MuSK by a conventional technique does not sufficiently transform the asserted claims such that they are directed to something more than the recited natural correlation. (*See id.* at 14.) Nor does appending the label by a conventional technique make the MuSK markedly different than natural MuSK. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 594-95 (2013) (holding cDNA patent eligible not because it was man-made, but because it was markedly different from what existed in nature).

This Court's finding in *AMP* that method claim 20 was patent eligible does not, and cannot, suggest that all methods involving a man-made component are patent eligible, as Appellants wish. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1335-37 (Fed. Cir. 2012). Rather, claim 20 required "growing host cells transformed with an altered BRCA1 gene," a new and novel step that was part of a new laboratory method for screening certain therapeutic agents. *Id.* at 1336. *AMP* clam 20 is more akin to the novel laboratory methods recited in the eligible claims of *CellzDirect* than it is to the asserted claims here, which append admittedly conventional steps involving a man-made component to a claim directed to the natural correlation between the presence of MuSK antibodies and certain neurological disorders.

Nor does Appellants' preemption argument, which the majority correctly addressed (at 13), save their claims. As this Court has explained, "[w]here a patent's claims are deemed only to disclose patent ineligible subject matter under the *Mayo*

framework, as they are in this case, preemption concerns are fully addressed and made moot." *Ariosa*, 788 F.3d at 1379; *see also id.* ("[Q]uestions on preemption are inherent in and resolved by the § 101 analysis.").

And because the asserted claims, like those in *Mayo*, "tie up the doctor's subsequent treatment decision" by covering any use of the correlation, rather than applying it in a specific way, they fail the preemption standard in any event. *Vanda*, 887 F.3d at 1135 (quoting *Mayo*, 566 U.S. at 86).

II. The Panel Correctly Found that the Well-Known Steps Recited in the Claim Do Not Impart an Inventive Concept to the Natural Correlation

At step two, the majority correctly determined that the claims lack an inventive concept because the recited method steps, standing alone or viewed as ordered combination, employ assay techniques that were undisputedly "standard" and "known" when the inventors filed their patent application. Indeed, as the majority notes, the additional process steps claimed for detecting autoantibodies to MuSK are, as described in the '820 patent and admitted by Appellants, "known per se in the art" and "standard techniques in the art." (Appx44 (3:33-35, 3:66-4:12); Appx318-319.) (Majority at 15-17.)

Though rejected by the majority, Appellants continue to argue that, because the claimed assays were allegedly the "first ever for detecting MuSK autoantibodies and diagnosing MuSK by reference to them," that the claims satisfy *Alice* step two. (*See*

Majority at 17-18.) That argument relies on the natural correlation itself as the innovation, which the Supreme Court and this Court's precedent forbid.

The novelty of a law of nature cannot supply an inventive concept; "instead, the application must provide something inventive, beyond mere 'well-understood, routine, conventional activity.'" *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016) (quoting *Mayo*, 566 U.S. at 73). The discovery of the BRCA1 and BRCA2 genes and test for them was surely a contribution to medicine, but the isolated genes were not patentable. *Myriad*, 569 U.S. at 591 ("Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry."). And the discovery that that "detecting cffDNA in maternal plasma or serum that before was discarded as waste material is a positive and valuable contribution to science," but still "f[e]ll short of statutory patentable subject matter." *Ariosa*, 788 F.3d at 1380.

The same is true here. Even if the inventors were the first to recognize the correlation between MuSK autoantibodies and certain neurological diseases, that does not automatically mean claims making use of that natural correlation are patentable.

Appellants attempt to make an analogy to *CellzDirect*, which found eligible claims to a new method of preparing cryopreserved hepatocytes to allow for a higher percentage that are viable at the end of the process. But Appellants did not claim a new laboratory method as in *CellzDirect*; instead, they wrote claims directed at the correlation that use conventional steps to observe that correlation. Although the

individual steps in *CellzDirect* had been performed before, the claims put them together in a new way—adding a second freeze cycle when the art taught to use one—to improve on prior results. *CellzDirect*, 827 F.3d at 1051. Appellants' claims do nothing of the sort.

CONCLUSION

The panel's decision invalidating the asserted claims as ineligible properly applied the two-step *Alice* framework in light of precedent, and the full Court need not reexamine it. Appellants' petition should be denied.

Dated: May 7, 2019

Respectfully submitted,

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CERTIFICATE OF SERVICE AND FILING

I hereby certify that I electronically filed the foregoing document with the Clerk of the Court of the United States Court of Appeal for the Federal Circuit by using the Court's CM/ECF filing system.

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/s/ Jonathan E. Singer
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CERTIFICATE OF COMPLIANCE

The undersigned attorney certifies that this brief complies with the type-volume limitation set forth in Fed. R. App. P. 32(a)(7)(B)(ii). The relevant portions of the brief, including all footnotes, contain 3,571 words as determined by Microsoft Word.

Dated: May 7, 2019

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