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Prometheus Rebound: Diagnostics, Nature, and Mathematical Algorithms

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The Supreme Court's decision last Term in Mayo v. Prometheus *left considerable uncertainty as to the boundaries of patentable subject matter for molecular diagnostic inventions. First, the Court took an expansive approach to what counts as an unpatentable natural law by applying that term to the relationship set forth in the challenged patent between a patient's levels of a drug metabolite and the indication of a need to adjust the patient's drug dosage. And second, in evaluating whether the patent claims add enough to this unpatentable natural law to be patent eligible, the Court did not consult precedents concerning the patentability of claims involving natural laws and natural products. Instead, it turned to two seemingly inconsistent decisions that reached opposing conclusions concerning the patent eligibility of industrial methods that used mathematical algorithms. The Court's analysis invites challenges to many issued patents, while offering little guidance for resolving them. This Term, in the* Association for Molecular Pathology *case, the Court has another opportunity to clarify the meaning of its exclusion of natural phenomena from patent eligibility.*

The promise of personalized medicine cannot be delivered without new precision diagnostic tools for tailoring treatment interventions to the needs of individual patients. The recent decision by the Supreme Court in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*,[1] raises doubts about the eligibility of these diagnostic tools for patent protection and calls into question the validity of many previously issued patents. In the *Association for Molecular*

1. No. 10-1150 (U.S. Mar. 20, 2012), http://www.supremecourt.gov/opinions/11pdf/10-1150.pdf (to be reported at 132 S. Ct. 1289).

Pathology case,[2] the Court has an opportunity to clarify the applicable rules by identifying the kinds of diagnostic inventions that fall within patentable subject matter as well as those that are excluded from patent protection. Otherwise, the federal courts are likely to face a stream of appeals on patentable subject matter in the years ahead.

The patent in *Mayo v. Prometheus* claimed a method of optimizing the dosage of thiopurine drugs for treatment of immune-mediated gastrointestinal disorders (such as irritable bowel syndrome). The method involved comparing a patient's levels of two drug metabolites with reference values specified in the patent.[3] Observed levels below certain values would indicate a need to raise the dosage, while observed levels above different values would indicate a need to lower it.[4] The Supreme Court thought that the patent impermissibly claimed laws of nature, "namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm."[5] Other steps in the process recited in the claim (such as administering a thiopurine drug to a patient or determining the patient's levels of drug metabolites) consisted of "well-understood, routine, conventional activity previously engaged in by scientists in the field."[6] In the Court's view, those process steps did not add enough to the natural laws to classify the claim as a patent-eligible *application* of the natural laws rather than an impermissible "patent upon the natural law itself."[7]

Two key moves in the Court's analysis cast a shadow of uncertainty over the validity of patents on diagnostic inventions. First, the Court took an expansive approach to what counts as a "law of nature" by attaching that label to the relationship set forth in the patent between a patient's drug metabolite levels and the indication of a need to adjust the patient's drug dosage. Because "laws of nature" are not patentable, the Court asked "whether the claims do

2. Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (*AMP II*), 689 F. 3d 1303 (Fed. Cir. 2012), *cert. granted sub nom.* Ass'n for Molecular Pathology v. Myriad Genetics, 133 S. Ct. 694 (2012) (No. 12-398).

3. *Mayo*, slip op. at 4-5.

4. *Id.*

5. *Id.* at 8. Patent claims define the boundaries of a patent right in roughly the same way that "metes and bounds" define the boundaries of rights in real property. *See* 35 U.S.C. § 112 (2006) ("The [patent] specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.").

6. *Mayo*, slip op. at 2.

7. *Id.* at 3.

significantly more than simply describe these natural relations."[8] Second, to answer this question, the Court did not consider prior cases on patents that involved natural laws and natural products, but turned instead to two prior cases involving computer-implemented industrial processes—*Parker v. Flook*[9] and *Diamond v. Diehr*[10]—as the "the cases most directly on point."[11] Those two cases reach opposing conclusions on similar facts and are difficult to reconcile, as Justice Stevens observed in dissent in *Diehr*.[12] Taken together, the Court's twin moves invite patent challenges while offering only vague guidance for resolving them.

The Court's characterization of the relationship between the observed metabolite levels and the need to adjust drug dosage as a "natural law" is puzzling. The Court acknowledged that it takes human action to administer a thiopurine drug to a patient and thereby trigger a "manifestation of this relation in a particular person."[13] But the Court nonetheless asserted that "the relation itself exists in principle apart from any human action" because thiopurine compounds are metabolized by the body according to "entirely natural processes."[14]

Perhaps what the Court meant was that a patient's reaction to a drug is controlled by biological processes that follow certain natural laws. The same is true of any method of using a drug in medical treatment, and yet many decisions have upheld the patent eligibility of such methods. Indeed, as the Court noted, "a typical patent on . . . a new way of using an existing drug" is patentable on the ground that it is limited to "particular applications of [natural] laws" rather than an impermissible patent on the natural law itself.[15] The Court did not explain why a method of treatment that makes use of a patient's biological response to a drug is a patent-eligible application of a natural law, while a diagnostic method that makes use of this same biological response is not.

8. *Id*. at 8.

9. 437 U.S. 584 (1978).

10. 450 U.S. 175 (1981).

11. *Mayo*, slip op. at 1.

12. 450 U.S. at 193 (Stevens, J., dissenting); *see also* Donald S. Chisum, *The Patentability of Algorithms*, 47 U. PITT. L. REV. 959, 961 (1986) (criticizing the "awkward distinctions and seemingly irreconcilable results of the case law" on the patent eligibility of computer-implemented inventions).

13. *Mayo*, slip op. at 8.

14. *Id*.

15. *Id*. at 18.

The Court may see the diagnostic method as involving too little value added by humans beyond the observation of a natural biological phenomenon to qualify as a human invention. However, even if natural laws determine a patient's response to drug therapy, nature does not determine when those consequences indicate a need to raise or lower the drug dosage. Nature does not specify when the miseries of irritable bowel syndrome outweigh the risks of myelosuppression and liver toxicity from the use of thiopurine drugs. At most, nature supplies the raw data, while human judgment is necessary to interpret the data and to guide medical intervention. The technological contribution of this particular invention is to quantify and systematize that judgment to improve treatment. Other methods are possible, and they might do a better or worse job of optimizing treatment. Indeed, after using the Prometheus Laboratories invention under license for a time, the defendant, Mayo Collaborative Services, decided to change the metabolite values that it thought called for adjusting the dosage (although the change was not enough to avoid infringement liability if the claims had been upheld). Those different views about what drug metabolite levels are problematic show that the levels recited in the claims represent a human technological choice that goes beyond mere recital of a natural law.

Many prior cases have struggled with the distinction between patent-eligible human inventions and patent-ineligible natural products and phenomena.[16] Rather than turning to those cases for guidance, the Court made its second puzzling move: it turned to two decisions from 1978 and 1981 concerning the patentability of methods that recite "mathematical algorithms" to resolve the patent eligibility of claims that recite "laws of nature."

Parker v. Flook held that a method using a mathematical algorithm to update alarm limits for process variables in a catalytic conversion process was *not* patentable subject matter.[17] On the other hand, *Diamond v. Diehr* held that a method of operating a rubber molding press using a mathematical algorithm to repeatedly recalculate the cure time *was* patentable subject matter.[18] To the *Diehr* majority, the relevant distinction was that Flook had sought to patent a

16. *See, e.g.*, Diamond v. Chakrabarty, 447 U.S. 303 (1980) (finding that bacteria transformed to incorporate multiple naturally occurring DNA plasmids were patent eligible); Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127 (1948) (finding that a mixed culture of root-nodule bacteria selected for the property of not inhibiting one another's effectiveness was not patent eligible); Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156 (4th Cir. 1958) (finding that a purified Vitamin B12 composition that was clinically superior to the product in its natural state was patent eligible).

17. 437 U.S. 584, 594 (1978).

18. 450 U.S. 175, 192-93 (1981).

method of computing a number, whereas Diehr sought to patent a method of curing synthetic rubber.[19] But upon closer examination the primary difference seemed to be a matter of claim-drafting, as Justice Stevens pointedly noted in his dissent in *Diehr*.[20]

The Court in *Mayo v. Prometheus* identified a different distinction in its own paraphrase of these inconsistent holdings, explaining that the patent-ineligible claim in *Flook* merely recited a mathematical formula—"the equivalent of a natural law"[21]—followed by a bare instruction to "apply it."[22] By contrast, the patent-eligible claim in *Diehr* recited additional steps that "apparently added . . . something that in terms of patent law's objectives had significance" and "transformed the process into an inventive application of the formula."[23] The claims in *Mayo v. Prometheus* struck the Court as tantamount to a recital of a natural law followed by a bare instruction to "apply it" because, once the Court sets aside as "natural laws" the metabolite levels specified in the claims, the other steps "add nothing specific to the laws of nature other than what is well-understood, routine, conventional activity, previously engaged in by those in the field."[24] But that observation does not explain the distinction between *Diehr* and *Flook*: both of those cases involved methods that applied new mathematical algorithms to familiar process steps.[25] Moreover, the Court in *Diehr* explicitly rejected the approach of excluding conventional process steps

19. *Id.* at 186-87.

20. *Id.* at 209 (Stevens, J., dissenting) ("[Diehr's] method of updating the curing time calculation is strikingly reminiscent of the method of updating alarm limits that Dale Flook sought to patent. . . . In *Flook*, the digital computer repetitively recalculated the 'alarm limit'—a number that might signal the need to terminate or modify the catalytic conversion process; in this case, the digital computer repetitively recalculates the correct curing time—a number that signals the time when the synthetic rubber molding press should open. The essence of the claimed discovery in both cases was an algorithm that could be programmed on a digital computer.").

21. *See Mayo*, slip op. at 11.

22. *Id.* at 3.

23. *Id*. at 12.

24. *Id*. at 13.

25. *See Diehr*, 450 U.S. at 177; *Parker v. Flook*, 437 U.S. 584, 585 (1978); *see also Diehr*, 450 U.S. at 208 (Stevens, J., dissenting) ("[T]he Patent and Trademark Office Board of Appeals expressly found that 'the only difference between the conventional methods of operating a molding press and that claimed in [the] application rests in those steps of the claims that relate to the calculation incident to the solution of the mathematical problem or formula used to control the mold heater and the automatic opening of the press.' This finding was not disturbed by the Court of Customs and Patent Appeals and is clearly correct." (second alteration in original) (footnote omitted) (citing *In re* Diehr, 602 F.2d 982, 984 (C.C.P.A. 1979), which also quotes the board's opinion)).

from consideration in determining whether a claim recites patentable subject matter.[26] The Court in *Mayo v. Prometheus* did not make a serious effort to compare the additional steps in the claims before it to those in *Flook* and *Diehr*. Instead, it left future courts to puzzle over how far *Mayo v. Prometheus* has reanimated these ghosts from the past and how to resolve their inconsistencies.

In its day, *Diehr* marked a turning point between an earlier era of parsimonious patent protection for computer-implemented inventions and a new era of expanded patent eligibility.[27] Subsequent case law offers little guidance in resolving the inconsistency between the two cases because, at the time, *Diehr* functioned more as a claim-drafting guide to avoid the outcome in *Flook* than as a counterexample to explain the limitations of *Flook*.

By returning to the elusive distinction between *Flook* and *Diehr* after more than three decades and assigning to those cases the new task of discerning the boundaries of patent eligibility for all claims that recite "laws of nature," the Court in *Mayo v. Prometheus* seemed to be on a new mission. Rather than restricting the reach of judicial limitations on patentable subject matter by affirming the claims before it, the Court appeared to be narrowing the boundaries of patentable subject matter in a field that has long taken for granted the availability of patent protection for its innovations. By broadly defining "laws of nature" to include human interpretation of biological responses to medical interventions, the Court seemed to call into question the validity of many previously allowed claims, inviting more litigation contesting patentable subject matter and drawing courts into the murky waters of *Diehr* and *Flook*.

The Court of Appeals for the Federal Circuit declined to step into those murky waters when it considered the patent eligibility of advances in medical diagnostics in *Association for Molecular Pathology v. U.S. Patent & Trademark Office*.[28] That case challenged the patent eligibility of claims to DNA sequences

26. *Diehr*, 450 U.S. at 188-89 (majority opinion) ("It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known . . . . The 'novelty' of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within . . . possibly patentable subject matter.").

27. *See* Maureen A. O'Rourke, *The Story of* Diamond v. Diehr*: Toward Patenting Software*, *in* INTELLECTUAL PROPERTY STORIES 194, 212-18 (Jane C. Ginsburg & Rochelle Cooper Dreyfuss eds., 2006).

28. Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (*AMP II*), 689 F.3d 1303, 1333-37 (Fed. Cir. 2012), *cert. granted sub nom.* Ass'n for Molecular Pathology v. Myriad Genetics, 133 S. Ct. 694 (2012) (No. 12-398).

for the BRCA1 and BRCA2 genes associated with breast cancer susceptibility as well as claims to diagnostic methods and drug-screening methods that make use of these sequences. The Federal Circuit has ruled on the case twice, once[29] before the Supreme Court's decision in *Mayo v. Prometheus* and again[30] on remand for reconsideration in light of that decision. Each member of the panel wrote separately each time, presenting a range of competing views to guide the Court in its consideration of the issues presented.

The Federal Circuit panel was divided on the patent eligibility of the claims to the BRCA1 and BRCA2 DNA molecules, the most prominent issue in the case and the only issue on which the Court has granted certiorari.[31] Yet each panel member joined Judge Lourie's analysis of the method claims, unanimously holding that (1) claims to diagnostic methods of "comparing" or "analyzing" DNA sequences from a tissue sample with reference sequences were not patent eligible because they are only "abstract mental steps" and that (2) claims to drug-screening methods that compare the growth rate of cells transformed with an altered BRCA1 gene in the presence or absence of a potential cancer therapy were patent-eligible chemical processes.[32] One might have expected the recent decision of the Supreme Court in *Mayo v. Prometheus* to play a significant role in the Federal Circuit's analysis of the method claims—especially given that the Court explicitly remanded for reconsideration in light of that decision—yet its teachings had little apparent impact on the analysis of the claims. Judge Lourie acknowledged that his analysis followed the Court's *holding* in *Mayo v. Prometheus*, but not its *reasoning*.[33] He did not seek to resolve whether the diagnostic method claims covered "laws of nature," instead holding the claims invalid because "comparing" or "analyzing" two gene sequences is an abstract mental process.[34] In upholding the patent eligibility of the drug-screening method claims, Judge Lourie focused on the fact that the method used human-modified bacteria that had been transformed with an altered BRCA1 gene. He considered it irrelevant to the patentable-subject-matter analysis that the other process steps of comparing growth rates

29. Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (*AMP I*), 653 F.3d 1329, 1355-58 (Fed. Cir. 2011), *vacated sub nom.* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 132 S. Ct. 1794 (2012) (No. 11-725).

30. *AMP II*, 689 F.3d 1303.

31. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 694, 695 (2012) (mem.).

32. *AMP I*, 653 F.3d at 1355-58.

33. *AMP II*, 689 F.3d at 1333.

34. *Id.* at 1333-34.

in the cells were conventional.[35] Responding to the Court's emphasis in *Mayo v. Prometheus* on the insufficiency of conventional steps to establish patentable subject matter, Judge Lourie noted that most chemical processes involve the use of known process steps and reactions and that this should not defeat patent eligibility where the process makes use of novel materials that are not naturally occurring.[36] The Federal Circuit's analysis of those claims was straightforward, although it did not even purport to follow the reasoning of *Mayo v. Prometheus*. On the other hand, although the Federal Circuit's reasoning was different, its ultimate decision on the patent eligibility of the method claims was broadly consistent with the Court's reinforcement of traditional exclusions from patentable subject matter. The Supreme Court declined to review the Federal Circuit's decision on the method claims, granting certiorari solely on the question whether human genes are patentable.[37] Perhaps the Court's acquiescence in the Federal Circuit's alternative analytical approach indicates that it is willing to defer to that court's expertise in patent matters so long as it seems to be vigorously policing the subject-matter boundaries of the patent system.

It remains to be seen how the Court will review the Federal Circuit panel's split decision affirming the patent eligibility of claims to isolated DNA molecules. The three separate opinions of the panel members on this question found limited guidance in the Supreme Court's decision in *Mayo v. Prometheus*.[38] Each opinion drew primarily upon prior cases on the exclusion for natural products and processes that the Court had largely ignored.[39] Those cases are hardly a model of consistency and clarity, yet they provide a more coherent baseline than the cases on the exclusion for mathematical algorithms. In reviewing the latest disposition of *Association for Molecular Pathology*, the Supreme Court could begin to restore predictability to the rules of patentable subject matter by setting aside *Parker v. Flook* and *Diamond v. Diehr* and

35. *Id.* at 1336.

36. *Id.* at 1325.

37. *See* Ass'n for Molecular Pathology v. Myriad Genetics, 133 S. Ct. 694 (2012) (No. 12-398).

38. *See, e.g.*, *AMP II*, 689 F.3d at 1325 (Lourie, J.) ("*Mayo* does not control the question of patent-eligibility of such claims. They are compositions of matter, expressly authorized as suitable patent-eligible subject matter in § 101."); *id.* at 1340 (Moore, J., concurring in part) ("*Prometheus* did not, however, overturn *Funk Brothers* or *Chakrabarty*; cases clearly more analogous to the one before us."); *cf. id.* at 1354 (Bryson, J., concurring in part and dissenting in part) ("The Supreme Court's recent decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* does not decide this case, but the Court's analysis is nonetheless instructive." (citation omitted)).

39. *See, e.g.*, cases cited *supra* note 16.

turning instead to these more pertinent authorities on the patentability of natural products and processes.

Perhaps the most important contribution of *Diamond v. Diehr* to the jurisprudence of patentable subject matter was that for the first time the Court identified claims to computer-implemented inventions that it considered patent eligible, thereby providing patent applicants with a model for patenting computer-implemented inventions properly. The Court now has an opportunity to make a similar contribution to the understanding of patentable subject matter for diagnostic inventions in *Association for Molecular Pathology*. The plaintiffs in that case have challenged the validity of multiple claims to DNA inventions that reflect different approaches to defining what constitutes a patentable invention. The three opinions from the panel offer distinct approaches to the patent-eligibility issues raised by these different claims, providing the Court with an unusually rich record for clarifying the distinction between unpatentable natural phenomena and patentable human inventions. If the Court can identify claims that it considers patent eligible, it will bring greater clarity to the issue than if it only identifies claims that lie outside the boundaries of patentable subject matter. In the absence of such clarity, the Court can expect many more appeals as the Patent and Trademark Office and the courts try to determine what the Supreme Court will deem patentable.

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