Intellectual Property ADVISORY

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Supreme Court Invalidates Patents for Certain Personalized Medicine Processes as Not Directed to Patentable Subject Matter

Summary

On March 20, 2012, the U.S. Supreme Court issued a unanimous decision in *Mayo Collaborative Services, et al. v. Prometheus Laboratories, Inc.*,[1] reversing the Federal Circuit and holding that Prometheus Laboratories, Inc.'s ("Prometheus") personalized medicine dosing processes were ineligible for patent protection under 35 U.S.C. § 101. The Court held that "[i]f a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." Slip Op., at 8-9. The Court ruled that Prometheus's processes were directed essentially to laws of nature, and the claims did not add enough to qualify them as patent-eligible processes that *apply* natural laws.

Background of the Case

The Prometheus patents—U.S. Patent Nos. 6,355,623 and 6,680,302—claim a method of optimizing therapeutic efficacy and reducing toxicity associated with drug treatments for a variety of auto-immune related disorders. According to the patents, thiopurine drugs are useful in the treatment of certain auto-immune diseases, such as Crohn's disease and ulcerative colitis. When a patient ingests a thiopurine compound, the patient's body metabolizes the compound, causing metabolites to form in the patient's bloodstream. According to the patents, certain patients metabolize thiopurine drugs less effectively than other patients, and doctors faced difficulty in determining whether a given dose of the drug was too high (risking harmful toxicity) or too low (rendering the drug ineffective).

The patents at issue solved this problem by allowing a doctor to determine whether a given dose was effective for an individual patient. Claim 1 of the '623 patent was deemed representative and describes one of the claimed processes as follows:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
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> a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

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[1] *Mayo Collaborative Services v. Prometheus Labs., Inc.*, No. 10-1150, 566 U.S. ___ (2012). Slip opinion available at http://www.supremecourt.gov/opinions/11pdf/10-1150.pdf.

b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

As claimed, the method recites two steps: administering the drug and determining the level of the relevant metabolites in the patient's blood. Performing those steps will indicate a need either to increase or to decrease the dosage given to the patient. Importantly, the claim language does not require that the physician change the dosage or do anything in response to the administering and determining steps. Indeed, the Supreme Court viewed the claims' "wherein" clauses as "simply tell[ing] a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient." Slip Op., at 9.

Prometheus is the sole and exclusive licensee of the patents at issue. Prometheus marketed and sold a diagnostic test that used the technology covered by the patented methods. Mayo Collaborative Services (d/b/a Mayo Medical Laboratories) and Mayo Clinic Rochester (collectively, "Mayo") initially had purchased and used Prometheus's test, but in 2004, Mayo announced that it intended to begin using and selling to other hospitals its own test. Mayo's test measured the same metabolites as Prometheus's test, but Mayo's test used different levels for determining efficacy or toxicity.

Prometheus sued Mayo for patent infringement in the U.S. District Court for the Southern District of California. The district court found that Mayo's test infringed at least one claim of the patents, but it subsequently ruled as a matter of law that the patent claims were invalid under § 101 because the claims were directed to correlations that were natural phenomena and thus not patentable.

On appeal, the Federal Circuit reversed. The Federal Circuit held that the claimed method steps of administering the drug and determining the resulting metabolite level require the transformation of blood taken from the human body. As a result, the Federal Circuit held that the claims met the "machine or transformation test" that was then in effect, meaning the claims were directed to patentable subject matter under § 101. Mayo petitioned the Supreme Court for certiorari, which the Court granted. The Supreme Court then decided *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), which clarified that the "machine or transformation test" is not the sole, definitive test for determining the patent eligibility of a process under § 101, but only an important and useful clue. The Court then vacated the Federal Circuit's *Prometheus* decision and remanded the case for reconsideration in light of *Bilski*.

On remand, the Federal Circuit again held that Prometheus's claims were patent-eligible under § 101. The Federal Circuit stated that, in light of *Bilski*, the case turned on "whether Prometheus's asserted claims are drawn to a natural phenomenon, the patenting of which would entirely preempt its use . . . , or whether the claims are drawn only to a particular application of that phenomenon . . . ." The court concluded that Prometheus's claims were drawn to the latter and thus were eligible for patenting. In the Federal Circuit's view, the claims "recite a patent-eligible application of naturally occurring correlations between metabolite levels and efficacy or toxicity, and thus do not wholly preempt all uses of the recited correlations." The Federal Circuit deemed important that "the claims recite specific treatment steps, not just the correlations themselves."

After the Federal Circuit reaffirmed Prometheus's claims, Mayo again petitioned the Supreme Court for certiorari, which the Court again granted.

The Supreme Court's Opinion

Justice Breyer wrote for a unanimous Court, reversing the Federal Circuit.[2] The Court framed the patent-eligibility of Prometheus's claims under § 101 as dependent on "whether the claims do significantly more than simply describe [certain] natural relations. To put the matter more precisely, do the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?" Slip Op., at 8 (emphasis in original). The Court answered this question in the negative. In so ruling, the Court recognized that the steps recited in the claims "are not themselves natural laws but neither are they sufficient to transform the nature of the claim." *Id*. at 9. The Court deemed the claimed combination of steps as amounting "to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients." *Id*. at 10.

The Court supported its decision based on its precedents, focusing on *Parker v. Flook*, 437 U.S. 584 (1978), and *Diamond v. Diehr*, 450 U.S. 175 (1981). In favorably comparing the instant claims with those of *Flook* (held not patentable) while distinguishing those of *Diehr* (held patent-eligible), the Court stated that the limitations in Prometheus's claims amount to instructions that "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." Slip Op., at 13. This statement, and others found throughout the Court's opinion, suggest possible conflation of an analysis of patent-eligibility under § 101 with analyses of novelty and obviousness under §§ 102 and 103. The Court even stated that "in evaluating the significance of additional steps, the § 101 patent-eligibility inquiry and, say, the § 102 novelty inquiry might sometimes overlap." *Id*. at 21.

The Court ruled, however, that an analysis of patentability under §§ 102, 103 and 112 (written description) does not supplant a § 101 analysis, as the federal government had proposed in its amicus brief. The government contended that these later sections of the Patent Act could perform the screening function served by § 101, suggesting that the claims in this case would likely fail for lack of novelty under § 102. The Court rejected the approach, stating that it "would make the 'law of nature' exception to § 101 a dead letter." Slip Op., at 21. The Court explained that a newly discovered law of nature might be novel and nonobvious, but nevertheless should be clearly excluded from patent-eligibility under § 101. Moreover, if the courts were to treat all laws of nature as prior art, then, at least in theory, this could "'make all inventions unpatentable because all inventions can be reduced to underlying principles of nature which, once known, make their implementation obvious.'" *Id*. at 21-22 (quoting *Diehr*, 450 U.S. at 189, n.12).

As part of its analysis, the Court repeated its "concern that patent law not inhibit further discovery by improperly tying up the future use of laws of nature." Slip Op., at 16. The danger is that patents will tie up the use of newly discovered laws and principles of nature, thus inhibiting future innovation premised upon them. The Court explained that this danger "becomes acute when a patented process amounts to no more than an instruction to 'apply the natural law,' or otherwise forecloses more future invention than the underlying discovery could

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[2] Justice Breyer also penned the dissent upon the Supreme Court's dismissal of the writ of certiorari in *Laboratory Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 138 (2006), as improvidently granted. In his dissent, Justice Breyer addressed claims that, somewhat analogous to the claims at issue in *Prometheus*, were directed to a process for using any test to measure the level of an amino acid called homocysteine in order to diagnose possible vitamin deficiencies. Perhaps foreshadowing the result in *Prometheus*, Justice Breyer stated in *LabCorp* that "[t]here can be little doubt that the correlation between homocysteine and vitamin deficiency set forth in Claim 13 is a natural phenomenon." *Id*. at 135 (Breyer, J., dissenting).

reasonably justify." *Id*. at 17. According to the Court, this concern, while apparent for fundamental laws such as Newton's discovery of the law of gravity, holds equally true for narrow laws of nature with limited applications, such as those at issue in this case. *See id*. at 18, 20 ("the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like").

The Court also rejected the reasoning offered by the Federal Circuit—namely, that the claims here at issue involve a transformation of the human body by administering a thiopurine drug and a transformation of a patient's blood by analyzing it to determine metabolite levels. *Id*. at 19. The Court ruled that the first of these transformations "is irrelevant" because the "administering" step of the claims "simply helps to pick out the group of individuals who are likely interested in applying the law of nature." The Court treated the "determining" step equally, stating that it "could be satisfied without transforming the blood, should science develop a totally different system for determining metabolite levels that did not involve such a transformation." *Id*. The Court thus remarked that although the "machine or transformation" test is an "important and useful clue" to patentability, the Court has "neither said nor implied that the test trumps the 'law of nature' exclusion." *Id*. Applying these principles, the Court held the Prometheus claims invalid under § 101.[3]

Discussion

Prometheus leaves many questions unanswered. In particular, how does one determine whether a claim adds "enough" to transform an unpatentable statement of a natural law into a patent-eligible application of a natural law? *Prometheus* gives little guidance beyond the inexact directive that a recitation of a law of nature must be accompanied by "additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself."

It remains unclear whether Prometheus's claims would have been patentable had the drafters used more active language in place of the "wherein" clauses. Would the outcome have been different if the claims had included a limitation requiring active correlation of the test results with a specific treatment protocol? What if the claims had instructed the physician to administer an altered dosage in response to the test results? These hypothetical alterations would bring the claims closer to those accepted in *Diehr*, but it remains uncertain whether they would pass muster under the Court's ruling in *Prometheus*. For example, such alterations might be viewed as limiting the claims to a particular application, but they just as readily might be viewed as constituting "a drafting effort designed to monopolize the law of nature itself." The lower courts will endeavor to apply *Prometheus*, but given the highly factual nature of the analysis and the vagaries of the Court's opinion, we do not expect the legal landscape to yield meaningful certainty any time soon.

One case that may soon provide guidance is *Association for Molecular Pathology v. Myriad Genetics, Inc.*, which the Supreme Court vacated and remanded for reconsideration in light of *Prometheus*. In *Myriad*, the Federal Circuit addressed the patentability of certain composition and method claims relating to human genetics, holding

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[3] The Court's opinion discusses only Claim 1 of the '623 patent, without separate analysis of whether limitations added by the patents' dependent claims add enough to the claimed correlations to qualify them as patent-eligible applications of natural laws. However, the ruling undoubtedly extends to all of the asserted claims, and perhaps to the entirety of the patents. The Court stated, without qualification, that "the patent claims at issue here effectively claim the underlying laws of nature themselves. The claims are consequently invalid." Slip Op., at 24. The Court also commented, quite simply, that "Prometheus' patents set forth laws of nature." *Id*. at 8.

some of the claims to be patent-eligible and others not. Specifically, in the now-vacated decision,[4] the Federal Circuit held to be patent-ineligible certain claims covering methods of "analyzing" or "comparing" a patient's BRCA sequence with the normal sequence to identify the presence of cancer-predisposing mutations. According to the Federal Circuit, these claims recite nothing more than the abstract mental steps necessary to compare two different nucleotide sequences. We do not expect this ruling to change in light of *Prometheus*.

The Federal Circuit upheld Myriad's remaining claims, ruling that their subject matter is indeed eligible for patenting under § 101. For instance, the challenged composition claims cover two "isolated" human genes, BRCA1 and BRCA2, and certain mutations in these genes associated with a predisposition to breast and ovarian cancers. The court ruled that these claims are drawn to patentable subject matter because they cover molecules that "are markedly different—have a distinctive chemical identity and nature—from molecules that exist in nature." Upon further consideration in light of *Prometheus*, the Federal Circuit likely will revisit whether the molecules are different *enough* from those that exist in nature, such that the claimed subject matter sufficiently applies or builds upon a law of nature or natural phenomenon, rather than monopolizes it.

Finally, the Federal Circuit also found to be patent-eligible a method claim directed to screening potential cancer therapeutics via changes in cell growth rates. The court determined that the claim includes transformative steps, which under the machine-or-transformation test is "an 'important clue' that it is drawn to a patent-eligible process." The Federal Circuit further determined that "[t]he claim does not cover all cells, all compounds, or all methods of determining the therapeutic effect of a compound." On remand, the Federal Circuit may or may not reach the same conclusion, given its stated rationale and the new guidance provided by *Prometheus*.

Until *Myriad* or other cases provide direction, we expect the uncertainty in analyzing patent-eligibility under § 101 to linger. One example of such uncertainty is exemplified by the claims at issue in *Diehr*. While the *Prometheus* Court relied on *Diehr* as reinforcing its conclusion, it is not immediately apparent why the *Diehr* claims were patent-eligible but those in *Prometheus* were not. The claimed method in *Diehr* "consisted in effect of the steps of: (1) continuously monitoring the temperature on the inside of the mold, (2) feeding the resulting numbers into a computer, which would use the Arrhenius equation to continuously recalculate the mold-opening time, and (3) configuring the computer so that at the appropriate moment it would signal 'a device' to open the press." Slip Op., at 11. The Court determined the overall process to be patent-eligible "because of the way the additional steps of the process integrated the equation into the process as a whole." *Id*. at 11-12. Curiously, the Court stated that "[t]hese other steps *apparently* added to the formula something that in terms of patent law's objectives had significance—they transformed the process into an inventive application of the formula." *Id*. at 12 (emphasis added). The Court's use of the word "apparently" suggests uncertainty, and underscores the lack of clear guidance in determining whether "enough" has been added to a natural law to render it a patent-eligible application of the law.

In describing *Diehr*, the Court commented that the *Diehr* opinion "nowhere suggested that all these steps, or at least the combination of those steps, were in context obvious, already in use, or purely conventional." Slip Op., at 12. Other portions of the Court's opinion in *Prometheus* include similar statements intertwining notions of obviousness and novelty into the § 101 analysis. For instance, addressing Prometheus's claims, the Court determined that the recited instructions "add nothing specific to the laws of nature other than what

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[4] *Association for Molecular Pathology v. U.S. Patent & Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011), *vacated by Association for Molecular Pathology v. Myriad Genetics, Inc.*, No. 11-725, __ S. Ct. __ (Mar. 26, 2012).

is well-understood, routine, conventional activity, previously engaged in by those in the field." Slip Op. at 13; *see also id.* at 14 (discussing several Court opinions that "offer further support for the view that simply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable").

These notions seem to derive from *Flook*, in which the Court stated that "post-solution activity" that is purely "conventional or obvious" "can[not] transform an unpatentable principle into a patentable process." *Flook*, 437 U.S. at 589, 590 (quoted in *Prometheus*, Slip Op., at 13). As described by the *Prometheus* Court, *Flook* involved a method for adjusting alarm limits based upon a mathematical formula, where many of the recited steps "were all 'well known,' to the point where, putting the formula to the side, there was no 'inventive concept' in the claimed application of the formula." Slip Op., at 13. Taken at face value, the Court is suggesting that issues of obviousness (§ 103) and novelty (§ 102) could bear on an analysis under § 101, even though the Court in *Bilski* referred to the § 101 eligibility inquiry as "a threshold test," *Bilski*, 130 S. Ct. at 3221, and even though the Court in *Diehr* stated the "novelty" of any steps in the process, or of the overall process, was "of no relevance" to the § 101 analysis, *Diehr*, 450 U.S. at 188-89. By contrast, the *Prometheus* Court "recognize[d] that, in evaluating the significance of additional steps, the § 101 patent-eligibility inquiry and, say, the § 102 novelty inquiry might sometimes overlap." Slip Op., at 21. Thus, the interplay between § 101, on one hand, and §§ 102, 103 and 112, on the other hand, will be worth monitoring and relying upon when suitable circumstances arise.

The Court's ruling is already impacting industry, with the ruling being hailed as a victory for medical professionals and health care providers, and decried as hindering diagnostic research and the field of personalized medicine. Importantly, the Court distinguished Prometheus's claims from "a typical patent on a new drug or a new way of using an existing drug" that "confine their reach to particular applications of [natural] laws." Such claims remain patent-eligible under § 101. We believe, however, that *Prometheus* could have a negative impact on biotechnology companies focused on personalized medicine and diagnostic methods. Existing patents and applications in this arena may be ripe for review to determine whether revision is needed or available.

Going forward, patent claims directed to tailoring medical treatment based upon characteristics manifested by patients will need to be written such that they cross the line into the realm of patent-eligible *applications* of natural laws. On March 23, 2012, the U.S. Patent and Trademark Office issued guidelines to examiners requiring them to reject applications directed to natural phenomena unless they include elements causing the claims to amount to "significantly more" than a law of nature. According to the USPTO, merely adding "well-understood, routine, conventional activity previously engaged in by researchers in the field" will not suffice, regardless of whether the steps result in a "transformation" under *Bilski*. Also, for instances where examiners issue rejections under § 101, applicants will need to stand ready to point to limitations in the claim showing that the claim suitably *applies* the law of nature, and does not merely monopolize it.

ALSTON+BIRD LLP

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For further information, please contact any of the attorneys in Alston & Bird's Intellectual Property and Patents Group listed below.

Wesley Cameron Achey
wes.achey@alston.com
404.881.4930

Blas P. Arroyo
blas.arroyo@alston.com
704.444.1012

William M. Atkinson
william.atkinson@alston.com
704.444.1026

William H. Baker
bill.baker@alston.com
212.210.9487

Timothy J. Balts
tim.balts@alston.com
704.444.1185

David H. Ben-Meir
david.ben-meir@alston.com
213.576.1076

Philippe Bennett
philippe.bennett@alston.com
212.210.9559

Kirk T. Bradley
kirk.bradley@alston.com
704.444.1030

Keith E. Broyles
keith.broyles@alston.com
404.881.7558

Rachel M. Capoccia
rachel.capoccia@alston.com
213.576.1037

Romy L. Celli
romy.celli@alston.com
650.838.2011

Michael S. Connor
mike.connor@alston.com
704.444.1022

Jason W. Cook
jason.cook@alston.com
214.922.3407

Jason P. Cooper
jason.cooper@alston.com
404.881.4831

Jeffrey A. Cooper
jeff.cooper@alston.com
404.881.7892

John W. Cox, Ph.D.
john.cox@alston.com
404.881.7333

Sean P. DeBruine
sean.debruine@alston.com
650.838.2121

Brian C. Ellsworth
brian.ellsworth@alston.com
704.444.1265

Patrick J. Flinn
patrick.flinn@alston.com
404.881.7920

Christopher J. Gegg
chris.gegg@alston.com
704.444.1024

Joseph J. Gleason
joe.gleason@alston.com
404.881.4966

Guy R. Gosnell
guy.gosnell@alston.com
704.444.1029

Gregory T. Gronholm
greg.gronholm@alston.com
404.881.7968

John D. Haynes
john.haynes@alston.com
404.881.7737

Steven D. Hemminger
steve.hemminger@alston.com
650.838.2029

Donald M. Hill, Jr.
donald.hill@alston.com
704.444.1006

Lara A. Holzman
lara.holzman@alston.com
212.210.9553

Yitai Hu
yitai.hu@alston.com
650.838.2020

Louis A. Karasik
lou.karasik@alston.com
213.576.1148

S.H. Michael Kim
michael.kim@alston.com
650.838.2100

Trent A. Kirk
trent.kirk@alston.com
704.444.1409

Ryan W. Koppelman
ryan.koppelman@alston.com
404.881. 7742

Robert L. Lee
bob.lee@alston.com
404.881.7635

Joe Liebeschuetz, Ph.D.
joe.liebeschuetz@alston.com
650.838.2038

Michael D. McCoy
mike.mccoy@alston.com
704.444.1011

Richard M. McDermott
rick.mcdermott@alston.com
704.444.1045

George Douglas Medlock, Jr.
george.medlock@alston.com
404.881.7765

Deepro R. Mukerjee
deepro.mukerjee@alston.com
212.210.9501

Marsha E. Mullin
marsha.mullin@alston.com
213.576.1020

Michael J. Newton
mike.newton@alston.com
214.922.3423

Thomas J. Parker
thomas.parker@alston.com
212.210.9529

Scott J. Pivnick
scott.pivnick@alston.com
202.239.3634

S. Benjamin Pleune
ben.pleune@alston.com
704.444.1098

Elizabeth H. Rader
elizabeth.rader@alston.com
650.838.2008

Bruce J. Rose
bruce.rose@alston.com
704.444.1036

David M. Saravitz, Ph.D.
david.saravitz@alston.com
919.862.2217

Walter Scott
walter.scott@alston.com
212.210.9518

Frank G. Smith
frank.smith@alston.com
404.881.7240

W. Murray Spruill, Ph.D.
murray.spruill@alston.com
919.862.2202

M. Scott Stevens
scott.stevens@alston.com
704.444.1025

R. Flynt Strean
flynt.strean@alston.com
704.444.1430

Kevin C. Trock
kevin.trock@alston.com
650.838.2004

Jamie D. Underwood
jamie.underwood@alston.com
202.239.3706

ATLANTA
One Atlantic Center
1201 West Peachtree Street
Atlanta, GA 30309-3424
404.881.7000

BRUSSELS
Level 20 Bastion Tower
Place du Champ de Mars
B-1050 Brussels, BE
+32 2 550 3700

CHARLOTTE
Bank of America Plaza
Suite 4000
101 South Tryon Street
Charlotte, NC 28280-4000
704.444.1000

DALLAS
2828 North Harwood Street
18th Floor
Dallas TX 75201
214.922.3400

LOS ANGELES
333 South Hope Street
16th Floor
Los Angeles, CA 90071-3004
213.576.1000

NEW YORK
90 Park Avenue
New York, NY 10016-1387
212.210.9400

RESEARCH TRIANGLE
4721 Emperor Boulevard
Suite 400
Durham, NC 27703-8580
919.862.2200

SILICON VALLEY
275 Middlefield Road
Suite 150
Menlo Park, CA 94025-4004
650.838.2000

VENTURA COUNTY
Suite 215
2801 Townsgate Road
Westlake Village, CA 91361
805.497.9474

WASHINGTON, D.C.
The Atlantic Building
950 F Street, NW
Washington, DC 20004-1404
202.239.3300

www.alston.com