2008-1403

IN THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

PROMETHEUS LABORATORIES, INC.,
Plaintiff-Appellant,

v.

MAYO COLLABORATIVE SERVICES (doing business as Mayo Medical Laboratories) and MAYO CLINIC ROCHESTER,
Defendants-Appellees.

Appeal from the United States District Court for the Southern District of California in Case No. 04-CV-1200, Judge John A. Houston.

BRIEF FOR APPELLANT

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Dated January 9, 2009

CERTIFICATE OF INTEREST

Counsel for Plaintiff-Appellant Prometheus Laboratories, Inc., certifies the following:

1. The full name of every party or amicus curiae represented by me is:

   Prometheus Laboratories Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

   None

3. All party corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   Apax Partners, Patricof & Co. Ventures, Inc., DLJ Banking Partners, Wachovia Capital Partners, the Sprout Group, St. Paul Venture Capital

4. The names of all law firms and the partners or associates that appeared for the party or amicus curiae now represented by me in the trial court or agency or are expected to appear in this court are:

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STATEMENT OF RELATED CASES

Prometheus Laboratories Inc. ("Prometheus") is not aware of any related cases, though another case currently pending before this Court may directly affect, or be affected by, the decision in this appeal. The central issue in this appeal is whether Prometheus's medical treatment method patents describe subject matter that is patentable under 35 U.S.C. § 101. In another pending case, *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, No. 2008-1248 (oral argument calendared Feb. 6, 2009), this Court is considering the application of § 101 to particular medical treatment methods.

JURISDICTIONAL STATEMENT

The district court had subject matter jurisdiction over this patent infringement action under 28 U.S.C. §§ 1331 and 1338(a), granted summary judgment to Mayo on March 28, 2008, and entered final judgment on May 16, 2008, disposing of all the parties' claims and counterclaims. A00021; A00043. Prometheus timely filed a notice of appeal on May 30, 2008. A13531. This Court has subject matter jurisdiction over this appeal under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUE

Whether the district court erred in holding that Prometheus's patents—which claim methods for individually calibrating the appropriate dosages of synthetic drugs for treatment of patients with various autoimmune diseases—are merely unpatentable "natural phenomena."

STATEMENT OF THE CASE

Patients battling autoimmune diseases, such as Crohn's disease, suffer debilitating symptoms and complications such as arthritis, anemia, and liver disease. There are drugs that treat these diseases by suppressing the body's natural immune system, but they can carry serious, potentially fatal, side-effects if the dosage is too high for a given patient. Because individual patients react differently, doctors are reluctant to prescribe such drugs absent some way to make sure that they will be effective without risking the toxic side-effects. Prometheus is the sole licensee of two method patents for calibrating the proper dosage of these drugs. *See* U.S. Pat. Nos. 6,355,623 (2002) ("the '623 patent"), A10001-18, and 6,680,302 (2004) ("the '302 patent"), A10019-35 (collectively "the patents-in-suit").

While the methods differ in certain particulars, each involves a common series of steps to adjust and optimize the dosage of the drugs for a given patient. First, the man-made drugs are administered to the patient and, within the body, are transformed into active metabolites—substances that would not occur in the body but for the administration of the drugs. Second, a bodily sample, such as blood, is collected and the patient's drug metabolite concentration levels are measured—a process that requires physical transformation of the sample. Finally, the metabolite concentration level measurements are compared to certain pre-determined levels to

warn the doctor if the dosage might need to be adjusted upwards or downwards to ensure efficacy and/or prevent toxicity. Numerous individuals and organizations have taken advantage of this method by purchasing Prometheus's readily-available PROMETHEUS Thiopurine Metabolites test (formerly known as the PRO-PredictRx® Metabolites test).

After several years of purchasing and using Prometheus's patented test, Mayo Medical Laboratories and its affiliates[1] decided to develop a similar competing product. In 2004, Mayo announced that it intended to begin offering its own test for sale to potential purchasers. Prometheus brought this patent infringement suit in the U.S. District Court for the Southern District of California. In 2005, on cross-motions for summary judgment, the district court held that Mayo's test "literally infringes all elements of the patents-in-suit." A12543.

In 2007, Mayo again moved for summary judgment, arguing that the patented methods merely recite a "natural phenomenon" and, thus, are not patentable under 35 U.S.C. § 101. A12669-74. After soliciting additional briefing on this Court's opinions in *In re Comiskey*, 499 F.3d 1365 (Fed. Cir. 2007), and *In re Nuijten*, 500 F.3d 1346 (Fed. Cir. 2007), *cert. denied*, 129 S. Ct. 70 (2008), the district court granted Mayo's motion and invalidated the asserted claims.

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[1] Throughout, Mayo Collaborative Services dba Mayo Medical Laboratories, which is a for-profit entity, and Mayo Clinic Rochester are referred to collectively, or individually, as "Mayo."

Prometheus Labs., Inc. v. Mayo Collaborative Servs., No. 04-cv-1200, 2008 WL 878910 (S.D. Cal. Mar. 28, 2008) (Houston, J.); A00021-42. Although the district court interpreted some of the patent terms in the course of its infringement holding, it never conducted a full *Markman* hearing.

When the district court resolved the cross-motions for summary judgment, this Court had not yet adopted the "machine-or-transformation" test it recently embraced *en banc* in *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008). Plaintiffs nonetheless argued that the treatment methods at issue here are clearly patentable subject matter under *any* of the tests that the Supreme Court and this Court had articulated—including "machine-or-transformation." Plaintiffs pointed out that in Prometheus's patented methods synthetic thiopurine drugs are administered to patients, transforming in their bodies and producing metabolite chemicals never found in nature; blood or tissue samples from those patients are transformed by sophisticated laboratory machines to determine levels of those metabolites; and that data is transformed into a warning to the doctors that each patient's treatment may need to be adjusted in concrete and specific ways.

The district court held that the presence of transformations and machines in Prometheus's patented methods was irrelevant, and that patentability under § 101 depends instead on whether those methods "recite" and "wholly preempt" some natural phenomenon. A00042. The district court dissected the methods into their

component parts, holding that the method steps involving the administration of thiopurine drugs to patients and the determination of the patient's resulting metabolite levels must be disregarded because they are "conventional method steps" (*i.e.*, not novel) or "merely data-gathering steps," and that the final "warning" step could be ignored because it was "only a mental step." A00029. On May 16, 2008, the district court issued a final judgment, and Prometheus timely appealed. A00043; A13531.

The district court's reasoning is inconsistent with this Court's recent *en banc* decision in *Bilski* and if endorsed by this Court would invalidate the entire field of medical therapeutic and diagnostic patents, including numerous patents held by Mayo itself. *See infra*, at 23-26, 46-52. Under *Bilski* and binding Supreme Court precedent, Prometheus's methods are patentable under § 101.

STATEMENT OF THE FACTS

I. STATUTORY BACKGROUND

The Patent Act 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, subject to the conditions and requirements of this title," 35 U.S.C. § 101—such as novelty and non-obviousness, *id.* §§ 102, 103. A "process," in turn, is defined as a "process, art or method, and includes a new use of a known process, machine, manufacture,

composition of matter, or material." *Id.* § 100(b). These categories are construed broadly, as § 101 is meant to include "anything under the sun made by man." *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). "[L]aws of nature, natural phenomena, and abstract ideas," however, are not patentable subject matter. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

In 1995, Congress considered exempting certain medical methods from patent protection, but ultimately declined to do so. H.R. 1127, 104th Cong. (introduced Mar. 3, 1995); A13067. In 1996, Congress provided limited immunity from patent infringement liability for the performance of certain medical procedures, but it did not exempt such procedures from patent protection. 35 U.S.C. § 287(c); *see* Pub. L. No. 104-208, § 616, 110 Stat. 3009, 3009-67 (1996).

II. FACTS

A. The Problem

Immune-mediated gastrointestinal disorders such as Crohn's disease afflict millions of individuals. A10007. Patients with these disorders often suffer from debilitating symptoms such as diarrhea, abdominal pain, arthritis, fever, anemia, weight loss, and rectal bleeding, along with complications such as eye inflammation, liver disease, and kidney stones. A10007; A10009-10. Physicians can treat the disorders with synthetic thiopurine drugs, such as azathiopurine (AZA) and 6-mercaptopurine (6-MP), to suppress the patient's immune system and

mitigate the symptoms. A10007; A10010-11; A13073-75; A13201. Synthetic thiopurine drugs and their therapeutic metabolites are central to the claims of the patents-in-suit.

Physicians often find it difficult, however, to determine the proper dosage for a particular patient, because individuals metabolize the drugs differently, A10007, and it can take 3 to 6 months for the drug to demonstrate clinical benefits, A13074. If a dosage turns out to be too much for a patient, it can result in severe, and potentially fatal, side-effects, including allergic reactions, neoplasia (cancer), infections, hepatitis, bone marrow suppression, and pancreatitis. A10007; A10012. Even "minimal doses" can have such toxic effects. A13074. Prior to the advent of the present patented methods, many physicians were thus reluctant to treat patients with these drugs, despite the potential benefits, absent a method for preventing toxic side-effects while still ensuring efficacy. A10007.

B. The Patents

Prometheus is a small San Diego company that develops products that help physicians treat gastrointestinal, autoimmune and inflammatory disorders. A11027. It is the exclusive licensee of the two patents at issue in this case: the '623 patent and the '302 patent, issued in 2002 and 2004, respectively. The patents differ in certain respects, but each describes a method of improving the treatment of autoimmune diseases, such Crohn's disease, with the following steps:

(1) administer synthetic thiopurine drugs to the patient; (2) determine the levels of certain metabolites (measured in picomoles per $8x10^8$ red blood cells) from a bodily sample, such as the patient's blood; and (3) be warned by the patient's metabolite concentrations that an upward or downward adjustment in dosage may be required based on particular, pre-determined metabolite levels. A00028-29. The patents thus address the problem of individually calibrating a patient's dosage without having to take a wait-and-see approach. The patented methods involve transformative processes, machines, and non-naturally occurring phenomena.

First, the physician administers the man-made thiopurine drugs to a patient, and the drugs are converted within the body to particular active metabolites, such as 6-thioguanine (6-TG)[2] and 6-methyl-mercaptopurine (6-MMP). A13073-75.[3] These metabolites do not otherwise naturally occur in the human body. A13073.

Second, the patient's metabolite levels are determined, which requires extracting a bodily sample, such as blood, DNA, or oral mucosa. A10011-12. Because "metabolite levels are not detectable in raw human tissue," all methods for measuring their concentration levels require "significant chemical and physical alteration of blood or human tissue" as well as sophisticated laboratory equipment

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[2] For purposes of this brief, 6-TG also refers to 6-thioguanine nucleotides (6-TGN). *See* A12530 n.7; A11026 n.2.

[3] One of the independent claims (and its associated dependent claims) assumes that the drugs have already been administered. A10018.

and machines. A13186-87; A13503; A10011. For example, one common measurement protocol, high pressure liquid chromatography (HPLC), entails an intricate series of operations on the blood (including heating, centrifuging, separating, and adding various reagents), running the resulting solution through a computer-controlled chromatography instrument, calculating the peak height or peak area, and feeding those figures into an equation, which finally outputs the metabolite levels. A13186.

Third, those calculated metabolite levels are transformed into a warning to the physician about the efficacy or toxicity of the ongoing treatment. In particular, a 6-TG level "greater than about 400" and a 6-MMP level "greater than about 7000," indicate that a downward adjustment in drug dosage may be required in order to avoid toxic side-effects. A10016-18. Conversely, according to the patented test, a 6-TG level of "less than about 230" indicates a need to increase the dosage to ensure therapeutic efficacy. *Id.*

The various independent claims each recite some combination of these three pre-determined levels. A10016-18; A10034-35. For example, Claim 1 of the '302 patent claims:

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

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the levels 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 levels 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.

A10034.

The various dependent claims further limit the method to certain disorders (such as inflammatory bowel disease), certain thiopurine drugs (such as 6-MP and the prodrug AZA, which is transformed in the body to efficacious metabolites 6-mercaptopurine and 6-thioinosinic acid), certain methods for determining metabolite levels (such as HPLC), certain measurement units (such as red blood cells), and certain toxic side-effects (such as hepatic toxicity). *See*, *e.g.*, A10016-17 ('623 Patent, dependent claims 2, 4, 5, 6, 12, 31, 32). For example, dependent claim 6 of the '623 Patent requires that the metabolite levels be "determined using high pressure liquid chromatography." A10016.

C. The Accused Test

For several years, Mayo has purchased and used Prometheus's patented methods—over 17,000 times from 1999 to 2007. A13136. In 2004, however, Mayo announced that it had developed a similar, competing test ("the accused test") to replace Prometheus's test. A11566. Mayo offered the accused test for sale to potential purchasers, *id.*, and was poised to earn a 60% profit margin on its

product, A13136. When Prometheus brought the present suit, Mayo rescinded that announcement. A10905. Nonetheless, Mayo recently noted that it was anxious to "begin selling its competitive product." Appellees' Opp. to Mot. to Stay 4 (filed Aug. 11, 2008).

III. DISTRICT COURT PROCEEDINGS

Prompted by Mayo's announcement, Prometheus filed this patent infringement action, seeking injunctive and declaratory relief and damages. A10036-41. Mayo counterclaimed for declaratory relief of non-infringement and of patent invalidity under 35 U.S.C. §§ 101, 102, 103, and 112. A10045. On cross-motions for summary judgment on the question of infringement, Prometheus argued that the accused test literally infringes Claim 7 of Prometheus's '623 patent, while Mayo argued that its accused test did not infringe any portion of Prometheus's patents. A11024; A12228.[4] The district court granted summary judgment to Prometheus, holding that Mayo's test "literally infringes all elements of the patents-in-suit." A12543.

Subsequently, Mayo sought summary judgment of invalidity under 35 U.S.C. § 101 as to "the asserted claims of the patents-in-suit." A12655; *see*

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[4] Claim 7 of the '623 patent, much like the other independent claims, is a "method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder" comprising administering a thiopurine drug, determining the levels of 6-TG and 6-MMP, comparing the levels to 400 and 7000, respectively, and resulting in a warning that the dosage might need to be decreased. A10016.

A12663 & n.3 (listing asserted claims). Mayo argued that the patents claim nothing more than a "natural phenomenon" consisting of the "correlations between, on the one hand, concentrations of certain thiopurine drug metabolites, and, on the other hand, the likelihood of therapeutic efficacy and/or toxicity of thiopurine drug treatment in autoimmune disease patients." A12659.

Prometheus pointed out that the metabolites in question "do not naturally exist in the [human] body," but are instead "created by the body as the result of the administration of a man-made drug." A12912 (emphases omitted); *see* A12921-22; A13073-75. Prometheus also explained that, viewed as a whole, the methods rely on machines and entail "transformations" of matter or data from one state to another, as the man-made drug is transformed in the body, the patient's bodily sample is necessarily transformed to a different state for analysis, and the metabolite data is transformed into a warning for subsequent treatment. A12913; A12927. Prometheus likened its treatment methods to the diagnostic methods in *Arrhythmia Research Technology, Inc. v. Corazonix Corp.*, 958 F.2d 1053 (Fed. Cir. 1992), where this Court held patentable a method for ascertaining the health of a patient's heart by converting the patient's heartbeat (an analog signal measured by an electrocardiograph machine) to digital form, processing the data to produce a numerical value, and comparing that value against a pre-determined level that correlated with increased risk. A12928.

On March 28, 2008, the district court granted Mayo's motion and invalidated the asserted claims. A00042. The district court held that it was irrelevant whether the processes in question "transform" matter or data, because it believed that test applied only to "industrial" processes. A00036. It also specifically rejected any argument "that the inclusion of a machine in the claim automatically makes the claim patentable." A00039.

The district court instead relied heavily on Justice Breyer's dissent in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) ("*Lab Corp.*"), on the Supreme Court's 1978 decision in *Parker v. Flook*, 437 U.S. 584 (1978), and on the decisions of this Court and its predecessor in *In re Meyer*, 688 F.2d 789 (CCPA 1982), and *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989). The district court dissected the patent claims into their three basic steps: administration of the drug, determining metabolite levels, and warning the physician of a need to adjust treatment. It then held that the first two could be disregarded under *Grams* and *Meyer* as merely "conventional" or "data-gathering" steps, and that the final "warning" step was "only a mental step," because "it is the metabolite levels themselves that 'warn' the doctor that an adjustment in dosage may be required." A00029.

Thus shorn, the court found that the patents-in-suit recite only correlations, which the court viewed as natural phenomena because they "result[] from innate

metabolic activity in the human body," A00030-35, even though the metabolites are not naturally-occurring in the human body and instead result from a physical transformation of the synthetic thiopurine drugs. The court further found that the patents "'wholly pre-empt' use of the natural phenomenon such that the 'practical effect is [an improper] patent on the [phenomenon] itself.'" A00035 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972)) (second alteration in original). The court rejected Prometheus's argument that the patents foreclosed use of the correlations only in the context of this specific method of patient treatment and did not prevent anyone from using those correlations in basic research or in the development of other treatment methods. A00037-38.

The district court invalidated Prometheus's asserted claims without conducting a full *Markman* hearing and without addressing all of the numerous dependent claims that are even more limited and specific than the independent claims that the court analyzed. *See, e.g.*, A00040; A10016-18.

IV. PROCEEDINGS IN THIS COURT

On September 2, 2008, this Court granted appellant's motion to stay the briefing schedule pending this Court's *en banc* decision in *In re Bilski*, 545 F.3d 943 (Oct. 30, 2008). On November 26, 2008, this Court granted the parties' joint motion to reinstate a briefing schedule.

SUMMARY OF ARGUMENT

The broad language of § 101 of the Patent Act extends to "'anything under the sun that is made by man'" and excludes only laws of nature, natural phenomena, and abstract ideas. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (citation omitted). The patents-in-suit are not abstract, and there is nothing "natural" about them—except in the sense that everything under the sun is, ultimately, a product of nature. These patents describe specific, concrete processes for adjusting and optimizing the treatment of patients with particular *man-made* drugs, which metabolize into particular pharmacologically active compounds (*e.g.*, 6-TG and 6-MMP) to achieve life-saving therapeutic efficacy while avoiding toxic side-effects. Such method of treatment claims accompany almost all patents on artificial drugs, and have routinely been enforced by this Court. To our knowledge no one, until this case, has ever suggested that such methods constitute unpatentable "natural phenomena" merely because the human body's reaction to an artificial substance is governed by natural laws. The same could be said of the foundational patents of the industrial age, like the Goodyear process for vulcanizing natural rubber or the Bessemer process for transforming molten iron into steel.

This Court and the Supreme Court have articulated a variety of approaches to the "natural phenomenon" question under § 101, including most recently the

"machine-or-transformation" test adopted by this Court *en banc* in *Bilski*. The patents-in-suit pass that test with flying colors. The whole point of these processes is to transform the patient's body from a life-threatening physical condition into a healthier one. Along the way, the patient's body is transformed by administration of a synthetic thiopurine drug, producing metabolites never seen in nature. A sample of bodily fluid or tissue is transformed, with the help of sophisticated laboratory machines, to permit measurement of the levels of those metabolites. And the resulting data is transformed into a warning to the physician about the possible need to increase or decrease the patient's dosage.

The district court disregarded all of that because it believed, pre-*Bilski*, that a transformation of matter or data establishes patentability only for "industrial" processes. Rather than examining the purposes and effects of these processes *as a whole*, the district court dissected the patents into distinct steps and found reasons to disregard most of them until nothing was left but a "correlation" that it could describe (wrongly) as a natural phenomenon. The district court drew that approach to § 101 from the Supreme Court's decision in *Flook*. But as this Court has recognized several times, including in *Bilski*, the Supreme Court squarely rejected

Flook's analysis in *Diehr*.[5] Many patentable processes can be dissected into steps that, standing alone, would not be patentable.

In any event, the district court's analysis must be rejected even on its own terms. The metabolic consequences of administering a man-made drug are not a "natural" phenomenon but an artificial one. Of course those effects are mediated by natural laws, but so is combustion inside an automobile engine. Nonetheless, an improved method for tuning a car is patentable. The district court's suggestion that the "administering" and "determining" steps of the patents-in-suit can be disregarded as "merely necessary data-gathering steps for any use of the correlations," A00029, also betrays its complete failure to appreciate the purpose of these processes. Thiopurine drugs are not administered, and tissue samples are not obtained and transformed, merely to gather data for an abstract calculation. These steps are part of the ongoing treatment of desperately ill patients. Presumably the district court would have dissected the patent in *Diehr* into data gathering steps (monitoring the temperature and pressure inside a rubber mold), a "natural" correlation (the prior art Arrhenius equation), and the "mental step" or "insubstantial post-solution activity" of sending a warning that it was time to open

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[5] *See Bilski*, 545 F.3d at 958-59; *AT&T Corp. v. Excel Commc'ns*, 172 F.3d 1352, 1359 (Fed. Cir. 1999); *Arrhythmia*, 958 F.2d at 1057 n.4 (noting that the Court's reasoning in *Diehr* "not only elaborated upon, but in part superseded, that of *Benson* and *Flook*").

the mold. But the Supreme Court recognized the patent in *Diehr* for what it was: an improved method for curing rubber.

The district court's analysis would, if endorsed by this Court, threaten to invalidate the entire field of medical treatment and diagnostic patents on which the innovative and lifesaving biotechnology industry is largely built. It would also crush in its infancy the promise of personalized and genomic medicine, which of course will depend largely on insights into how man-made therapies interact with a particular patient's "natural" genes and body chemistry. There is absolutely no evidence that Congress intended to disincentivize such concrete, life-saving innovations in medicine and the life sciences. And there is no justification for reaching such a misguided policy result by needlessly expanding the narrow, judicially-created exclusion that denies patentability to abstract ideas and phenomena of nature.

The district court's summary judgment order should be reversed, and this case should be remanded with instructions to enter summary judgment under § 101 to Prometheus.

ARGUMENT

I. STANDARD OF REVIEW

This Court reviews the district court's grant of summary judgment *de novo*. *AT&T Corp. v. Excel Commc'ns*, 172 F.3d 1352, 1355 (Fed. Cir. 1999). Summary

judgment is appropriate if there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. *Id.*; Fed. R. Civ. P. 56(c). Whether a patent claim is directed to statutory subject matter is a question of law that this Court reviews *de novo*. *AT&T*, 172 F.3d at 1355; *Arrhythmia*, 958 F.2d at 1055. However, "determination of this question may require findings of underlying facts specific to the particular subject matter and its mode of claiming." *Arrhythmia*, 958 F.3d at 1056. Duly issued patents are presumed valid, and the challenger bears the burden to demonstrate otherwise by clear and convincing evidence. *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1346 (Fed. Cir. 2000); 35 U.S.C. § 282.

II. PROMETHEUS'S PATENTS SATISFY SECTION 101

The Supreme Court has confirmed that the language of § 101 is "extremely broad." *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130 (2001); *see also Chakrabarty*, 447 U.S. at 308, 309 (Congress intended that patent laws "be given wide scope" and extend to "'anything under the sun that is made by man'"). However, courts have long recognized that "laws of nature, natural phenomena, and abstract ideas" are not patentable standing alone. *Diehr*, 450 U.S. at 185. Patentable processes must not "pre-empt" the use of such natural phenomena and abstractions, but may only foreclose their use "in conjunction with all of the other steps in their claimed process." *Id.* at 187. Of course, that principle

must be approached carefully, because every step of every invention can be expressed as simply a reflection of fundamental natural laws of physics, chemistry, or other sciences. *See id.* at 189 n.12 ("[A]ll inventions can be reduced to underlying principles of nature . . . ."); *accord Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 134-35 (1948) (Frankfurter, J., concurring); *Arrhythmia*, 958 F.2d at 1063 (Rader, J., concurring).

Recently, in *In re Bilski*, this Court articulated a standard for determining whether a given claimed process improperly pre-empts "substantially all uses" of laws of nature, natural phenomena, or abstract ideas—referred to collectively as "fundamental principles." 545 F.3d at 952 n.5. This Court explained that a process is patent-eligible under § 101 if "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." *Id.* at 954 & n.7 ("machine-or-transformation test"); *see also Benson*, 409 U.S. at 70 ("Transformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines."); *Diehr*, 450 U.S. at 184; *Cochrane v. Deener*, 94 U.S. 780, 787-88 (1877). Such machine-ties or transformations must be "central to the purpose of the claimed process," and not merely "insignificant extra-solution activity." *Bilski*, 545 F.3d at 962. But the claims must be considered "as a whole," not dissected, and "it is irrelevant that any individual step or limitation . . . by itself would be

unpatentable under § 101." *Id.* at 958 (citing *Flook*, 437 U.S. at 594; *Diehr*, 450 U.S. at 187-88; *In re Alappat*, 33 F.3d 1526, 1543-44 (Fed. Cir. 1994) (*en banc*)).

Prometheus's medical processes are patentable under either prong of the *Bilski* machine-or-transformation test. Indeed, the entire purpose of Prometheus's patents is to improve patient treatment through a new process that requires physical transformations and particular machines in order to transform the patient's body.

A. Prometheus's Patents Satisfy Section 101 Because They Rely Upon Multiple Transformations

Under *Bilski*, a process is patentable if "it transforms a particular article into a different state or thing." 545 F.3d at 954. Prometheus's patents are directed at improving patient treatment by calibrating the dosage of synthetic medication necessary to suppress the patient's natural immune system optimally without causing deadly side-effects. To that end, Prometheus's methods require several transformations, both as integral steps of the process and as the fundamental output of the process, each of which would independently satisfy *Bilski*'s test.

First, these methods of treatment require administration of particular synthetic drugs, which are transformed by the body into particular non-naturally occurring metabolites, such as 6-TG and 6-MMP. The process therefore uses as its foundation a man-made substance, which is then administered to a patient specifically to transform the biochemical makeup of a patient's body for the purpose of treating disease. Chemical transformations like these are sufficient to

establish the patentability of a process, standing alone. *See id.* at 962 ("It is virtually self-evident that a process for a chemical or physical transformation of physical objects or substances is patent-eligible subject matter."); *see also*, *e.g.*, *Diehr*, 450 U.S. at 184 (transformation of raw, uncured rubber into molded, cured rubber products is sufficient); *Tilghman v. Proctor*, 102 U.S. 707, 721, 729 (1881) (transformation consists of "chemical union between the fatty elements and water"); *Cochrane*, 94 U.S. at 787-88 (transformation occurs when "one of the steps of a process [is] that a certain substance is to be reduced to a powder").

These chemical transformations are obviously "central to the purpose of the claimed process," *Bilski*, 545 F.3d at 962, and are not themselves merely a "natural" phenomenon. Thiopurine drugs do not exist in nature; they are the product of a transformation of natural ingredients into a new, synthetic compound by artificial chemistry. The human body's metabolic reaction to those artificial compounds is similarly an artificial phenomenon that would never occur in nature without the intervention of human intelligence. In fact, in certain of the claimed thiopurine drugs, *i.e.*, azathioprine, the administered therapeutic is a "prodrug" designed to use human body chemistry to transform it into an active efficacious new drug of 6-mercaptopurine and 6-thioinosinic acid. Of course these reactions are "natural" in the superficial sense that *everything* is natural. But physical transformations initiated by human actions and artificial chemical compounds

cannot be ignored, for purposes of the *Bilski* test, simply because they proceed according to natural laws (as everything does) or occur within the human body. As this Court recognized in *Bilski*, the narrow exception to patentability for natural phenomena ensures that fundamental principles are "'part of the storehouse of knowledge of all men.'" *Id.* at 952 (quoting *Funk Bros.*, 333 U.S. at 130). But novel treatment and diagnostic procedures applying man-made drugs present no such concerns about pre-empting an inventor's ability to draw on fundamental principles, and a rule that any reaction of the human body falls outside the scope of patentability would radically undermine life-saving developments in patient treatment. At a minimum, the transformation test must be satisfied by methods of treatment involving *synthetic* drugs, such as the ones at issue here.

Such methods of treatment have long been thought patentable and this Court has enforced such patents with no suggestion that § 101 poses a barrier, even though it is well-established that "'[t]he first door which must be opened on the difficult path to patentability is § 101.'" *In re Comiskey*, 499 F.3d 1365, 1371 (Fed. Cir. 2007) (citation omitted) (alteration in original) (raising § 101 *sua sponte*); *see also Flook*, 437 U.S. at 593 ("The obligation to determine what type of discovery is sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious."); *cf. Bilski*, 545 F.3d at 950 n.1 ("[A]n

examiner should generally first satisfy herself that the application's claims are drawn to patent-eligible subject matter.").

For example, in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 347 F.3d 1367 (Fed. Cir. 2003), this Court found valid claims of a patent, issued in 1986, drawn to a "method of treatment of urolithiasis and inhibiting bone reabsorption" consisting entirely of the following: "administering to a patient in need thereof an effective amount of 4-amino-1-hydroxybutane-1,1-biphosphonic acid." *Id.* at 1369. More recently, in *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008), this Court upheld method claims in a patent for using riluzole to treat Lou Gehrig's disease. *See also In re Chupp*, 816 F.2d 643, 645, 647 (Fed. Cir. 1987) (patent drawn to a method for using compounds to treat weeds in crops); *In re Zierden*, 411 F.2d 1325, 1326, 1329 (CCPA 1969) (rejecting challenge to patented method for using compound to purify water and noting that "there is express statutory authority for a patent on a process which is a new use of a known process, composition of matter, or material" (citing 35 U.S.C. §§ 100, 101)); *cf. Dawson Chem. Co. v. Rohm & Haas Co.*, 448 U.S. 176, 185 (1980) (assuming, without deciding, validity of patent drawn to method of using propanil as an herbicide). Often, inventors patent methods of treatment simultaneously with the underlying compounds, as in *Burroughs Wellcome Co. v. Barr Laboratories, Inc.*, 40 F.3d 1223, 1224, 1230-32 (Fed. Cir. 1994), where this

Court upheld five patents that "encompass compositions and methods of using AZT to treat AIDS." *See also* U.S. Pat. No. 3,983,233, cols. 15-16, 18 (claims 1, 18) (1976) (claiming steroid compound and its use in a method of treating inflammation).[6]

Consistent with this decades-long understanding, patents have issued on methods of treatment employing the same drugs (*e.g.*, azathioprine) used in Prometheus's patents-in-suit. *See*, *e.g.*, U.S. Pat. No. 5,733,915 (1998) ("Use of Azathioprine to Treat Crohn's Disease"). Indeed, Mayo itself was assigned a patent on a "therapeutic method of treating inflammatory bowel disease comprising topically administering to the colon of a patient in need of such treatment . . . an amount of azathioprine effective to relieve the symptoms of said inflammatory bowel disease." U.S. Pat. No. 5,691,343 (1997) ("Use of Topical Azathioprine to Treat Inflammatory Bowel Disorders"); *see also* U.S. Pat. No. 6,166,024 (2000) ("Use of Topical Azathioprine and Thioguanine to Treat Colorectal Adenomas") (assigned to Mayo). Such methods of treatment all use synthetic compounds to transform the patient's body into a healthier physical state

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[6] Even when this Court has invalidated specific treatment method patents, including in a case decided on the same day as *Bilski*, it has done so under the other, substantive patent law provisions, rather than at the § 101 threshold. *See*, *e.g.*, *In re Alonso*, 545 F.3d 1015, 1017-19 (Fed. Cir. 2008) (method patent for treating rare cancer using monoclonal antibodies lacked written description, § 112); *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1255-56, 1259 (Fed. Cir. 2007) (method for treating ear infections with topical compound was obvious, § 103).

and are, thus, unquestionably patentable under *Bilski*. This is no less true for the patents-in-suit, which simply represent an improved method of treatment that is at least as transformational in its use of synthetic compounds. Such patents are all wholly consistent with *Bilski*'s animating concern of excluding fundamental *natural* principles from the ambit of § 101.

Second, Prometheus's patented method for calibrating effective and safe treatment with thiopurine drugs requires the transformation of a patient's bodily sample, such as blood, in order to measure the newly-created metabolites' concentration levels. The specific 6-TG and 6-MMP metabolites that form the foundation of the patented processes "are not detectable in raw human tissue." A13186-87. There are several methods for performing such transformations, all of which "require[] significant chemical and physical alteration of blood or human tissue" in order to extract the metabolites and determine the concentration levels of the metabolites in the blood. *Id.* In the end, "the human blood sample is no longer human blood; human tissue is no longer human tissue." A13186. The altered bodily sample has been transformed into a number representing the patient's metabolite levels.

Finally, as the ultimate end of the processes is to transform—and improve—the patient's treatment regime while avoiding deadly side-effects, the metabolite levels are transformed into a warning to alter the dosage in subsequent patient

treatment. The patented processes thereby address the reality that, because all patients metabolize thiopurine drugs at different rates, administration of a given dosage to several patients can result in different metabolite levels in each patient—with some exposed to toxic levels and others to levels too low to provide therapy. The inventors determined the therapeutic window for safe and effective drug therapy, which correlates with metabolite concentrations greater than about 230 pmol and less than about 400 pmol per $8x10^8$ of 6-TG and less than about 7000 pmol per $8x10^8$ of 6-MMP. Metabolite levels outside of this therapeutic window thus indicate a need for an alteration in dosage. Subsequent physical changes will, of course, ensue given that any change in dosage will, in turn, alter the patient's body chemistry.

Prometheus's patented therapeutic methods are similar to, but even more clearly patent-eligible than, the medical diagnostic methods found patentable in *In re Abele*, 684 F.2d 902 (CCPA 1982), and *Arrhythmia Research Technology, Inc. v. Corazonix Corp.*, 958 F.2d 1053 (Fed. Cir. 1992). In *Abele*, the patented method was a method of manipulating and performing calculations on CAT scan data and displaying the results in a field. The practical result was an improved CAT scan process. 684 F.2d at 908. This Court reaffirmed in *Bilski* that mere transformations of *data*, such as in *Abele*, are sufficient for patentability so long as the data corresponds to physical objects or events in the real world rather than

mere abstractions or legal relationships. *Bilski*, 545 F.3d at 962-63 (discussing *Abele* approvingly). Given that the X-ray data "clearly represented physical and tangible objects, namely the structure of bones, organs, and other body tissues[,] . . . the transformation of that raw data into a particular visual depiction of a physical object on a display was sufficient" for patent-eligibility in *Abele*. *Id.* at 963.

Similarly, in *Arrhythmia*, the diagnostic process entailed converting a patient's heartbeat (as measured by an electrocardiograph machine) from analog to digital form, applying a mathematical formula, and comparing the resulting output to a predetermined level to determine the risk of a particular heart arrhythmia. 958 F.2d at 1055, 1059. As in *Abele* "[t]hese input signals are not abstractions" but are instead "related to the patient's heart function." *Id.* at 1059. The transformation of those signals is therefore sufficient for patentability. *See Bilski*, 545 F.3d at 963-64 ("transformation" can be either of a "physical object or substance" or of "an electronic signal representative of [a] physical object or substance"; "the claim was not required to involve any transformation of the underlying physical object that the data represented"); *accord In re Warmerdam*, 33 F.3d 1354, 1360 n.5 (Fed. Cir. 1994).[7]

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[7] The result in *Arrhythmia* survives *Bilski*, even if the underlying test does not. *Bilski* reiterated that the *Freeman-Walter-Abele* test is "inadequate" given that the court has "already recognized that a claim failing that test may nonetheless be

Prometheus's methods similarly manipulate and transform data that represents real facts about the patient's physical condition, as opposed to the mere business risks and legal abstractions that this Court held to be insufficient in *Bilski* and in *Comiskey*.[8] Indeed, Prometheus's methods involve far more substantial transformations than the simple manipulations of data held to be sufficient in *Abele* and in *Arrhythmia*. In those cases, no artificial drugs were administered; the observation and measurement of the patient's biology required no transformation of bodily samples; and the resulting data was simply used to observe bodily

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patent-eligible." *Bilski*, 545 F.3d at 959. This reasoning suggests that where patents were found eligible under the *Freeman-Walter-Abele* test, such results are still valid, even if the test is not. *See State St. Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373-74 (Fed. Cir. 1998). *Bilski* nowhere stated that the result in *Arrhythmia*—affirming the patentability of diagnostic methods—is no longer good law, just that the *Freeman-Walter-Abele* test "should no longer be relied on." *Bilski*, 545 F.3d at 959 n.17. Indeed, this Court has previously disparaged the *Freeman-Walter-Abele* test while discussing *Arrhythmia* with great approval. *See AT&T*, 172 F.3d at 1359; *State St.*, 149 F.3d at 1373-74. Moreover, *Bilski* spoke approvingly of the patent-eligible method in *Abele*—the capstone case of the *Freeman-Walter-Abele* test.

[8] As this Court explained in *Bilski*, "[p]urported transformations or manipulations simply of public or private legal obligations or relationships, business risks, or other such abstractions cannot meet the test because they are not physical objects or substances, and they are not representative of physical objects or substances." *Bilski*, 545 F.3d at 963; *see also id.* at 1008 (Mayer, J., dissenting) ("Bilski's claimed method consists essentially of two conversations."). Bilski's unpatentable process was, "as a whole," merely "directed to the mental and mathematical process of identifying transactions that would hedge risk," just as the unpatentable claims in *Comiskey* "as a whole were directed to the mental process of arbitrating a dispute to decide its resolution." *Id.* at 965. On the other hand, *Comiskey* also held that certain other similar claims *were* patentable because they were implemented on a computer. 499 F.3d at 1379-80.

attributes or diagnose a problem, not to generate a specific warning about the possible need for adjustment of the patient's treatment regime.

The district court's conclusion that the transformation test is not relevant to the § 101 inquiry in this case is now clearly error in light of *Bilski*. *See* A00036 ("Defendants need not meet the additional burden of showing that the claims do not 'transform' an article or physical object to a different state or thing[.]"). The processes at issue here integrally involve multiple transformations, which is amply sufficient to satisfy § 101.

B. Prometheus's Patents Satisfy Section 101 Because They Rely Upon Machines

Under *Bilski*, a process is also patentable if "it is tied to a particular machine or apparatus." 545 F.3d at 954. Prometheus's treatment methods satisfy this test for two independent reasons. *First*, the patents-in-suit inextricably rely on numerous particular machines in order to process the bodily sample, determine the metabolite levels, and, thereby, calibrate the proper dose for a method of treatment. *Second*, the only coherent way to understand the role of "machines" in the *Bilski* test is as a shorthand reference to the other categories of patentable subject matter expressly referenced in § 101, namely "machine, manufacture, or composition of matter." Nothing in the *Bilski* opinion or the text of the statute provides any justification for treating machines as some kind of special favorite of the patent laws, privileged above the other categories of tangible subject matter that Congress

determined should be patentable. The claimed processes' central reliance on specific patentable compositions of matter—synthetic pharmaceuticals—is itself sufficient to meet the "machine" prong of the *Bilski* test. In the alternative, this Court can simply recognize that the *Bilski* test does not apply at all where, as here, the treatment methods use synthetic drugs and, thus, do not recite any "natural" phenomenon whatsoever. That is, Prometheus's patents do not implicate *Bilski*'s animating concern for avoiding the preemption of fundamental principles.

1. Prometheus's patents integrally rely on medical machines and apparatuses

Prometheus's treatment methods integrally rely on machines in order to optimize drug efficacy without incurring deadly side-effects. In order to calibrate the proper dosage and improve individualized patient treatment, the methods require measuring the patient's metabolite levels. Since it is impossible to determine the metabolite levels with the naked eye or through any unaided manual process, a human blood or tissue sample must be processed using medical machines or apparatuses, such as detectors, pumps, and injectors. Although there are a variety of methods for measuring the metabolite levels, *all* of them require particular machines or apparatuses. A13503 ("[A]ll methods . . . for determining

6-TG and 6-MMP metabolite levels require the use of a machine."); A10011; A10029.[9]

This Court has held that claims need not expressly reference a machine when the only practical means of performing a given step requires a machine. *See Comiskey*, 499 F.3d at 1379 ("These claims, under the broadest reasonable interpretation, could require the use of a computer . . . ."); *In re Application of Gelnovatch*, 595 F.2d 32, 35 (CCPA 1979) (noting that "as a practical matter [the process] can only be performed by the computer" (citing *Benson*)). As this Court has repeatedly stated, "'each invention must be evaluated as claimed; yet semantogenic considerations preclude a determination based solely on words appearing in the claims. In the final analysis under § 101, the claimed invention, as a whole, must be evaluated for what it is.'" *Grams*, 888 F.2d at 839 (citation omitted); *Abele*, 684 F.2d at 907; *In re Sarkar*, 588 F.2d 1330, 1333 (CCPA 1978). In this case, the only way to measure the patient's metabolite levels consistent with the claimed process is to use particular machines. *See* A13503.[10]

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[9] *See, e.g.*, A13228-29 (describing apparatuses required for "capillary electrophoresis with laser-induced fluorescence"—including a "high voltage power supply," a "helium-cadmium laser," a lens, a "microscope objective," a "photomultiplier tube," and a centrifuge, among others); A13211-12 (describing apparatuses used for "liquid chromatography-mass spectrometry," infrared spectroscopy, and "nuclear magnetic resonance" spectroscopy).

[10] Even if Mayo could dispute whether all methods of measuring the metabolite levels require machines, that would simply present a question of fact rendering

Regardless, several asserted dependent claims specify measurement through high pressure liquid chromatography (HPLC), *see* A10017-18 (claims 6, 14, 24, 30, and 53), which requires several apparatuses for performing intricate operations on the blood (including heating, centrifuging, separating, and adding various reagents); running the resulting solution through a computer-controlled chromatography instrument; calculating the peak height or peak area and, ultimately, the metabolite levels. A13186; A13503. At the very least, these dependent claims satisfy any interpretation of the machine test.

The district court plainly erred by failing to analyze the dependent claims separately. The district court only mentioned the dependent HPLC claims in passing, without making an individualized determination, and utterly failed even to mention various other dependent claims. *See* A00040. The district court's approach is inconsistent with *Comiskey*, where this Court analyzed each independent and dependent claim on its own merits and held that certain dependent claims were valid even though the related independent claims were not. 499 F.3d at 1379 ("[I]t is appropriate to separately consider dependent claims . . . ."). Indeed, the district court's approach thwarts the statutory command that

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summary judgment inappropriate and warranting reversal. As this Court explained in *Arrhythmia*, although the § 101 inquiry is generally a question of law appropriate for resolution on summary judgment, "determination of this question may require findings of underlying facts specific to the particular subject matter and its mode of claiming." 958 F.2d at 1056.

"dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim." 35 U.S.C. § 282. This alone warrants reversal as to the dependent claims.[11]

2. Prometheus's patents integrally rely on compositions of matter

Prometheus's patented methods also satisfy the *Bilski* test for the independent reason that they incorporate and integrally rely on a patentable composition of matter: synthetic thiopurine drugs. This Court should understand the "machine" prong of the *Bilski* test as a shorthand reference to all of the other categories of patentable subject matter included by Congress in § 101.

First, that is how this Court understood the "machine" test prior to *Bilski*, and nothing in the *Bilski* opinion suggests any rationale for treating processes that happen to involve a patentable machine as somehow more worthy than processes involving a patentable composition of matter. In *Bilski*, this Court acknowledged that it had recently explained in *Comiskey* that a process is always patentable if it "'is embodied in, operates on, transforms, or otherwise involves another class of statutory subject matter, *i.e.*, a machine, manufacture, or composition of matter.'"

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[11] The district court's error is consistent with its persistent refusal throughout the litigation to rigorously analyze the discrete significance of each of the individual claims, as when the court previously found that Mayo's test "literally infringes all elements of the patents-in-suit," despite Prometheus only seeking summary judgment on Claim 7 of the '623 Patent. *See* A12543; A11024. Similarly, the district court failed to make clear that its § 101 ruling could not invalidate the patents *in toto*, but could only affect the asserted claims. *See* A12655; A12663 & n.3.

545 F.3d at 961 n.24 (quoting *Comiskey*, 499 F.3d at 1376). The quoted passage from *Comiskey* makes clear that a manufacture or composition of matter can play the same role in the test as a machine. *See also Zierden*, 411 F.2d at 1329 ("[T]here is express statutory authority for a patent on a process which is a new use of a known process, composition of matter, or material" (citing 35 U.S.C. §§ 100, 101)).

In a footnote, the *Bilski* court explained that the *Comiskey* formulation was "simply a summarization of the Supreme Court's machine-or-transformation test" that "should not be understood as altering that test." 545 F.3d at 961 n.24. That statement is cryptic, but is best understood as an acknowledgment that *Comiskey* correctly states the Supreme Court's test—that a process that depends on a manufacture or composition of matter is patentable. *Bilski* certainly should not be read to *reject* the broader understanding of "machine-or-transformation" explained in *Comiskey*, particularly since anything *Bilski* said about the "machine" prong is dicta. *See, e.g., id.* at 962 ("[I]ssues specific to the machine implementation part of the test are not before us today. We leave to future cases the elaboration of the precise contours of machine implementation . . . ."). The *Bilski* court also acknowledged that the test it announced would require further explication and possible modification in appropriate future cases. *See id.* at 956.

Second, a distinction between machines and compositions of matter makes no sense. There is no evidence that Congress intended to single out machines for special status under the patent laws. Section 101 by its express terms covers machines, manufactures, and compositions of matter, with no distinction among them. If a process for separating water into hydrogen and oxygen using a particular machine is patentable, a process for achieving the same result with an artificial chemical catalyst should be patentable as well. Nothing in the patent laws suggests that Congress wanted to bias the development of science toward solutions relying on mechanical engineering but not chemistry. And the creation of a new, artificial chemical catalyst reflects no less ingenuity or human invention merely because it does not constitute a mechanical apparatus. Indeed, the conceptual distinction between a "machine" and a "manufacture" or "composition of matter" is slippery at best. A molecule can do work just as complex and important as any "machine" man has devised (*see, e.g.,* deoxyribonucleic acid). The Supreme Court appears to have assumed that the engineered micro-organisms in *Chakrabarty* were manufactures or compositions, *see* 447 U.S. at 309, but it seems more accurate to describe them as tiny biological machines. And is a simple lever like a crowbar a "machine" or a "manufacture"? There is absolutely no reason to suspect that Congress or the Supreme Court ever expected the patentability of processes to turn on semantic disputes like these.

Third, any distinction between machines and manufactures or compositions also severs the *Bilski* test from its purpose—which is to implement the traditional rule that natural phenomena or fundamental principles are not patentable. Processes involving synthetic, patentable compositions of matter, such as the thiopurine drugs at the heart of the patents-in-suit, no more preempt "natural laws" or "fundamental principles" than processes involving man-made machines do.

This Court also explained in *Bilski* that the problem with the patents in cases like *Grams* and *Meyer* is that they "effectively sought to pre-empt the fundamental mental process of diagnosing the location of a malfunction in a system." *Bilski*, 545 F.3d at 965. In other words, the patents were drawn so broadly and were so untethered from any specific context that they threatened to preempt basic natural principles or methods of problem-solving. Requiring that a process be tied to a specific man-made machine ensures that the patent will not sweep that broadly into natural principles; but requiring a tie to a specific man-made *composition of matter* fulfills exactly the same purpose. A broad interpretation of the "machine" prong of the *Bilski* test is therefore consistent with its purpose, and would ensure that *Bilski* does not accidentally invalidate all of the method of use patents that routinely accompany patents on man-made substances—such as method of treatment patents for synthetic pharmaceuticals. *See supra*, at 23-26.

3. Prometheus's patents do not implicate *Bilski* because they do not recite any natural phenomenon

In the alternative, if this Court did not wish to adopt a broad understanding of the "machine" prong at this time, it could reach a similarly sensible result simply by holding that the *Bilski* test does not apply at all to processes that do not recite any "natural" phenomenon—including methods of treatment or diagnosis using synthetic drugs. Indeed, the jurisprudential problem with which this Court was wrestling in *Bilski* is not present in cases like this one at all. *Bilski* attempted to fashion a test for assessing whether a process that recites a *natural* phenomenon (or other fundamental principle) "is tailored narrowly enough to encompass only a particular application of a fundamental principle rather than to pre-empt the principle itself." 545 F.3d at 954. Prometheus's patents, on their face, do not claim "natural phenomena" in any meaningful sense as they consist of a specific *man-made* course of treatment, involving administering synthetic drugs into the body and assessing the efficacy or toxicity of the drugs by measuring the resulting levels of metabolites that would not exist but for the handiwork of man.[12] There is no danger that Prometheus's patents will wholly preempt use of a natural

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[12] *See* A13073-75. *Compare Chakrabarty*, 447 U.S. at 309-10 (patentable man-made bacteria for cleaning up oil spills), *and Waxham v. Smith*, 294 U.S. 20, 22 (1935) (patentable means of incubating eggs "which had never occurred in nature"), *with Funk Bros.*, 333 U.S. at 131-32 (unpatentable natural bacteria), *and Lab Corp.*, 548 U.S. at 129, 134 (Breyer, J., dissenting) (arguing unpatentability of method relying on "natural relationship between homocysteine and vitamin deficiency" that exists in any "warm-blooded animal").

phenomenon when they operate wholly within the confines of a situation that could never occur in nature.

C. The Transformations and Machines Are Central to the Purpose of Prometheus's Patents and Are Not Confined to Insignificant Extra-Solution Activity

The *Bilski* court suggested that a machine or a transformation might not be sufficient to establish patentability if it involves mere "insignificant extra-solution activity," such as mere "data-gathering," that is not "central to the purpose of the claimed process." 545 F.3d at 962-63. In making this determination, courts must assess the purpose of the processes "as a whole" because "even though a fundamental principle itself is not patent-eligible, processes incorporating a fundamental principle may be patent-eligible." *Id.* at 958; *see Diehr*, 450 U.S. at 188.

The central purpose of Prometheus's treatment methods is to improve patient care by calibrating the proper dosage of a specific class of drugs to ensure efficacy while preventing life-threatening side-effects. In other words, the processes aim to physically transform the patient's body into a healthier state. This purpose requires administration of the synthetic drug to the patient (which transforms both the drug and the patient's body), transformation of bodily samples with machines in order to measure levels of metabolic byproducts, and transformation of that data into a warning that will alter future treatment. All of

the transformations and machines in Prometheus's patents are "central to the purpose of the claimed process," 545 F.3d at 962, and cannot be dismissed as "mere" data-gathering or insignificant extra-solution activity. Patients are not being treated with thiopurine drugs "mere[ly]" to gather data for an abstract calculation, but to treat very significant medical problems. And there is simply no way to conceive of or articulate the claimed process without the crucial steps of administering man-made drugs, and measuring the resulting metabolites.

The transformations and machines in the patents in suit are just as central to the patents-in-suit as the similar steps in *Diehr* and *Abele*. In those cases, as here, the data in question represented specific physical articles in a specific, concrete context directly tied to the purpose of process and, moreover, the steps generating the data would be a patentable process in their own right.

In *Diehr*, the patentable method recited an improved process for curing rubber, which utilized time and temperature data, fed into a mathematical formula (the well-known Arrhenius equation), to calculate the time remaining until the curing was complete, and then generated a signal (a warning) when it was time to terminate the curing process. As *Bilski* explained, the process in *Diehr* had "several specific steps to control the curing of rubber more precisely." *Bilski*, 545 F.3d at 953. The Supreme Court could have parsed the steps into data gathering, a mathematical formula already known in the prior art, and the "insignificant post-

solution activity" of warning that it was time to terminate the cure. But the Court specifically rejected that approach. Instead, the Supreme Court recognized that the process as a whole was directed to "'curing synthetic rubber.'" *Id.* at 952 (quoting *Diehr*, 450 U.S. at 187). The data that was gathered, and the warning that was generated, were central to the obvious purpose of the process: to improve the reliability of that curing. Indeed, even without applying the mathematical formula (or fundamental principle) to the data, there would still have been a patentable process, albeit a marginally less useful one.

Likewise, in *Abele*, this Court's predecessor approved the patent-eligibility of a "narrowly-claimed" method for improving CAT scans by performing certain mathematical calculations on the resulting X-ray data before visually displaying it. *Bilski*, 545 F.3d at 963; *see Abele*, 684 F.2d at 903-04, 908-09. Those calculations resulted both in a clearer visual display and less exposure of the patient to radiation. *Abele*, 684 F.2d at 904. The data at issue "clearly represented physical and tangible objects, namely the structure of bones, organs, and other body tissues." *Bilski*, 545 F.3d at 963. *Abele* concluded that the initial "production" of the X-ray beam and the subsequent "detection" of the beam once it has passed through the patient were not mere data-gathering steps for performing the calculations. *Abele*, 684 F.2d at 908. To the contrary, they were part and parcel of a process patentable in its own right, and with diagnostic and therapeutic value in

its own right. As the court explained, "absent the algorithm, the production, detection and display steps would still be present and would result in a conventional CAT-scan process. Accordingly, production and detection cannot be considered mere antecedent steps to obtain values for solving the algorithm . . . ." *Id.* Analogizing to *Diehr*, the court noted that "[t]he improvement in either case resides in the application of a mathematical formula within the context of a process which encompasses significantly more than the algorithm alone." *Id.* at 909.

Similarly, Prometheus's processes are "narrowly-claimed" to provide an improved method of treating certain diseases, and transforming the patient's body, using immunosuppressant drugs. *See Bilski*, 545 F.3d at 963. The administration of the drugs and the determination of the metabolite levels after the drugs have been processed within the patient's body are in no way "mere antecedent steps to obtain values" to perform an abstract calculation. Those steps, with all of the necessary transformations and machines, are essential to the purpose of adjusting dosage to improve patient care while decreasing exposure to toxicity, just as the steps in *Diehr* and *Abele* were essential to improving the vulcanization of rubber and the calibration of a CAT scan imaging process. Indeed, the patents in suit are best understood as a method of improving the performance of an underlying process (patient treatment with synthetic thiopurine drugs) that is itself independently within the scope of § 101—just like the vulcanization process in

Diehr or the CAT scan in *Abele*. In short, Prometheus's processes "encompass[] significantly more than the [correlation] alone," *Abele*, 684 F.2d at 909, and the machines and transformations integral to the "data gathering" and "warning" steps are not "insignificant" but are plainly "central to the purpose of the claimed process," *Bilski*, 545 F.3d at 962-63.

On the other hand, the patents-in-suit differ markedly from the processes found unpatentable in *Meyer*, *Grams*, and *Abele*. In *Meyer* and *Grams*, the processes were directed toward general diagnostic concepts rather than any specific steps to perform particular diagnoses. *See Bilski*, 545 F.3d at 965. In *Meyer*, the claimed process required unspecified "diagnostic tests" on an "undefined 'complex system.'" *Id.* at 962, 965. "The diagnostic tests were not identified, and the 'factors' were not tied to any particular measurement; indeed they could be arbitrary." *Id.* at 965. "No machine was recited in the claim, and the only potential 'transformation' was of the disembodied 'factors' from one number to another." *Id.*

In *Grams*, this Court rejected a process claim for diagnosing an unspecified "abnormal condition" in a person by identifying and noticing discrepancies in the results of "unspecified clinical tests" of different parts of the body. *Id.* at 965; *see Grams*, 888 F.2d at 840 ("The specification does not bulge with disclosure on those tests" and only "briefly refers to, without describing, the clinical tests that

provide data.."). In fact, the invention in *Grams* was so generalized that it was "applicable to *any complex system*, whether it be electrical, mechanical, chemical, biological, or combinations thereof." *Grams*, 888 F.2d at 836 (emphasis added). *Grams* distinguished the patentable narrowly-tailored claim in *Abele*, where the "production and detection steps were not viewed as mere antecedent steps to obtain values to solve the algorithm" because the purpose was "to improve the CAT-scan process" and the process "'encompasse[d] significantly more than the algorithm alone.'" *Id.* at 840 (quoting *Abele*, 684 F.2d at 909). In *Abele*, the court also held patent-*in*eligible a "broad" independent process claim that "did not specify any particular type or nature of data" and did not "specify how or from where the data was obtained or what the data represented." *Bilski*, 545 F.3d at 962.

In contrast to *Meyer*, *Grams*, and the unpatentable process in *Abele*, the patents-in-suit are set in a specific, concrete context that entails "significantly more" than an abstract calculation, as its purpose is an improved method of treatment for particular diseases with particular immunosuppressant drugs. Prometheus's methods of treatment do not merely encompass the "fundamental mental process of diagnosing the location of a malfunction" in an "unspecified multi-component system" using unspecified tests and data. *Bilski*, 545 F.3d at 965. The patents specify the nature and source of the data (metabolite levels of the patients taking the drugs), various methods for measuring the data (such as HPLC),

what the data represents (efficacy or toxicity), and the specific conclusions to be drawn (the need to alter the dosage). Although the initial steps produce data, they are clearly central to the purpose of the process and cannot be dismissed as insubstantial extra-solution activity.[13]

Indeed, by parsing the steps independently and ignoring how they fit together into the overall purpose of the process, the district court committed an error that both the Supreme Court and this Court have repeatedly warned against—including, most recently, in *Bilski* itself. As this Court explained, process claims must be viewed "as a whole" and "it is irrelevant that any individual step or limitation . . . by itself would be unpatentable under § 101." *Id.* at 958; *see Diehr*, 450 U.S. at 188. But the district court's failure to grasp the central purpose of the processes led it to dismiss "the 'administering' and 'determining' steps" as "merely necessary data-gathering steps for any use of the correlations," A00029; A00037, when, as shown above, those steps are essential to the goal of providing improved

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[13] In a footnote, this Court in *Bilski* commented, in dicta, that the process in *Lab Corp.* for determining a vitamin deficiency by assaying amino acid levels—which three Justices would have found unpatentable—was "similar" to those found unpatentable in *Grams* and *Meyer*. *Bilski*, 545 F.3d at 965 & n.27. Unlike those in *Lab Corp*, however, Prometheus's processes are directed not just at observing a naturally-occurring characteristic of the body, but at *treating* (transforming) the body itself by administering a safe and effective dose of a synthetic drug. Unlike the vitamin deficiency correlations in *Lab Corp.*, the correlations utilized by the patents-in-suit describe an *artificial* state of affairs. In any case, *Bilski* did not purport to adopt the non-binding three-Justice opinion dissenting from the dismissal of certiorari in *Lab Corp*.

treatment. Similarly, the district court dismissed "the final step—the 'warning' step"—as a mere "mental step" precisely because the court refused to acknowledge that the warning is part and parcel of improving the patient's treatment. A00029. Having thus erroneously discarded individual constituent steps that are integral to the overall purpose, the district court concluded that the patents here "embody only the correlations," which it concluded represent a "natural" phenomenon. A00028; A00029. But a great many patentable processed can be parsed into individual steps that would, standing alone, appear to be unpatentable. That includes the process that the Supreme Court held to be patentable in *Diehr*—which consisted of data measurements, a calculation governed by natural laws, and a warning. The district court's reasoning squarely "conflict[s] with the Supreme Court's proscription against dissecting a claim and evaluating patent-eligibility on the basis of individual limitations." *Bilski*, 545 F.3d at 959.

III. AN EXPANSIVE MISREADING OF *BILSKI* WOULD ELIMINATE ALL MEDICAL TREATMENT AND DIAGNOSTIC PATENTS AND USURP CONGRESS'S PREROGATIVE

The district court's reasoning in this case, and any interpretation of the "machine-or-transformation" test that would invalidate the patents-in-suit, would threaten to destroy the entire field of medical treatment and diagnostic patents. Thousands, if not tens of thousands, of such patents have been granted, and they have become the essential underpinning of a vibrant and innovative industry of

inestimable value to mankind. *See, e.g.*, A12939-13013 (collecting numerous such patents, including many held by Mayo itself); *supra* at 23-26 (discussing this Court's well-established recognition of patentability of medical treatment methods). Neither the statutory language nor this Court's decision in *Bilski* requires such a tragic result.

The Supreme Court and this Court have both recognized the danger that an overly-restrictive test under § 101 will stifle innovation. The Supreme Court, for example, has stressed that it has no intention of "freez[ing] process patents to old technologies, leaving no room for the revelations of the new, onrushing technology." *Benson*, 409 U.S. at 71. And, in *Bilski*, this Court made clear that its test must be "properly applied" and "refined" as necessary so as to tread lightly on future scientific and technological advancements. *Bilski*, 545 F.3d at 956; *see id.* ("[W]e agree that future developments in technology and the sciences may present difficult challenges to the machine-or-transformation test . . . .").

Mayo itself has been rewarded over the years with several medical diagnostic patents that would be invalid under the litigation position it is taking, strategically, in this case. For example, in 1999, Mayo was issued a patent on a "diagnostic method" to detect the presence of inflammatory bowel disorder, consisting of "obtaining a physiological sample" and "determining the level" of a certain protein, "wherein the level is *correlated* to the presence or absence of said

inflammatory bowel disorder." A12940. More recently, Mayo has received patents on methods for evaluating or detecting other "naturally occurring" conditions such as plaque deposits in mammalian brains, the Epstein-Barr virus, and lung cancer. U.S. Pat. Nos. 7,371,365 (May 13, 2008), 7,368,233 (May 6, 2008), 7,365,176 (Apr. 29, 2008). And Mayo is not unique. A diverse range of institutions have obtained patents on improved medical treatment and diagnostic methods for conditions such as bone loss, urolithiasis, breast cancer, ovarian cancer, prostate cancer, Alzheimer's disease, and fibromyalgia. *See* U.S. Pat. Nos. 5,541,221 (1996) (Allergan), 4,621,077 (1986) (Instituto Gentili S.p.A.), 4,968,603 (1990) (Univ. of Cal.), 5,840,501 (1998) (Bayer Corp.), 5,599,677 (1997) (Abbott Labs.), 7,323,346 (2008) (Mass. Gen. Hosp. and Harvard Univ.), 7,056,686 (2006) (Cedars-Sinai Med. Ctr.).

The principal medical advances of the next century will likely include treatments optimized for individual patients on the basis of genetic or other testing, such as the patents-in-suit or processes that identify genetic markers that make a patient likely to benefit (or not) from a uniquely targeted cancer treatment. Educational institutions, non-profit organizations, corporations and scientists have spent tens of millions of dollars in recent years uncovering the correlations between naturally-occurring genes in the human body and the efficacy of various man-made treatment strategies, opening the way to new and highly effective

treatment and diagnostic protocols.[14] These innovations have consistently been held patentable by the U.S. Patent and Trademark Office, and recognized by this Court. *See, e.g.*, *Fiers v. Revel*, 984 F.2d 1164, 1166, 1172 (Fed. Cir. 1993); *In re Bell*, 991 F.2d 781, 782 (Fed. Cir. 1993).[15]

The patentability of such discoveries is vital to enabling the educational institution, non-profit organization or scientist to recover the research investment and continue to invest in future research. Indeed, prominent *amici* have warned of the tremendous dangers of an overly restrictive interpretation of § 101. In *Lab Corp.*, the Intellectual Property Owners Association urged the Supreme Court not to "disturb the existing property rights of patentees and disrupt incentives for current and future scientific and technological research." Br. Amicus Curiae of Intellectual Property Owners Ass'n at 2, *Lab Corp.*, 2005 WL 3476621 (Dec. 15, 2005). Also, the American Intellectual Property Law Association warned that "[t]he rapid discovery of biomarkers for disease, . . . as well as prediction of an

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[14] For example, Myriad Genetics developed and patented a widely-used diagnostic test based on their discovery of the BRCA1 and BRCA2 genes—known as BRACAnalysis®—which determines a patient's risk of developing hereditary breast and ovarian cancer. Patients testing positive have up to a 92 percent risk of developing breast or ovarian cancer, or both, by age 70.

[15] Mayo owns a number of patents that claim genes, gene fragments, and proteins. *See, e.g.*, U.S. Pat. Nos. 6,475,723 (2002), 6,407,211 (2002), 6,303,370 (2001), 6,177,610 (2001), 5,747,283 (1998), 5,744,355 (1998). There have been unsuccessful attempts in Congress to curtail patents on genetic material. *See, e.g.*, H.R. 977, 110th Cong. (introduced Feb. 9, 2007); H.R. 3967, 107th Cong. (introduced Mar. 14, 2002).

individual's response to therapy, is launching a new era of personalized medicine that will rely heavily on patent exclusivity for the financial stability and incentive to stimulate commercialization of new diagnostic tools." Br. Amicus Curiae of Am. Intellectual Property Law Ass'n at 22, *Lab Corp.*, 2006 WL 303907 (Feb. 6, 2006). Similarly, in *Bilski*, the Biotechnology Industry Organization pointed out that constricting the scope of § 101 "would . . . frustrate advancements in the biotechnological arts." Br. Amicus Curiae of Biotechnology Indus. Org. at 18-20, *In re Bilski*, 2008 WL 1842268 (Apr. 7, 2008).

The Supreme Court has repeatedly emphasized that "[t]he subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts,'" and that if restrictions are appropriate they should come from Congress. *Chakrabarty*, 447 U.S. at 315-18 (quoting U.S. Const. art. I, § 8, cl. 8). Despite various opportunities, Congress has chosen not to restrict the patent protection on which innovation in medical biotechnology is built. For example, in 1995, Congress considered, but did not enact, a bill exempting certain medical methods from patent protection. H.R. 1127, 104th Cong. (1995); A13067. Then, in 1996, Congress provided limited immunity from patent infringement liability for the performance of certain medical procedures, but conspicuously declined to exempt such procedures from patent protection. *See* 35 U.S.C. § 287(c); Pub. L.

No. 104-208, § 616, 110 Stat. 3009, 3009-67 (1996); *see also J.E.M.*, 534 U.S. at 145 (reasoning that, in the face of numerous plant patents, Congress "not only failed to pass legislation indicating that it disagrees with the PTO's interpretation of § 101, it has even recognized the availability of [§ 101] patents for plants").

A holding that Prometheus's treatment methods are unpatentable would have to rest on premises—such as a needlessly narrow conception of transformation or "machines," or an overly expansive exclusion of what constitutes "mere data gathering" or "insignificant extra-solution activity"—that would threaten to render all medical treatment and diagnostic methods unpatentable. There is no reason or justification for this Court to squelch the promise of genetic and personalized medicine with an approach to § 101 that is arbitrarily hostile to innovation in medicine and biotechnology, and that treats anything involving the human body as an unpatentable natural phenomenon. The statute provides no warrant for such expansive and misguided judicial policymaking, which would wrongly usurp Congress's fundamental authority to set public policy for the patent system. And the dangers would extend well beyond medicine and biotechnology. Essentially any mechanical or chemical process relies for its efficacy on the "correlation" between a human action and its "natural" consequences under scientific laws.

This Court and the Supreme Court recognize a narrow judicially-created exception to the otherwise sweeping scope of § 101, which prevents anyone from

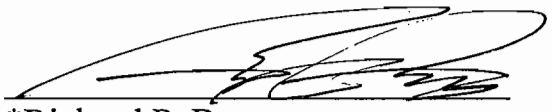
claiming a patent on a fundamental principle in the abstract. But that exception must be handled cautiously, and construed narrowly, or it threatens to render entire fields of crucial innovation unpatentable. Nothing in the letter or spirit of *Bilski*'s machine-or-transformation test compels such a result.

CONCLUSION

For the foregoing reasons, the district court's grant of summary judgment to Mayo on the ground of patent invalidity should be reversed.

Dated: January 9, 2009

Respectfully submitted,



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I hereby certify that on January 9, 2009, I caused twelve (12) copies of the foregoing **BRIEF FOR APPELLANT** to be delivered by hand to Mr. Jan Horbaly, Clerk, United States Court of Appeals for the Federal Circuit, 717 Madison Place, NW, Room 401, Washington, DC 20439, and two (2) copies of the foregoing brief to be served via FedEx upon the following:

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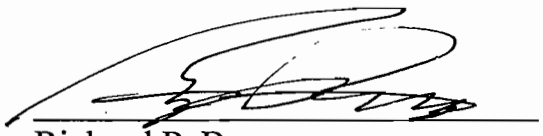

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