No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

PETITIONERS,

V.

PROMETHEUS LABORATORIES, INC.,

RESPONDENT.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE RESPONDENT

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QUESTION PRESENTED

Whether the Federal Circuit correctly held that concrete methods for improving the treatment of patients suffering from autoimmune diseases by using individualized metabolite measurements to inform the calibration of the patient's dosages of synthetic thiopurines are patentable processes under 35 U.S.C. §101.

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INTRODUCTION

Mayo's brief distorts the record and ignores the Federal Circuit's unchallenged construction of the patents-in-suit.[1] Prometheus's claims are not drawn to scientific facts in the abstract, and they do not "preempt" broad principles like the laws of chemistry or the idea of measuring metabolites.[2] No one can infringe these claims merely by thinking about correlations. The claims describe concrete and specific physical processes, employing synthetic drugs and machines, that are used only to improve the clinical treatment of seriously ill patients.

Mayo argues that the claims' physical steps should be disregarded because they were old in the art, but that is precisely the discredited "point-of-novelty" approach to 35 U.S.C. §101 that this Court flatly rejected thirty years ago in *Diamond v. Diehr*, 450 U.S. 175 (1981), and again recently in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). This Court has made clear that a process must be evaluated for patent eligibility under §101 *as a whole*. Novelty and non-obviousness are distinct, fact-intensive questions that are not before this Court. And there certainly is no reason, at the dawn of the 21st century, for this Court to adopt special rules that would render personalized medicine

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[1] Petitioners Mayo Collaborative Services, which does business as Mayo Medical Laboratories ("Mayo Labs"), a for-profit commercial laboratory, and its affiliated non-profit co-defendant Mayo Clinic Rochester ("Mayo Clinic") are referred to herein collectively as "Mayo" unless otherwise specified.

[2] Respondent Prometheus Laboratories Inc. is referred to herein as "Prometheus."

inventions, or other processes designed to produce useful information, uniquely unpatentable under §101.

The Federal Circuit correctly held that the patents-in-suit are "squarely" patent-eligible "processes." This Court should affirm.

STATEMENT

A. Factual Background

Because this petition arises from Mayo's motion for summary judgment, all of Prometheus's "evidence … is to be believed, and all justifiable inferences are to be drawn in [its] favor." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

1. *The Medical Problem.* Immune-mediated gastrointestinal disorders, such as Crohn's disease and ulcerative colitis, are incurable conditions that afflict millions of individuals. 2JA7.[3] Patients with these disorders suffer from debilitating symptoms and complications, including arthritis, anemia, rectal bleeding, diarrhea, abdominal pain, liver disease, skin ulcers, colon carcinoma, and intestinal cancer. 2JA7, 9-10. Although physicians have long treated these disorders with powerful corticosteroids to provide short-term relief from acute symptoms, such drugs cannot be used to control the disorders on a long-term basis without risking serious side effects. *See, e.g.*, Dkt.141 at 398; Barbara S. Kirschner, *Safety of Azathioprine and 6-Mercaptopurine in Pediatric Patients with Inflammatory Disease*, 115 Gastroenterology 813, 813 (1998); Daniel H. Present et

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[3] "_JA___" refers the Joint Appendix; "Pet.App.___" refers to the Petition Appendix; "CA_____" refers to the Joint Appendix in the Court of Appeals; and "Dkt.___" refers to the District Court docket.

al., *6-Mercaptopurine in the Management of Inflammatory Bowel Disease: Short- and Long-Term Toxicity*, 111 Annals of Internal Med. 641, 641 (1989).

These autoimmune disorders can also be treated effectively with synthetic thiopurine compounds, such as 6-mercaptopurine (6-MP) and azathiopurine (AZA), which transform inside the body into metabolites that suppress the patient's immune system and mitigate the symptoms. 2JA7, 10-11; 1JA25-27, 31-32. If administered in appropriate dosages, thiopurines are a safe and effective option for many patients, allowing doctors to avoid or minimize the need for potent steroids. *See* 1JA31.

The practical problem addressed by the patents-in-suit is determining the proper thiopurine dose for each patient. Because of variations in the activity level of the enzyme that breaks down these drugs (thiopurine methyltransferase, or TPMT), everyone metabolizes thiopurines differently. 2JA7. If a dose turns out to be too high for a particular patient, it could cause severe, potentially fatal, side-effects. 2JA7, 12, 25. Even "minimal doses" can be fatal for a minority of the population. 1JA26; 2JA7. These risks typically led doctors who used thiopurines to start with a very low dose and work slowly upwards while continually monitoring and testing their patients' blood and liver for toxicity. *See*, *e.g.*, Sanjoy Banerjee & Warren P. Bishop, *Evolution of Thiopurine Use in Pediatric Inflammatory Bowel Disease in an Academic Center*, 43 J. Pediatric Gastroenterology & Nutrition 324, 328-29 (2006). This "start low, go slow" approach multiplied office visits and costs and dramatically delayed the drug's effectiveness. *See* Marla C. Dubinsky et al., *A Cost-Effectiveness Analysis of Alternative Disease*

Management Strategies in Patients with Crohn's Disease Treated with Azathioprine or 6-Mercaptopurine, 100 Am. J. Gastroenterology 2239, 2243-45 (2005). And doctors still risked toxic consequences if they overshot the appropriate dosage for a particular patient. Many physicians, accordingly, were reluctant to treat their patients with thiopurines despite the potential benefits. 2JA7; 1JA31; Present, 111 Annals of Internal Med. at 641.

Researchers appreciated, in theory, that determining a patient's thiopurine metabolite levels could provide valuable information about the efficiency with which that patient metabolizes the drug. 2JA10. And laboratories had the technology to determine those metabolite levels from blood or bodily samples. 2JA11. But developing and validating a metabolite-based treatment protocol proved difficult because the complex metabolic pathways at issue were not completely understood. *See, e.g.*, 1JA26; Dkt.502 McClenahan Decl. Ex. I at 60.

Once administered, thiopurines are converted within the body into various metabolites, including 6-thioguanine (6-TG),[4] which is thought to be the active metabolite, and 6-methyl mercaptopurine (6-MMP). *See* 2JA7, 11; 1JA31; Dkt.45 at 194. In 1996, researchers at Hôpital Sainte-Justine in Montreal, led by Drs. Ernest Seidman and Yves Théorêt, concluded that measuring the level of those two metabolites in red blood cells can permit doctors to assess "responsiveness to treatment" in patients with gastrointestinal autoimmune disorders. Dkt.502

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[4] For purposes of this brief, 6-TG also refers to 6-thioguanine nucleotides (6-TGN). *See* Pet.App.3a n.1.

McClenahan Decl. Ex. I at 65; *see* 2JA1, 10; Dkt.43 at 128. After additional clinical research, they identified certain metabolite levels as useful targets for calibrating the treatment of these patients. In particular, they determined that a dose that results in a level of 6-TG between 230 and 400 picomoles (pmol) per 8 x 10^8 red blood cells and a level of 6-MMP below 7000 pmol per 8x10^8 red blood cells should be therapeutically effective and nontoxic. *See* 2JA10-13, 16-18; *see also* Dkt.45 at 194-95 (discussing 1995-1998 study period). Based on that research, Seidman and Théorêt filed a provisional patent application on improved treatment methods in 1998. *See* 2JA1, 19. The patents-in-suit both stem from that application.

No evidence in this record supports Mayo's suggestion (at 21) that, when that application was filed, doctors were already using measured metabolite levels clinically to calibrate thiopurine dosages for patients suffering from autoimmune disorders. To the contrary, at the time, there was persistent skepticism about whether monitoring metabolite levels would improve patient treatment. In 1997, for example, Mayo's own Dr. Sandborn wrote that "measurement of [red blood cell] 6-TGN and 6-MMP in patients with Crohn's disease treated with AZA or 6-MP remains investigational and cannot be recommended for routine clinical use." Dkt.43 at 128.[5] It was not until 1999,

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[5] *See also, e.g.*, Dkt.43 at 128 (1997 editor's note) (future studies needed to conclusively "establish a 'therapeutic window'"); Dkt.44 at 252 (declaration of Dr. Stephan R. Targan ¶ 7) (noting "skepticism of experts"); Dkt.16 at 300 ("[6-TG] target levels remain controversial"); Dkt.43 at 151 (2004 Sandborn article) ("routine determination" of such metabolites remains a "debated topic").

when Prometheus introduced its test, that metabolite measuring tests became commercially available to practicing gastroenterologists. Dkt.45 at 190-91.

2. *Prometheus's Claimed Treatment Methods*. When Seidman and Théorêt were awarded the patents-in-suit on their new treatment methods they assigned them to their employer hospital. *See* Pet.App.2a-5a; 2JA1-18 (No. 6,355,623, "the '623 patent"); 2JA19-35 (No. 6,680,302, "the '302 patent").[6] And the hospital granted an exclusive license to Prometheus, a pharmaceutical and diagnostic company that specializes in the development and commercialization of products that help physicians treat gastrointestinal autoimmune disorders. Pet.App.2a; CA12596.[7]

The various asserted claims in the two patents differ in certain respects, but all describe similar multi-step processes for improving the thiopurine-based treatment of patients suffering from autoimmune diseases by using metabolite measurements to help calibrate optimal doses. *See* 2JA16-18, 34-35.[8]

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[6] Although the actual motivations of the inventors in this case are irrelevant, nothing in the record supports Mayo's counter-intuitive conjecture (at 5) that they and their employer, which licensed their patents, were not motivated at all at the outset by the possibility of obtaining licensing fees.

[7] A redacted version of the license agreement is under seal in the district court. Dkt.275 Ex.H. No party or court has disputed that Prometheus has all substantial rights necessary to maintain this suit. *Cf.* U.S. Br. 5 n.2.

[8] Prometheus only asserted certain independent claims ('623 patent claims 1, 7, 22, 25, and 46, and '302 patent claim 1) and certain dependent claims ('623 patent claims 6, 14, 24, 30, 32, 33, 35, 36 and 53) in this litigation. *See* Pet.App.6a. Hereafter, any

First, most of the claims begin with the administration of a thiopurine compound to a patient with an autoimmune disorder. As noted, the thiopurine converts within the body into metabolites that do not otherwise exist in nature. 1JA26.[9]

Second, the patient's metabolite levels are determined. Because "metabolite levels are not detectable in raw human tissue," all methods for measuring their concentration require "significant chemical and physical alteration of blood or human tissue" and sophisticated laboratory equipment and machines. 1JA29-31, 42-43; 2JA11. Some of the dependant claims, for example, specify the use of high pressure liquid chromatography (HPLC), which 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. 1JA29-30.

Third, the metabolite measurements are compared to the patents' reference levels, "warning" the physician about the potential efficacy or toxicity of the patient's dosage. Pet.App.21a.

Claim 1 of the '623 patent is representative of the three-step claims at issue. It recites:

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discussion of the patents is limited to the asserted claims unless otherwise noted.

[9] Claim 46 of the '623 patent, and its associated dependent claims, omit that first "administering" step and start with the second step: "determining" the metabolite levels "in a subject administered a [thiopurine] drug …, said subject having said immune-mediated gastrointestinal disorder." 2JA18.

> 1. 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 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.

2JA16.

The patents' various dependent claims further limit the methods to treatment with specified thiopurine compounds (such as AZA), using specified methods for determining metabolite levels (such as HPLC), and determining the results in specified measurement units (such as red blood cells). *E.g.*, 2JA16-17 (cl. 6, 32).[10] The patents do not claim the use of other drugs (such

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[10] Other *un*asserted claims limit the methods to the treatment of certain classes of patients (children) or certain autoimmune disorders (such as collagenous colitis) or to the consideration of certain toxic side-effects (such as hepatic toxicity). *E.g.*, 2JA16-17 (cl. 9, 10, 12).

as steroids) to treat autoimmune diseases or the use of thiopurines to treat other diseases (such as breast cancer or leukemia).

Since their introduction, Prometheus's patented methods have improved the lives of countless individuals suffering from autoimmune diseases. *See*, *e.g.*, Banerjee & Bishop, 43 J. Pediatric Gastroenterology & Nutrition at 326-29. With these tools, doctors are both more willing and better able to treat patients effectively with thiopurines and minimize resort to more toxic or less effective drugs.

The patented test, moreover, is both cost-effective and readily available. Hospitals and physicians wishing to use Prometheus's PROMETHEUS Thiopurine Metabolites test (formerly known as the PROPredictRx® Metabolites test) send Prometheus a blood sample, and Prometheus provides the results of the test with a risk assessment based on the metabolite levels. *See* 2JA36 (sample test results form). The test costs about $260. 1JA28. One study found that use of the test reduces net thiopurine treatment costs by about 10% (about $700 per patient in the first year) and reduces the time to effectiveness by about 14% (nearly four weeks). Dubinsky, 100 Am. J. Gastroenterology at 2245 tbl.5 (2005).

3. *Mayo's Competing Commercial Test.* Mayo is a substantial Prometheus customer, purchasing and using Prometheus's patented test over 17,000 times between 1999 and 2007. Pet.App.5a-6a; 1JA28; Pet. Br. 9.[11] In 2004, however, Mayo announced its intent to

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[11] Prometheus's test remains in Mayo's test catalog. *See* http://www.mayomedicallaboratories.com/test-catalog/Overview/91564 (last visited Oct. 25, 2011).

sell its own competing test called "Azathioprine Metabolites Profile, Blood." *See* Pet.App.6a; 2JA40; *see also* 1JA9-13 (recounting Mayo's business motive).

Mayo's test (like Prometheus's) is intended for "[p]hysicians who are treating patients," 1JA7; it measures the same metabolites as Prometheus's test; and it specifies similar metabolite levels for ensuring efficacy and avoiding toxicity. Pet.App.6a, 111a-12a; 2JA40. Indeed, Mayo developed its test using Prometheus's test as a model. *See* Dkt.146 at 67-69. One of the test developers explained that, because "Prometheus was the only other provider of this method," Mayo used Prometheus's test "[a]s a measure of accuracy" to "validat[e]" Mayo's method. *Id.* at 69; *see also id.* at 52 ("Prometheus is the only lab in the United States doing Azathioprine metabolite …. Why reinvent the wheel?"); Dkt.528 Morgan Decl. Ex. 17.

Mayo was poised to earn a 60% profit margin on this commercial test. 1JA28. When Prometheus brought the present suit, Mayo stayed its hand. Pet.App.6a; CA10905. But Mayo is anxious to "begin selling its competitive product." Appellees' Opp. to Mot. to Stay 4 (Fed. Cir. Aug. 11, 2008).

B. Procedural Background

1. *District Court Proceedings.* When Prometheus learned that Mayo Labs, Mayo's for-profit arm, intended to market a practically identical competing test, it filed this action for patent infringement. Pet.App.6a; CA10036-41. Prometheus alleged that Mayo Labs infringed "directly, contributorily, and by inducement of others, by making, using selling, importing and/or offering for sale methods … covered by [the patents]." CA10037-38. Mayo Labs counterclaimed for declaratory relief of non-

infringement and of patent invalidity under 35 U.S.C. §§101, 102, 103, and 112. CA10045.

On cross-motions for summary judgment, the district court held that Mayo's test, as offered for sale, "literally infringes all elements of the patents-in-suit." Pet.App.115a. Mayo Labs had argued that it did not infringe because it specified a slightly different range of metabolites as the optimal therapeutic window. The district court, however, found that the term "about" as used in the claims' "wherein" clauses means plus-or-minus-15%, and concluded that Mayo's test infringed because Mayo's upper 6-TG threshold (450 pmol per $8x10^8$ red blood cells) was within 15% of Prometheus's upper level (400 pmol per $8x10^8$ red blood cells). Pet.App.113a-14a.[12] Mayo has not contested that construction.

Prometheus later amended its complaint to add Mayo Clinic, Mayo's non-profit arm. *See* 1JA14; Dkt. 110, 234. Prometheus alleged that Mayo Labs and Mayo Clinic infringed the asserted claims by, respectively, offering Mayo's test for sale and using Mayo's test, 2JA43, 58. Prometheus also alleged that Mayo Labs induced Mayo Clinic to infringe by performing the patented methods on patients of Mayo Clinic's employees, including Dr. Rokea el-Azhary. 2JA48, 53-54, 64-65, 70.[13]

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[12] The court did not need to address whether Mayo's 5700 upper 6-MMP threshold infringed Prometheus's 7000 level. Pet.App.113a n.16.

[13] Mayo's characterizations of Dr. el-Azhary's peripheral involvement in this matter are both irrelevant (because the district court has not addressed the issues) and highly misleading. *See* Pet. Br. 11-13, 25, 34, 44, 47, 56. It is undisputed that Dr. el-

The district court then granted Mayo's motion to invalidate Prometheus's claims for lack of patentable subject matter under 35 U.S.C. §101. Pet.App.83a. The court concluded that Prometheus's claims do not

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Azhary's patients were administered thiopurines for treatment of an autoimmune disease covered by the patented claims, and that Mayo measured the level of the indicated metabolites and provided a report of the metabolite measurements along with Prometheus's 6-TG correlation. *See* 2JA53-57; 1JA5-6, 20-22; Dkt.146 Ex.27. Mayo insists that Dr. el-Azhary did not believe that Prometheus's thiopurine metabolite correlations accurately describe the therapeutic range for the disease at issue. Pet. Br. 11-13, 34. But that is a disputed question of fact. One of Mayo's test developers conceded that, when Mayo reported the blood metabolite levels to Dr. el-Azhary, it noted "in the patient's interest" that the "therapeutic range" for 6-TG was between 235 and 400 in "an attempt to alert her that [some of] those values seemed abnormal according to literature values." 1JA5. If Mayo is correct that Dr. el-Azhary ignored or disbelieved Mayo's alert, Prometheus would agree that this particular allegation of induced infringement would fail (because Dr. el-Azhary would not have been "warned" by a comparison of the metabolite measurements to Prometheus's correlations).

Contrary to Mayo's assertion (at 13), moreover, Prometheus has never claimed that Dr. el-Azhary must stop her dermatological research until she purges her memory of the correlations. If she is using meaningfully different correlations to calibrate her patients' thiopurine treatments, she is not infringing the patents. If she is using Prometheus's correlations (and performing the other steps of the asserted claims) in patient treatment, Mayo can pay Prometheus for her tests as it has routinely for its other physicians since 1999.

Finally, Prometheus has never contended—and would never contend—that Dr. el-Azhary or Mayo would infringe the patents merely by publishing an article that says that Prometheus's correlations are inaccurate (or, for that matter, accurate). Mayo cites no evidence for its repeated insistence that Dr. el-Azhary (irrationally) did not "dare[]" publish an article for fear of infringing these patents. *See* Pet. Br. 13, 25, 47.

describe a "process" only after dissecting the claims into their constituent parts and disregarding the physical steps. The court held that the claims' first two steps (administering the thiopurine compound and determining the resulting metabolite concentrations) should be disregarded because they are mere "conventional" or "data-gathering" steps that are not independently novel. Pet.App.62a. Having limited its analysis to the third—"warning"—step, the court concluded that the patents improperly claim dominion over "the correlations themselves." Pet.App.62a-63a.[14] The court considered these correlations to be "natural phenomena" because they "result[] from innate metabolic activity in the human body," Pet.App.63a-71a, even though thiopurine metabolites indisputably do not occur naturally in the human body and are created only through human intervention. The court further concluded that the patents "'wholly pre-empt' use of the natural phenomenon such that the 'practical effect is [an improper] patent on the [phenomenon] itself.'" Pet.App.72a (quoting *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972)) (second alteration in original).

2. *Federal Circuit's First Decision.* The Federal Circuit reversed. Applying the machine-or-

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[14] The district court rejected Prometheus's argument that the third step requires "that the doctor (or any person) 'provide' a warning." Pet.App.63a. Under the district court's claim construction, by reference to the correlations "it is the metabolite levels themselves that 'warn' the doctor that an adjustment in dosage may be required." *Id.* Accordingly, a doctor who does not believe Prometheus's correlations are accurate is not "warned" within the meaning of these patents of a potential need to alter dosage–and thus does not infringe the claims. Prometheus has not challenged that ruling.

transformation test, the court held that Prometheus's methods "squarely fall within the realm of patentable subject matter because they 'transform an article into a different state or thing,' and this transformation is 'central to the purpose of the claimed process.'" Pet.App.40a (citation omitted). Specifically, it determined that the claims entail at least two integral transformations. First, "[w]hen administering a drug such as AZA or 6-MP, the human body *necessarily* undergoes a transformation" in response to the administration of these synthetic drugs. Pet.App.41a (emphasis added). Second, "[d]etermining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation," because "[s]ome form of manipulation, such as the high pressure liquid chromatography … is necessary to extract the metabolites from a bodily sample." Pet.App.42a-43a. "'[A]t the end of the [determination] process, the human blood sample is no longer human blood; human tissue is no longer human tissue.'" Pet.App.43a (citation omitted).

The Federal Circuit concluded that these transformations cannot be disregarded as "mere[] data-gathering" or "'insignificant extra-solution activity'" appended to a bare recitation of the correlations, Pet.App.44a-45a (citation omitted), because it construed the claims as limited to the *patient treatment* context. *See*, *e.g.*, Pet.App.41a ("The invention's purpose to treat the human body is made clear in the specification and preambles of the asserted claims."). It explained that "the administering step provides thiopurine drugs *for the purpose of treating disease*, and the determining step measures the drugs' metabolite levels *for the purpose of assessing the drugs' dosage during the course of treatment*."

Pet.App.44a (emphasis added). The transformations, therefore, are not peripheral or tacked-on, but "central to the claimed methods" and "'sufficiently definite to confine the patent monopoly within rather definite bounds.'" Pet.App.42a (citation omitted).

Further, the court held that the inclusion of a mental step—even as the final step—does not render an otherwise patentable process unpatentable. Pet.App.45a-47a. It explained that, "[a]lthough a physician is not required" in the "warning" step "to make any upward or downward adjustment in dosage," the process taken as a whole "provide[s] useful information for possible dosage adjustments to the method of treatment using thiopurine drugs for a particular subject." Pet.App.47a.

Although it believed the integral involvement of transformations was dispositive of the §101 inquiry, the Federal Circuit distinctly addressed, and rejected, the district court's finding that the claims impermissibly preempt all practical uses of a natural phenomenon. The court explained that "the claims do not preempt natural processes" but instead "utilize them in a series of specific steps … comprising particular methods of treatment." Pet.App.48a. (citing *Diehr*, 450 U.S. at 187). As in *Diehr*, Prometheus's method patents "'seek only to foreclose from others the use of that [principle] in conjunction with all of the other steps in their claimed process.'" *Id.* (quoting *Diehr*, 450 U.S. at 187).

The Federal Circuit emphasized that "the only issue" it was addressing was "whether the claims meet the requirements of §101" and that the appeal did "not raise any questions about lack of novelty, obviousness, or overbreadth, since those are separate statutory

requirements for patentability under §§102, 103, and 112, respectively." Pet.App.39a.

3. *This Court's Initial Grant of Certiorari.* While Mayo's first certiorari petition was pending, this Court decided *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). The Court in *Bilski* rejected two proposed nonstatutory "categorical" limitations on §101 patentability. *Id.* at 3229. First, the Court held that the machine-or-transformation test is an important tool for determining patent eligibility, but that an invention may be patent-eligible even if it does not satisfy that test. *Id.* at 3227. Second, the Court held that business method patents are not *per se* unpatentable. *Id.* at 3228-29. Ultimately, however, the Court found that the particular business method claims at issue did not constitute statutory "processes" because, evaluated as a whole, they merely described the abstract idea of risk hedging and would "preempt" use of that broad concept "in all fields." *Id.* at 3229-31 (applying *Benson* and *Parker v. Flook*, 437 U.S. 584 (1978), as "limited" by *Diehr*).

The Court then vacated the Federal Circuit's first decision in this case and remanded for further consideration in light of *Bilski*. Pet.App.24a.

4. *Federal Circuit's Second Decision.* After supplemental briefing, the Federal Circuit (with two new panel members) again held Prometheus's methods patentable under §101. The court explained that, under *Bilski*, patent eligibility turns on whether Prometheus's claims "are drawn to a natural phenomenon, the patenting of which would entirely preempt its use as in *Benson* or *Flook*, or whether the claims are drawn only to a particular application of that

phenomenon as in *Diehr*." Pet.App.12a (citing *Bilski*, 130 S. Ct. at 3230).

The Federal Circuit cited *Bilski*'s reaffirmation that the machine-or-transformation test remains a "'useful and important clue'" to patentability, and once again found that Prometheus's patents satisfy the "transformation prong" of that test because the claimed methods transform an article into a "'different state or thing'" and the transformations are central to the treatment purpose of the claims. Pet.App.14a-16a (quoting *Bilski*, 130 S. Ct. at 3227). The court also reaffirmed that the patents do not impermissibly preempt a natural phenomenon by claiming particular applications of the recited thiopurine correlations. Pet.App.15a.

SUMMARY OF ARGUMENT

I. The judicially crafted principle that "natural phenomena" and "abstract ideas" are not eligible for patent protection under §101 reflects two distinct concerns. First, to be patent-eligible, a process must really be a *process*—a series of steps that involve physical action in the real world, as opposed to merely an idea or principle stated in the abstract. Second, that process must be described at a narrow and specific enough level of generality that it does not preempt abstract ideas or basic building blocks of science that go far beyond what the patentee actually invented: A process for using a telegraph is patentable; the basic idea that information might be transmitted at a distance by exploiting laws of electromagnetism is not.

A. Prometheus's patented methods describe concrete methods for improving treatment of seriously ill patients with specific synthetic drugs. These patents do not claim the "correlations" they employ in

the abstract, but as part of specific physical processes employing drugs and machines. The traditional machine-or-transformation test provides an important clue to patentability because it crisply distinguishes mere abstractions from processes that operate in the real world. As the Federal Circuit recognized, the patents-in-suit pass that test with flying colors and easily satisfy the requirements of §101.

Mayo attempts to avoid that conclusion in three ways, none of which has merit. First, Mayo invites this Court to discard the two initial steps (administering the thiopurines and determining the resulting metabolite levels) because they were "well known" in the art. But this Court rejected that "point-of-novelty" approach over 30 years ago in *Diehr* and again recently in *Bilski*. Second, Mayo argues that those same two initial steps should be disregarded because, according to Mayo, they are not "central" to the patents' purpose. Mayo does this only by ignoring the Federal Circuit's settled construction that the claims are limited to patient treatment (a question not presented here) and that those two steps are *essential* to that purpose. Third, Mayo invites this Court to invent, out of whole cloth, a categorical rule that processes ending with the provision of useful information cannot be patentable—even if preceding steps involve machines and physical transformations. That argument also is inconsistent with *Bilski*, and it would impose an arbitrary and (in the information age) absurd limitation on patentability.

B. The patents-in-suit do not preempt natural phenomena in any relevant sense. Their "correlations" concern certain properties attending certain uses of non-natural thiopurine compounds, which would not exist but for the handiwork of man. A patent system

that recognizes thiopurine compounds themselves as potentially patentable subject matter, allowing preemption of *all* uses of these compounds, cannot be concerned that a process patent may preempt *some* of their uses. The extent of any preemption, moreover, is exceedingly narrow. These patents do not claim the abstract idea of calibrating drug doses by measuring metabolites or all ways of calibrating thiopurines. The transformations, ties to statutory subject matter, and limitation to treatment ensure that these patents merely claim, and preempt, one particular way to improve the treatment of patients suffering from certain diseases. That is precisely the sort of monopoly the patent system is meant to convey, not one of the basic building blocks of nature with which this Court's preemption analysis is concerned.

C. Prometheus agrees with the United States that the Patent Act's express statutory criteria for patentability—under 35 U.S.C. §§102, 103, and 112—make expansive judicial lawmaking under §101, of the sort invited by Mayo's arguments, unnecessary. But the application of those provisions is not before the Court in this case, and presents difficult and fact-bound questions that the lower courts should address in the first instance on remand.

II. Mayo proposes to transform §101 into an invitation for *ad hoc*, case-by-case evaluation of whether granting a particular patent will promote or retard the progress of the useful arts. That would create an unadministrable morass for courts and patent examiners, doom any hope for consistent administration of the patent laws, and usurp *Congress's* authority to determine the appropriate scope of the patent laws.

III. Any change in the Court's §101 jurisprudence that permitted a ruling in Mayo's favor, on whatever grounds, would have drastic and unfortunate consequences. It would upend settled expectations by invalidating thousands of diagnostic and personalized treatment patents. And it would stifle investment and innovation in the nascent field of personalized medicine. Contrary to Mayo's understanding, government funding does not translate pure academic research into practical products that benefit patients, and doctors themselves cannot bring to bear the resources necessary to fuel innovation and commercialize inventions on a large scale.

Mayo's contention that patents like these hinder medical care is also unpersuasive. The United States is the world leader in biotechnology and personalized medicine, in part because investors have committed billions of dollars in capital in reliance on the prospect of patents like these. Thousands have been issued, including many to Mayo itself. Mayo's short-sighted view would exchange long-term innovation (including cost reductions) for ephemeral savings. In any event, Congress already considered Mayo's invitation to broadly restrict patent protection for medical diagnostic and treatment methods—and chose to adopt a limited personal immunity for doctors instead.

ARGUMENT

I. PROMETHEUS'S METHOD PATENTS FALL SQUARELY WITHIN §101

In the Patent Act of 1793, Congress authorized patent protection for "any new and useful art, machine, manufacture or composition of matter, or any new or useful improvement on [such statutory subject matter], not known or used before the application." Act of Feb.

21, 1793, ch. 11, §1, 1 Stat. 318, 319. That language remained relatively constant until 1952, when Congress reorganized and amended the statute. 35 U.S.C. §101 *et seq*.

The Patent Act of 1952 separated the basic subject matter definition (§101) from the novelty requirement (§102), and created a new "non-obviousness" provision (§103) that codified and provided a more definite standard for the necessary level of inventiveness. *See Diehr*, 450 U.S. at 189-91; *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 12-17 (1966); *see also* S. Rep. No. 82-1979, at 5-6 (1952). The 1952 legislation also replaced "art" with "process" and defined "process" to mean "process, art or method, … includ[ing] a new use of a known process [or other statutory subject matter]." 35 U.S.C. §§100(b), 101 note. As enacted in 1952, §101 provides:

> Whoever 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 (emphasis added).

"'In choosing such expansive terms … modified by the comprehensive "any," Congress plainly contemplated that the patent laws would be given wide scope.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). As this Court has explained, §101 "is a 'dynamic provision designed to encompass new and unforeseen inventions,'" and courts are not free to "impose limitations … that are inconsistent with the Act's text." *Id.* at 3227, 3231 (citation omitted).

Despite the Act's broad language, courts have long recognized an implicit limitation that patents cannot issue for "'laws of nature, natural phenomena, and abstract ideas.'" *Bilski*, 130 S. Ct. at 3238 (quoting *Diehr*, 450 U.S. at 185). But that limitation must be approached carefully, because "all inventions can be reduced to underlying principles of nature," *see Diehr*, 450 U.S. at 189 n.12, and §101 is intended as "only a threshold test" that "defines the subject matter that may be patented" and leaves the fact-intensive analyses of novelty, non-obviousness, and written description to the Act's substantive "'conditions and requirements.'" *Bilski*, 130 S. Ct. at 3225 (quoting §101).

Under this framework, distinguishing between a patentable "process" and an unpatentable "principle" has not always been a straightforward inquiry. *See Flook*, 437 U.S. at 589. But two related strands emerge consistently from this Court's jurisprudence. The first strand derives from the text, and focuses on whether a patent claims an incorporeal principle or instead an application of that principle within a physical process. *See* U.S. Br. 13 (exception "follows directly from the text" because principles and abstractions are not "processes"). The second strand is atextual but reflects a longstanding judicial appreciation that process patents cannot be crafted at such a high level of generality that they effectively preempt "basic tools of scientific and technological work," *Benson*, 409 U.S. at 67, and grant dominion over inventions that the patentee may never have envisioned, *O'Reilly v. Morse*, 56 U.S. 62, 112-14 (1854).

Prometheus's patents do not run afoul of either limitation: they claim concrete applications of principles

(not the principles themselves), and to the extent they can be said practically to preempt any scientific knowledge—*i.e.*, the relationship of particular metabolite levels to the efficacy or toxicity of the doses of particular synthetic drugs used to treat patients with particular diseases—it is only at the very granular level at which all patents, by design, preempt particular applications of scientific knowledge. Hence, as the United States recognizes, the patents in suit fall "squarely" within §101. U.S. Br. 32.

A. Prometheus's Patents Claim "Processes" Under §101

As this Court long ago explained, a "process" cognizable under the Patent Act is "a mode of treatment of certain materials to produce a given result"; it "requires that certain things should be done with certain substances, and in a certain order." *Cochrane v. Deener*, 94 U.S. 780, 788 (1877). On that understanding, a scientific fact or abstract idea—such as the Pythagorean Theorem, the law of gravity, the natural characteristics of bacteria, or "the basic concept of hedging"—is not a patentable process. *Bilski*, 130 S. Ct. at 3231. "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented …." *Le Roy v. Tatham*, 55 U.S. 156, 175 (1853).

Because all real-world processes must operate according to natural principles, concrete *applications* of such principles have always been understood to be patentable.[15] As one early court explained, "[t]he

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[15] *See, e.g.*, *Bilski*, 130 S. Ct. at 3230 ("'an *application* of a law of nature … to a known structure or process'" is patentable (quoting *Diehr*, 450 U.S. at 187)); *Tilghman v. Proctor*, 102 U.S. 707, 724

instant that the principle, although discovered for the first time, is stated … as the agent of[] producing a certain specified effect, it is no longer an abstract principle, it is then clothed with the language of practical application, and receives the impress of tangible direction to the actual business of human life." *Househill Coal & Iron Co. v. Neilson*, 1 Webs. Pat. Cas. 673, 684 (1843) (lower court op.). The process claims at issue here are patentable because they claim concrete applications of scientific principles, not principles in isolation.

Mayo urges this Court to ignore the initial physical steps of these treatment methods (either because they are not novel or because they are merely incidental) and reverse the decision below because the "warning" step *standing alone* would not be a §101 process. Alternatively Mayo contends that, regardless of the character of their initial steps, methods such as these must be categorically excluded from §101 because they end with an information-providing mental step. None of those arguments has merit.

1. These Patents Claim Concrete Applications

Prometheus's patents do not claim in the abstract the inventors' scientific discoveries about the relationship between 6-TG and 6-MMP metabolite levels and the efficacy or toxicity of a patient's dose, but instead claim processes which apply that

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(1881) ("[H]aving invented and practically exemplified a process for utilizing this [scientific] principle, … he was entitled to a patent …."); *Le Roy*, 55 U.S. at 175 ("The elements of the power exist; the invention is not in discovering them, but in applying them to useful objects.").

knowledge in a series of physical steps that enable physicians to improve patient treatment.

The traditional machine-or-transformation test confirms that Prometheus's patented methods do not claim principles in the abstract. In *Bilski*, this Court rejected the Federal Circuit's holding that a §101 process *necessarily requires* a machine or transformation. 130 S. Ct. at 3227. But every Justice in *Bilski* reaffirmed that the machine-or-transformation test remains "a useful and important clue" to patentability. *Id.*; *id.* at 3232 ("[T]he entire Court agrees[] that … the machine-or-transformation test is reliable in most cases ….") (Stevens, J., concurring in judgment); *id.* at 3258 ("'[T]ransformation 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.'") (Breyer, J., concurring in judgment) (citation omitted).

The Court has repeatedly looked to the machine-or-transformation test because a process necessarily constitutes a concrete application, and not merely an incorporeal fact or idea, if it transforms materials or works through other specific statutory subject matter, such as particular classes of machines or compositions of matter. Thus, for example, in *Diehr*, this Court affirmed the subject-matter eligibility of a patent on a process for curing synthetic rubber, which functioned by continuously updating a mathematical calculation of the time to cure, as a function of temperature and pressure, in order to determine when to open the mold. 450 U.S. at 177-78. Of course that mathematical function (the "Arrhenius equation") standing alone was an abstract scientific principle. But the Court

reaffirmed its appreciation that a process constitutes a patentable application rather than a mere abstract principle when it "perform[s] a function which the patent laws were designed to protect" such as "transforming or reducing an article to a different state or thing." *Id.* at 192; *see also*, *e.g.*, *Benson*, 409 U.S. at 70.

The same conclusion should obtain here. Prometheus's patents claim the application of scientific knowledge, and not that knowledge in isolation, because they describe processes for improved medical treatment that operate through a series of specific, concrete steps that collectively satisfy both prongs of the machine-or-transformation test.

First, the patent claims entail two fundamental transformations. As the Federal Circuit explained, when thiopurines are administered "the human body *necessarily* undergoes a transformation" that produces 6-TG and 6-MMP. Pet.App.17a. And the subsequent "[d]etermin[ation] [of] the levels of 6-TG or 6-MMP in a subject [also] necessarily involves a transformation"; "'at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue.'" Pet.App.18a. (citation omitted); *see* 1JA30-31. These transformations, moreover, are integral to the patents' core purpose of improving treatment of patients with the indicated autoimmune diseases. The administered thiopurines create within the body active metabolites that transform the patient's physiology to a healthier state and, when measured in transformed blood or tissue samples, the indicated metabolites provide a means to better calibrate subsequent doses.

Second, although the Federal Circuit found it unnecessary to reach the issue, the patents also satisfy the "machine" prong of the test. The "determining" step of each claim necessarily requires the use of machines to determine metabolite levels from human blood or tissue samples. Several dependent claims specifically require HPLC, a multi-step, machine-bound process. *See supra* at 7-8. The claimed processes also require and are inextricably tied to synthetic thiopurine drugs, which are a potentially patentable "composition of matter" under §101. This Court's precedents have discussed statutory subject matter ties in terms of "machines," but there is no reason for these purposes to discriminate among the classes of statutory subject matter. The Patent Act's definition of "process"—including "a new use of a known process, machine, manufacture, composition of matter, or material," 35 U.S.C. §100(b)—draws no such distinctions, and this Court has long understood that "where the result or effect is produced by chemical action, by the operation or application of some element or power of nature, or of one substance to another, such modes, methods, or operations are [equally] called processes" within the statutory subject matter, *Tilghman v. Proctor*, 102 U.S. 707, 722 (1881). A tie to a particular class of compositions of matter, no less than a tie to a particular class of machines, ensures that the claim is to a concrete application rather than an abstract principle.[16]

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[16] Indeed, the lines between the different classes of statutory subject matter are increasingly indistinct. Proteins, for example, frequently do work (such as self-replication, transport of intracellular materials, and catalysis of a chemical reaction) analogous to work done by machines.

The administration of thiopurines and measurement of thiopurine metabolites, in the course of treating patients with particular autoimmune conditions, distinguishes the concrete and valid process claims at issue here from an abstract (and unpatentable) claim to the naked idea that doctors generally may calibrate medicine based on metabolite measurements. Mayo has never disputed that, in principle, both of the process's first two steps (administering thiopurines and determining metabolite levels) *standing alone* would constitute patentable "process[es]" under §101. Those steps do not become abstract or any less a "process" when they are combined and followed by an additional step that uses an algorithm (comparing the measurements to the threshold levels stated in the "wherein" clauses) to generate information useful for patient treatment. Indeed, the statutory definition explicitly contemplates that a patentable "process" can be built on other patentable processes, because a new use of an old process is patentable. 35 U.S.C. §100(b).

2. Novelty And Inventiveness Have No Role In The Threshold §101 Analysis

Throughout this litigation, Mayo has argued that the initial "administering" and "determining" steps should be disregarded under §101 because they were already "well known" in the art—and that Prometheus's patented methods therefore must be analyzed as if they constituted *solely* the final warning step.[17] Consistent with that argument, Mayo has

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[17] *See, e.g.*, Br. for Appellees 2, 4-5, 23-24, 30, 33-36 (Fed. Cir. Mar. 30, 2009); Cert. Pet. i, 3-6, 12, 15, 18, 19, 22, 24, 28 (Oct. 22, 2009) (No. 09-490); Supp. Br. of Defendants-Appellees 3, 11-12

suggested that these treatment methods might be patentable if Prometheus had invented thiopurines or the processes for measuring metabolites. *See, e.g.*, Pet. Br. 24, 35-36; *accord* ARUP Br. 10. But §101 is not about who invented what, or when. The internal combustion engine is still a "machine" and the method in *Diehr* is still a "process" under §101 today even though neither is novel anymore.

Mayo's mode of analysis is precisely the old "point-of-novelty" approach to §101 that this Court briefly embraced in *Flook*[18] but then unequivocally rejected in *Diehr* as an improper conflation of patentable subject matter with novelty issues that are properly treated under §102. *Diehr* stressed (and *Bilski* reiterated) that courts must consider the invention "as a whole" under §101 rather than "dissect[ing]" and discarding the old elements. 450 U.S. at 188; *see Bilski*, 130 S. Ct. at 3230. As the United States explains, *Diehr* superseded *Flook* and "subsequently clarified" that for §101 purposes a process claim must be considered as a whole, including both its old and its new elements. U.S. Br. 16-17; *see also Bilski*, 130 S. Ct. at 3230 (*Diehr* "limit[ed]" prior case law).

This Court could not have stated that point more clearly than when it said, without qualification, that considerations of the novelty or nonobviousness "of any element or steps in a process, or even of the process

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(Fed. Cir. Oct. 1, 2010); Pet. i, 3, 5 & n.2, 15, 24, 26, 30 (Mar. 17, 2011) (No. 10-1150); Pet. Br. 5, 19, 24, 35-37.

[18] The Court in *Flook*, 437 U.S. at 591, relied on dicta from *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948), which was decided before the 1952 Act moved the statute's novelty condition to §102 and codified the judicial concern for inventiveness as non-obviousness in §103.

itself," are of "no relevance in determining whether the subject matter of a claim falls within the §101 categories of possibly patentable subject matter." *Diehr*, 450 U.S. at 188-89. The Court took pains to refute the specific argument Mayo now advances, explaining that "an *application* of a law of nature or mathematical formula to a *known … process*" is patentable. *See id.* at 187 (second emphasis added). Indeed, *Diehr* declared that a series of steps is a patentable process even if "all the constituents of the combination were well known and in common use." *Id.* at 188.

In reaching those conclusions, this Court adhered to the plain language of the statute. Section 100(b)'s definition of "process" expressly includes "a new use of a known process, machine, manufacture, composition of matter, or material." 35 U.S.C. §100(b). That language was intended to dispel any prior doubts[19] about whether "new uses" of old processes are patentable. *See, e.g.*, 35 U.S.C. §101 note; S. Rep. No. 82-1979, at 5. It equally dispels Mayo's argument. If "process" embraces new uses of old statutory subject matter, it unquestionably embraces a new treatment protocol that combines well-known and independently patent-eligible processes (administration of thiopurines and measurement of resulting metabolites) with useful knowledge about patient physiology.

Mayo and its *amici* also urge the Court to peek at novelty and non-obviousness during the §101 inquiry by assuming that any natural principle expressed in a

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[19] *See, e.g.*, *In Re Thuau*, 135 F.2d 344, 346 (C.C.P.A. 1943) ("[A] new use of an old thing or an old process, quite unchanged, can under no circumstances be patentable ….").

claim is old in the art and requiring a demonstration that the principle has been used in an "inventive" manner. *See*, *e.g.*, Pet. Br. 35-37; Law Professors Br. 2-4; ACMG Br. 18-33; ARUP Br. 19; *cf.* Pet. Br. 19 (steps that are "well known" and "long prevalent" "do nothing to narrow the scope of preemption of the biological phenomenon"). This is merely the point-of-novelty approach in new garb. It conflicts just as squarely with *Diehr*'s emphatic holding that novelty and non-obviousness are irrelevant to the §101 analysis. 450 U.S. at 191. And it blatantly ignores the fact that, in the 1952 Act, Congress moved the statute's novelty condition to §102 and created a new §103 to codify with "uniformity and definiteness" the judicial requirement of inventiveness that had previously been enforced under §101's predecessors. *See Graham*, 383 U.S. at 15; S. Rep. No. 82-1979, at 5-6.

There is no reason for this Court to reconsider its holding in *Diehr*, which it so recently reaffirmed in *Bilski*. The Professors protest (at 29-33) that the Court must import "inventiveness" back into §101 because, otherwise, the claims here might survive under §§102 and 103. But arguing backwards from a desired outcome is hardly persuasive. The Professors offer no coherent statutory justification for introducing into §101 a quick-and-dirty "inventive creativity" requirement that differs substantively from the express standards of §§102 and 103. Ultimately, the Professors rest on their belief that considering inventiveness as a threshold inquiry would send a clearer "signal[]" than analyzing the issue under the Act's express novelty and non-obviousness standards. That is dubious, but in any event an issue for Congress not the courts.

3. The Claims' Initial Steps Cannot Be Disregarded As Incidental

Mayo presumes throughout its brief that Prometheus's patented methods are not limited to actual medical treatment and instead would make an infringer of anyone who even thinks about the indicated correlations in the abstract. *See, e.g.*, Pet. Br. 2, 6, 7, 17-18. Mayo attempts in that way to recast the claims' administering and determining steps as mere incidental, extra-solution, data-gathering activity that "have no limiting effect on the claimed monopoly." Pet. Br. 20, 39. But the straw man that Mayo attacks bears no resemblance to the case that is actually before this Court.

Two different panels of the Federal Circuit analyzed the patents-in-suit as a whole and construed the claims as being limited to patient treatment. Pet.App.16a-17a, 40a-41a. Mayo did not ask this Court to review the Federal Circuit's claim construction. And this Court surely would not have taken the case for that purpose. The Federal Circuit's construction of these claims should, therefore, be respected as law of the case.

In any event, the Federal Circuit's claim construction is plainly correct. The first process step—"administ[ration] of [a thiopurine compound] to a subject having [an autoimmune disease]," *e.g.*, 2JA16—by definition only happens in the context of patient treatment because thiopurines are highly toxic and would not otherwise be used. *See*, *e.g.*, CA12705. Similarly, the "wherein" clauses—which require a warning of a potential therapeutic "need to increase the amount of said drug subsequently administered to said subject," *e.g.*, 2JA16—only make sense in the

context of medical treatment. The rest of the intrinsic record, moreover, including the claim preambles and specification, confirms that the claims are limited to methods of actual patient treatment, *see, e.g.*, 2JA7, 16-17—as the Federal Circuit found, Pet.App.16a-17a, 40a-41a.

Mayo thus wrongly asserts that the patents-in-suit might randomly ensnare doctors or researchers who do nothing more than inadvertently hear or think about the identified correlations between metabolite levels and drug efficacy or toxicity. *E.g.*, Pet. Br. 34, 37, 46-47. No one infringes these treatment patents merely by thinking about correlations or performing research outside of the treatment setting.[20] Infringement occurs only when thiopurines are administered to a patient suffering from an autoimmune disorder, blood or tissue samples are extracted, specified metabolites' levels are measured using sophisticated scientific instruments, and the doctor is warned (by a comparison of those measurements with the indicated correlations) of a possible need to adjust subsequent dosages for better treatment. As the Federal Circuit explained, "a physician who only evaluates the result of the claimed methods, without carrying out the administering and/or determining steps that are present in all the claims, cannot infringe." Pet.App.21a-22a. Mayo cannot render the initial physical steps of these

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[20] Mayo's (and its *amici*'s) invocation of the First Amendment is therefore inapposite. *See, e.g.*, Pet. Br. 46-47; ACLU Br. 16-23. And, in any event, no First Amendment concerns were properly raised or passed upon below, and they cannot be smuggled in via "constitutional doubt" because a decision affirming the patentability of these claims under §101 would not determine whether the claims are valid in other respects, *see infra* §I.C.

methods incidental by wishing away the Federal Circuit's construction of the claims.

4. Section 101 Does Not Categorically Exclude Processes That End By Providing Useful Information

Mayo argues that Prometheus's claims are invalid under §101 because they do not *require* an adjustment of dosage and instead end in a "mental step" that merely provides "useful information." Pet. Br. 18-19, 22-24, 33-34. That argument has no basis in the statute, precedent, or logic.

Mayo's proposed categorical limitation is untethered to anything in the Patent Act's language or history, and ignores *Bilski*'s recent, emphatic rejection of judicially created, bright-line exclusions. 130 S. Ct. at 3229. As the Federal Circuit explained, "the addition of the mental steps to the claimed methods … does not remove the prior two steps from that realm." Pet.App.21a. In *Diehr*, this Court similarly affirmed the patentability of process claims for curing rubber that used a mathematical equation (that could be solved mentally) to provide information about when to open a rubber mold. *See* 450 U.S. at 179 n.5. For §101 purposes, it cannot make any difference whether a patent uses an information-providing step as those claims did, in the *middle* of the process, or, as these claims do, at the *end* of the process. In either event, the patentee might face challenges proving that element of its infringement claim (*i.e.*, showing that the alleged infringer actually *performed* the mental step), but that is no reason to reject the patent-eligibility of such methods under §101.

Mayo's insistence that these patents should end with a physical step requiring the doctor to increase or decrease the next thiopurine dose in response to the information generated also makes no practical sense. As Mayo concedes, "[c]ase-by-case judgment" is "needed because patient-to-patient variability cannot be removed entirely even by observing metabolite levels." Pet. Br. 3. How a doctor incorporates information respecting these metabolite levels into particular treatment decisions may be affected by a host of other variables (*e.g.*, the severity of the autoimmune condition, the patient's general health, other medications, lifestyle choices, and risk tolerance). Mayo's categorical rule that all claims must end with an action step would just multiply byzantine claim drafting. A patentee would be required to attempt to set out and claim all of the manifold branches of possible therapeutic decision trees just in order to ensure that each process ends with an action step. That exercise is wasteful and unnecessary. This Court has routinely recognized that patents can properly leave ample room for "the judgment of the operator." *Mowry v. Whitney*, 81 U.S. 620, 645-46 (1872); *see also Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71 (1916). And that recognition is particularly apt here, as modern medicine is far too individualized for the rigid patent drafting requirement that Mayo advocates to be practical or desirable.

Nor would it make sense more generally, in today's information age, for this Court to rule under §101 that a process ending with a step that produces useful information is less patentable than a process that produces soap, rubber, or flour. The categorical prohibition that Mayo advocates would have precisely

the sorts of "wide-ranging and unforeseen impacts" that concerned this Court in *Bilski*, 130 S. Ct. at 3229-30. PTO has issued thousands of patents on medical and other methods that "end" precisely this way and the courts have long recognized their validity. *See infra* §III. And patents on information-producing methods are hardly limited to the medical context. PTO has issued innumerable similar patents in other fields, for uses ranging from sensing and diagnosing aircraft turbine engine conditions, to modeling the spread and containment of an oil spill, to "detecting airborne contaminants in real-time." U.S. Pat. Nos. 5,018,069, 7,136,793, 7,287,929; *see also*, *e.g.*, U.S. Pat. Nos. 5,633,173 (method for detecting defects in a semiconductor wafer), 6,313,640 ("method for diagnosing and measuring partial discharge on-line in a power transmission system"), 7,310,062 ("method to detect GPS signal tampering"). Nothing in *Bilski* was intended to "create uncertainty as to the patentability of … advanced diagnostic medicine techniques," 130 S. Ct. at 3227 (Kennedy, J., plurality opinion), let alone all processes providing valuable information. Mayo's approach would do just that.

B. Prometheus's Patents Do Not Preempt All Practical Use Of Any Relevant Principle

Prometheus's claims do not inappropriately preempt all practical uses of natural phenomena, laws of nature or abstract ideas.

As the Federal Circuit emphasized, this aspect of the Court's §101 jurisprudence must be approached with care. Almost *any* patent will preempt all practical uses of a "natural principle" or "abstract idea" if the principles or ideas are described with great specificity.

All real-world processes operate according to natural laws, and "preempting" others from exploiting particular phenomena in particular ways is, after all, the point of a patent.

As the United States recognizes (at 19, 24 n.5), this judicially created preemption exception to §101 has been applied only when patents would practically foreclose all uses of truly fundamental principles, in the abstract and across a broad range of potential endeavors and future applications, monopolizing future inventions the patentee may never have conceived. The seminal case is *O'Reilly v. Morse*, 56 U.S. 62 (1854), which approved Samuel Morse's patents on the telegraph (and use thereof) but disapproved a broader claim to "'the use of the motive power of the electric or galvanic current … however developed for marking or printing intelligible characters, signs, or letters, at any distances.'" *Id.* at 112 (quoting patent). This Court presciently anticipated that "[f]or aught that we now know some future inventor, in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in the plaintiff's specification," and that Morse therefore "claims an exclusive right to use a manner and process which he has not described and indeed had not invented." *Id.* at 113.

In the same vein, in *Benson*, this Court was concerned that the claim to the use on a computer of a formula for binary-coded decimal to pure-binary conversion was "not limited to any particular art or technology, to any particular apparatus or machinery, or to any particular end use." 409 U.S. at 64. "[T]he 'process' claim [was] so abstract and sweeping as to

cover both known and unknown uses" of the formula, which could "vary from the operation of a train to verification of drivers' licenses to researching the law books for precedents and … be performed through any existing machinery or future-devised machinery or without any apparatus." *Id.* at 68.

The Court voiced similar concerns in *Flook*. There the patent "d[id] not purport to explain" how to select the numerical constants (the weighting factor and the margin of safety) or the process variable (*e.g.*, temperature), how to monitor the process variables, how the chemical processes work, or how to set off or adjust an alarm. 437 U.S. at 586. Instead "[a]ll that it provide[d] [was] a formula for computing an updated alarm limit," which might be applied to any process that a person might choose to monitor. *Id.*

And, in *Bilski*, the Court rejected a patent on "[t]he concept of hedging [risk]" because it was "an unpatentable abstract idea, just like the algorithms at issue in *Benson* and *Flook*" and "[a]llowing petitioners to patent risk hedging would pre-empt use of this approach in all fields." 130 S. Ct. at 3231; *see also*, *e.g.*, *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989) (invalidating patent covering abstract concept of diagnosing "'any complex system, whether it be electrical, mechanical, chemical, or biological, or combinations thereof'") (quoting patent); *see generally* Mark A. Lemley et al., *Life After* Bilski, 63 Stan. L. Rev. 1315, 1332-37 (2011) (§101 prohibits overclaiming that would hinder future innovation) .

On the other hand, this Court has had no concern with claims that preempt more narrowly defined scientific facts or principles. In *Tilghman*, 102 U.S. at 709, for example, the Court found patentable a process

for producing "fat acids and glycerine from fatty bodies by the action of water at a high temperature and pressure." That patent wholly preempted the "natural phenomenon" that water applied at high temperature and pressure would have the stated effect on fatty bodies. But it did not preempt the broader natural principle that high temperature and pressure tend to break chemical bonds, and it did not preclude the use of other methods to separate fat acids and glycerine from fatty bodies, such as sulfuric-acid distillation or steam distillation. *Id.*

Similarly, the patent in *Neilson* wholly preempted the "natural phenomenon" that "heating the blast, in a receptacle, between the blowing apparatus and the furnace" would cause iron to smelt more rapidly in a furnace. *Id.* at 724 (discussing *Neilson v. Harford*, 151 Eng. Rep. 1266 (Ex. 1841)). The classic Goodyear vulcanization patent wholly preempted the "natural phenomenon" that "subjecting [India rubber] to a high degree of heat when mixed with sulphur and a mineral salt" would make it more durable and useful. *Id.* at 722. And the patent at issue in *Diehr* wholly preempted the "natural phenomena" that the Arrhenius equation, continually applied, predicts the optimal time for opening a rubber mold. But none of those preempted the broader phenomenon that matter changes phase with temperature or prevented achievement of the same results (smelting iron or curing rubber) through other means. *See also Telephone Cases*, 126 U.S. 1, 532-35 (1888) (upholding patent on method for using electricity in a certain way to transmit voice at a distance); *O'Reilly*, 56 U.S. at 112 (upholding patent on method for using electricity in a certain way to transmit characters at a distance).

Prometheus's claims likewise do not preempt a natural phenomenon in any relevant (and prohibited) way. The "natural" correlations purportedly being preempted are, in fact, wholly *non*-natural. And those non-natural correlations are only being claimed in a narrow application.

1. Prometheus's Patents Do Not Recite Natural Phenomena

Mayo argues that Prometheus's patents, in reciting certain metabolite levels correlating to warnings for future treatment purposes, preempt all practical uses of the correlations. But to the extent the patents preempt most practical uses of those correlations, they do not preempt "natural phenomena" in any meaningful sense.

This Court's cases applying the "natural phenomena" exclusion from patentability have distinguished between phenomena that exist unchanged in their natural state (which may not be claimed) and those that would not exist but for the intervention of man (which may be claimed). In *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948), for example, in holding the composition patent invalid, the Court emphasized that the combined bacteria "perform in their natural way," that the "combination does not improve in any way their natural functioning," and that "[t]hey serve the ends nature originally provided and act quite independently of any effort of the patentee." In *Chakrabarty*, in contrast, the Court held that a "nonnaturally occurring" bacterium could be patented because it had "markedly different characteristics from any found in nature," unlike, for example, "a new mineral discovered in the earth or a new plant found in the wild." 447 U.S.

at 309-10. The altered bacteria in *Chakrabarty* were of course no less governed by natural laws than the unaltered bacteria in *Funk Bros.* But from a patentability perspective, the Court explained the crucial distinction is "between products of nature … and human-made invention." *Id.* at 313.

Although *Funk Bros.* and *Chakrabarty* were not "process" cases, the distinction that drove their holdings applies *a fortiori* in the process context. If the initial patent on a man-made invention can lawfully preempt the manufacture and all uses of that invention, the law cannot be concerned with a process patent that preempts less than that. In this way, an integral tie to statutory subject matter will ensure that a patent does not preempt a "natural phenomenon" in any objectionable sense. Combustion inside an automobile engine is surely mediated by natural laws, but both the engine itself and an improved method for tuning the engine are nonetheless patentable.

That principle is sufficient to reject Mayo's preemption arguments. The claimed processes here introduce a synthetic thiopurine compound into a patient's body, determine the levels of certain resulting metabolites (that would not exist but for the introduction of that synthetic compound), and then based on those levels warn the physician of a potential need to increase or decrease the next dose of the synthetic compound. None of these steps would occur but for the handiwork of man. *See* 1JA25-27. (Ironically, what Mayo considers the body's "natural" response is, in fact, an artificial *suppression* of the body's natural immune system.) The correlations discovered and utilized by the inventors are, for §101 purposes, entirely *unnatural*. As the United States

explains, the correlations "exist[] *because* of human ingenuity, not antecedent to it." U.S. Br. 20.

At bottom, the patents here simply utilize scientific principles discovered about certain applications of thiopurines in processes to optimize those applications. Because all applications of thiopurines could in theory be preempted by a composition of matter patent, principles governing certain applications are not basic building blocks of science with which preemption analysis is concerned.

2. These Claims Are Preemptive Only In The Narrow, And Permissible, Sense That All Inventions Are

Even if these phenomena were "natural," Prometheus's patents on specific methods of improving the treatment of autoimmune diseases with specific drugs are narrowly drawn and do not preempt abstract principles or ideas in a relevant sense. The transformations, ties to statutory subject matter, and limitation to patient treatment confine the scope of the claims sufficiently to ensure that no fundamental building blocks are removed from the public realm. These patents have no far-reaching designs on fundamental concepts like the diagnosis of abnormalities in a "complex system," *see In re Grams*, 888 F.2d at 836, or on basic principles of biochemistry or pharmacology that govern how drugs are transformed into metabolites. Nor do they seek to preempt the abstract notion that the efficacy or toxicity of any drug might be correlated with the levels of resulting metabolites produced by the body.

These patents do not affect the use of other drugs (such as steroids) to treat the indicated diseases or the

use of thiopurines to treat other diseases (such as breast cancer or leukemia). Indeed, the patents do not even foreclose other means of calibrating thiopurines for treatment of the covered (autoimmune) diseases. In addition to the traditional "start low, go slow" technique, doctors also calibrate doses of these drugs by determining, via genotype and phenotype, the efficiency with which each individual (via the TPMT enzyme) will convert the drugs into 6-TG and 6-MMP metabolites. *See*, *e.g.*, 2JA13, 16; Ernest G. Seidman, *Clinical Use and Practical Application of TPMT Enzyme and 6-Mercaptopurine Metabolite Monitoring in IBD*, 3 Rev. Gastroenterological Disorders S30, S31 (2003). And doctors and scientists of course remain free to develop new and better ways to treat these diseases and to calibrate the drugs at issue. Indeed, Mayo itself implicitly acknowledges as much, claiming that its 5700 level for 6-MMP is "widely used today." *See* Pet. Br. 8 n.3. Processes that use that correlation do not infringe the patents-in-suit because 5700 is not "about 7000," *See* Pet.App.113a-14a (interpreting "about" as +/- 15%). The narrowly drafted patents-in-suit will thus pose no substantial "obstruction[] to follow-on innovation." Lemley, 63 Stan. L. Rev. at 1330; *see id.* at 1344 (concluding that the claims at issue here are "not generative, nor will [they] unduly bar future inventors").

For all of Mayo's complaints about "patent monopolies that interfere with the work of scientists," Pet. Br. 41, and "countless researchers and innovators who are paralyzed," Pet. 19, Mayo has yet to identify any substantial activity that is preempted by Prometheus's patents, aside from Mayo's desire to copy and market a competing commercial test for the exact

same application. These patents do not even arguably preempt researchers' use of the indicated correlations outside of active patient treatment. Mayo's incessant references to Dr. el-Azhary are red herrings. Prometheus has never claimed that its patents cover pure research. Dr. el-Azhary is peripherally involved in this case only because Mayo Labs, a for-profit commercial laboratory, induced Mayo Clinic to infringe by urging its employees—such as Dr. el-Azhary—to use Mayo's infringing test in lieu of Prometheus' product. If Dr. el-Azhary was not treating patients, there was no infringement. If she truly did not consider Prometheus's correlations when making treatment decisions for her patients (although there is evidence to the contrary) then there was also no infringement. *See supra* at 11 n.13. And Mayo's repeated assertion that Prometheus's patents prevented Dr. el-Azhary from publishing findings disputing Prometheus' correlations is fanciful. *Id.*

On their face, Prometheus's claims to particularized medical treatment methods look nothing like the abstractions rejected in *O'Reilly*, 56 U.S. at 112 (claiming all uses of electricity to write at a distance, "'however developed'" (quoting patent)); or *Benson*, 409 U.S. at 68 (where the uses of the mathematical algorithm could "vary from the operation of a train to verification of drivers' licenses to researching the law books for precedents"); or *Flook*, 437 U.S. at 586 (where there were a "broad range of potential uses of the method" because "[a]ll that it provides is a formula"); or *Bilski*, 130 S. Ct. at 3231 (where the method claimed "the basic concept of hedging [risk]"). In those cases, this Court was legitimately concerned that the abstract nature of the claims would allow the

patentees to preempt innovations they never conceived of. Not so here.

The claims in this case are also drawn far more narrowly than the diagnostic method that the dissenters found objectionable in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124, 125-39 (2006) ("*LabCorp*") (Breyer, J., dissenting from dismissal of writ). Unlike Prometheus's claims, the claim in *LabCorp* was not limited to improving a specific *medical treatment*; instead it recited a "method for detecting" a vitamin deficiency in any warm-blooded animal that could be used for any purpose, including pure research. Unlike Prometheus's claims, moreover, the claim in *LabCorp* did not recite specific trigger levels; instead it merely taught that "elevated" total homocysteine levels correlates to a particular vitamin deficiency. *Id.* at 129. And unlike Prometheus's claims, the claim in *LabCorp* did not involve synthetic drugs and non-naturally occurring correlations; instead, it was based on a "natural relationship between homocysteine and vitamin deficiency" that exists without any human intervention. *Id.*

This case is instead like *Diehr*, where this Court held that the patentee's rubber curing processes did not "seek to pre-empt the use of [a well-known mathematical] equation" but sought "only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." 450 U.S. at 187. Prometheus likewise claims "a series of steps comprising particular methods of treatment." Pet.App.15a. And, as in *Diehr*, the addition and application of a principle ("natural" or not) to an otherwise patentable series of method steps, does not

(and *cannot*) render the resulting process *un*patentable.

C. Sections 102 and 103 Must Await Remand

The patents–in-suit might well eventually be analyzed under §§102 and 103 (and §112). But the application of those provisions to this case now would be premature. It was not addressed by the lower courts; it is not within the question presented, *see* S. Ct. R. 14.1(a); and the factual record of how those provisions might apply to this case has not yet been developed. As the United States recognizes, "[t]his Court should not resolve such questions in the first instance." U.S. Br. 27. Resolution of those issues, to the extent preserved, must await remand. *Id.* at 11-12.

Nonetheless, the United States suggests that this "Court's analysis of the Section 101 question … should be informed by" the government's "understanding of the way in which other Patent Act provisions address petitioners' central objection to the '623 and '302 patents." *Id.* at 27. The United States then urges this Court to share its view that, because they "differ[] from the prior art only with respect to the mental inference a doctor may draw after the 'administering' and 'determining' steps have been completed," the claims at issue are inherently anticipated by prior art—making them either non-novel or obvious. *Id.* at 26-31. With due respect to the government's preliminary thoughts, the complexity of the issues it raises argues powerfully against this Court making any determination about the appropriate analysis of these claims under §§102 or 103 without the benefit of factual development and full briefing. As Professors Burk and Lemley have explained, inherency is "perhaps the most

elusive doctrine in all of patent law." Dan L. Burk & Mark A. Lemley, *Inherency*, 47 Wm. & Mary L. Rev. 371, 373 (2005). Indeed, Mayo's law professor *amici* acknowledge (at 31) that claims like those at issue may satisfy §§102 and 103.

To weigh in prematurely, even in dicta, would risk unforeseen consequences and untoward damage to countless diagnostic patents and computer-aided inventions that end with algorithms permitting users to interpret information. For example, in *Arrhythmia Research Technology, Inc. v. Corazonix Corp.*, 958 F.2d 1053 (Fed. Cir. 1992), the Federal Circuit approved a method patent for processing electrocardiograph signals (which were ubiquitous in the art) through a complex mathematical algorithm and then "comparing" the resulting value with a level that had previously been determined to gauge the patient's risk of ventricular tachycardia. 958 F.2d at 1055; *see also In re Abele*, 684 F.2d 902 (C.C.P.A. 1982) (affirming patent-eligibility of process using algorithm to improve graphic images in CAT scans). Under the government's view, all such information-generating processes in the medical and computer fields would apparently fail under §§102 and 103. An issue of this magnitude must be approached with deliberation and due care.

Contrary to the United States's suggestion, moreover, Prometheus's patented methods do not fit neatly into the cited inherency precedents. Under those precedents, if the prior art cannot be practiced without also *inevitably* performing the purportedly new claim limitations, the new process is inherently anticipated by the prior art. *See, e.g.*, *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir.

1991). Likewise, merely recognizing a new benefit already inherently conferred by an old process does nothing to transform the existing process. *See, e.g.*, *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1277-79 (Fed. Cir. 2010). But at the same time it is well established that others' "incomplete and imperfect experiments" will not render a later successful invention anticipated. *Am. Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566, 595 (1874); *accord Telephone Cases*, 126 U.S. at 545 ("The difference between the two is just the difference between failure and success.").

On remand, Prometheus believes Mayo will be unable to demonstrate that the patented methods here involve steps and limitations that were *necessarily and inevitably* performed in the prior art (or are otherwise invalid under §§102 or 103). Although thiopurine drugs were administered for autoimmune diseases and researchers knew how to measure 6-TG and 6-MMP concentrations, there is no evidence that physicians treating autoimmune diseases measured thiopurine metabolites for clinical purposes before Prometheus's patents. *See supra* at 5-6. Prometheus, therefore, did not "'merely discover[] and claim[] a new benefit of an old process.'" *King Pharma*, 616 F.3d at 1275 (citation omitted). It identified the information necessary to make the combined steps clinically useful. *See* Burk & Lemley, 47 Wm. & Mary L. Rev. at 374 ("[I]f the public doesn't [already] benefit from the invention, there is no inherency.").

Prometheus will litigate all of these issues fully, with the benefit of briefing and factual development, if and when they are properly raised below. But they are not currently before this Court.

II. SECTION 101 DOES NOT INVITE A FREEWHEELING EXAMINATION OF THE LIKELY VALUE OF EACH PATENT

Mayo insists that, to decide the threshold question whether "'certain subject matter'" falls within §101, the federal courts (and, presumably, thousands of individual PTO examiners) should in each case "'ask whether granting [the] patents … in fact will promote [scientific] progress' or instead 'hinder competition that can effectively spur innovation.'" Pet. Br. 43 (quoting a 2003 FTC report). This Court should reject that proposition. As the Court has recognized, "the decision as to what will accomplish the greatest good for the inventor, the Government and the public rests with the Congress," *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 198-99 (1933), and "courts should not read into the patent laws limitations and conditions which the legislature has not expressed," *Diehr*, 450 U.S. at 182 (internal quotation marks and citations omitted).

When this Court explained in *Diehr* that subject matter eligibility must be confined to the kinds of inventions that "the patent laws were designed to protect," *id.* at 193, that was not, as Mayo would have it (Pet. Br. 46), an invitation for *ad hoc* judicial policymaking. As Chief Judge Rader recently explained, parties like Mayo who advocate a sweeping role for §101 threaten to turn the Patent Act's limited threshold inquiry into a new "substantive due process" of patent law, with all of the practical and legal problems that would entail. *Classen Immunotherapies, Inc. v. Biogen IDEC*, --- F.3d ----, Nos. 2006-1634, 2006-1649, 2011 WL 3835409, at *15 (Fed. Cir. Aug. 31, 2011) (additional views). Adding such amorphous and labor-intensive inquiries would

"exacerbate PTO's already formidable task of ensuring that more than 6500 patent examiners apply Section 101 in a predictable and consistent fashion," U.S. Br. 32, and burden district courts and litigants with indeterminate policy questions that the judiciary is not equipped to resolve. "Clear definitions of the classes of subject matter in Section 101 provide critical guidance to the public, inventors, and the PTO regarding the boundaries of the patent laws." U.S. *Bilski* Br. 44 (Sept. 25, 2009). A system that asks thousands of examiners and hundreds of courts to decide for themselves, in the abstract, whether patent protection for an invention would promote or retard scientific progress would impose staggering costs on the patent system, eliminate predictability, and diminish incentives for innovation.

Judge Hand's observation a half-century ago is no less true today: "It is not for [the courts] to decide what 'discoveries' shall 'promote the progress of science and the useful arts' sufficiently to grant any 'exclusive right' of inventors." *Reiner v. I. Leon Co.*, 285 F.2d 501, 503 (2d Cir. 1960).

III. A RULING FOR MAYO WOULD DISRUPT SETTLED EXPECTATIONS AND HINDER INNOVATION

Contrary to Mayo's insistence (at 45-48) that it is merely seeking to enforce existing limits on subject-matter patentability, a ruling for Mayo, whatever the rationale, would mark a significant change in the law that would dramatically alter the status quo and upset settled expectations. The impact, moreover, would be widespread because essential features of Prometheus's methods—the application of scientific knowledge to identified and measured biomarkers to produce

information useful for clinical diagnosis and treatment—describe the core of personalized medicine and underlie thousands of existing patents in the field of personalized medicine.

A ruling for Mayo would eviscerate existing patents for a host of important diagnostic and treatment processes, ranging from a method for "determining increased risk of developing type II diabetes," to a method of predicting T-cell lymphoma patients' response to treatment, to a method for "test[ing] for West Nile virus." U.S. Pat. Nos. 7,635,559, 7,919,261, 7,384,785.[21] A diverse range of institutions have obtained such patents. *See, e.g.*, U.S. Pat. Nos. 4,968,603 (Univ. of Cal.) (breast and ovarian cancer), 7,993,830 (Laboratory Corp. of America) (prostate cancer), 7,323,346 (Mass. Gen. Hosp. and Harvard Univ.) (gestational disorders), 6,316,197 (United States) (anthrax exposure). Indeed, Mayo itself has obtained numerous such patents, including for 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

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[21] *See also, e.g.*, U.S. Pat. Nos. 7,897,400 ("[n]on-invasive rapid diagnostic test for M. Tuberculosis infection"), 7,811,774 (method for classifying a breast tumor and assessing the prognosis), 7,709,222 (methods for making colon cancer prognoses using biomarkers), 7,670,792 (method for early detection of ovarian cancer using biomarkers), 7,482,135 (method for detecting kidney disorder), 6,972,180 (method of using saliva to diagnose and monitor breast cancer), 7,232,661 ("diagnostic method for prenatal identification of an increased risk of preterm delivery of a pregnant woman without clinical symptoms of preterm labor"); CA12939-3013 (collecting numerous such patents).

disorder." U.S. Pat. No. 5,928,883, CA12940. And examiners and courts have long recognized them as patentable. *See, e.g.*, *Arrhythmia Research Tech.*, 958 F.2d at 1054; *In re Abele*, 684 F.2d at 903-04, 908 & n.9; *see also* John F. Duffy, *Rules and Standards on the Forefront of Patentability*, 51 Wm. & Mary L. Rev. 609, 634-37 (2009) (discussing rise and demise of common law rule against patenting medial methods).

The consequences of an adverse ruling would of course not be limited to upsetting expectations on existing patents. More destructively, even, it would diminish the patent-based incentives that have made the United States the world leader in this field and decrease funding for future research and development. The principal medical advances of this century will likely arise from diagnoses of, and treatments optimized for, individual patients on the basis of genetic or other testing, like those described in the patents-in-suit or processes that identify biomarkers that make a patient likely to benefit (or not) from a uniquely targeted treatment. Such personalized medicine holds great promise for both enhancing patient care and reducing costs by permitting physicians to diagnose diseases earlier and more accurately, select the most effective treatment for a given patient, avoid unnecessary and costly treatments that are unlikely to work, and reduce adverse reactions. *See, e.g.*, Mara G. Aspinall & Richard G. Hamermesh, *Realizing the Promise of Personalized Medicine*, 85 Harv. Bus. Rev. 108, 109-11 (2007); Frances Toneguzzo, *Impact of Gene Patents on the Development of Molecular Diagnostics*, 5 Expert Op. Med. Diag. 273, 273 (2011); Personalized Medicine Coalition, *The Case For Personalized Medicine* 4-7

(2009) ("*Personalized Medicine*"); Roche Br. 2-3, 14. Personalized medicine also facilitates a shift to preventative care, which is typically less invasive and less expensive. *See Personalized Medicine* at 4.

The savings in health care costs from biomarker-related information that allows physicians immediately to identify optimal treatment and avoid adverse events are considerable—in some cases millions or billions from a single diagnostic regime. *See, e.g.*, *Personalized Medicine* at 7; PriceWaterhouseCoopers, *The New Science of Personalized Medicine: Translating the Promise Into Practice* 17 (Oct. 2009). For example, a genetic test to determine the proper dosage of a blood thinner could save $1.1 billion annually. Andrew McWilliam et al., AEI-Brookings Joint Center, *Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin*, Working Paper 06-23, at 12 (Nov. 2006). Doctors using Prometheus's patented methods are able to calibrate appropriate thiopurine dosage faster and at a lower cost than under the older "start low, go slow" approach. *See, e.g.*, Dubinsky, 100 Am. J. Gastroenterology at 2243 (finding that monitoring metabolites reduces costs by about 10% and time to effectiveness by about 14%).

But these innovations in personalized medicine are not free. Advancing the science and practice requires substantial investments—not only in the discovery of relevant biomarkers but also in completing the trials necessary to run the regulatory and third-party patient reimbursement gauntlets, and commercializing the basic science into products that actually benefit patients. *See* Roche Br. 4-16. Billions are invested annually in research and development of diagnostics and personalized medicine; indeed, bringing a single

diagnostic product to market can cost $10-$100 million. Roche Br. 3, 14-15 & n.6.

As Roche and Abbott Laboratories explain, strong patent protection is essential to incentivizing such private investment. *See* Roche Br. 4; *see also* Toneguzzo, 5 Expert Op. Med. Diag. at 274 ("industry has consistently confirmed that the protection that a patent affords is a key consideration for making an investment"); President's Council of Advisors on Sci. & Tech., *Priorities for Personalized Medicine* 21 (Sept. 2008) (patents are "essential" for the "large, high-risk R&D investments required to develop ... genomics-based molecular diagnostics"). Numerous *amici* in this and other cases— academics, universities, bar associations, trade organizations, and business interests—have recognized the same basic point.[22]

Conversely, weak or uncertain patent protection discourages capital investment. *See, e.g.*, Henry Grabowski et al., *The Market for Follow-On Biologics: How Will It Evolve?*, 25 Health Affairs 1291, 1300 (2006) ("[I]ncreased uncertainty and IP litigation in biotech also would have major negative-incentive effects on capital market decisions for developing private and public biotech firms with promising

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[22] *See, e.g.*, Br. of *Amici Curiae* Interested Patent Law Professors 13-16 (Fed. Cir. Jan. 18, 2009); Br. of *Amicus Curiae* Am. I.P. Law Ass'n 18-21 (Fed. Cir. Jan. 22, 2009); Br. of *Amici Curiae* Biotechnology Industry Org., Advanced Med. Tech. Ass'n, Wis. Alumni Research Found., and Regents of the Univ. of Cal. 4-5, *Bilski* (Aug. 6, 2009) ("BIO/University *Bilski* Br."); Br. *Amici Curiae* of Twenty Law and Business Professors 23, *Bilski* (Aug. 6, 2009); Br. of *Amici Curiae* Rosetta Genomics and George Mason University 9, *Ass'n for Molecular Pathology v. U.S. PTO*, No. 2010-1406 (Fed. Cir. Oct. 29, 2010).

pipelines."); Roche Br. 13-19; *see also* Federalist No. 62 ("What farmer or manufacturer will lay himself out for the encouragement given to any particular cultivation or establishment when he can have no assurance that his preparatory labors and advances will not render him a victim to an inconstant government?"). Invalidating the patents–in-suit and, by extension, countless others like them, would effect a "sea change" that creates "immeasurable uncertainty" and, "[w]ithout the confidence that investment-backed expectations can be realized, innovation will be retarded." Lawrence M. Sung, *Medical Alert: Alarming Challenges Facing Medical Technology Innovation*, 6 J. Bus. & Tech. L. 35, 58 (2011).

Mayo and its *amici* insist that federal government funding of basic research would fill the breach and provide the necessary dollars to incentivize innovation in personalized medicine. *See*, *e.g.*, Pet. Br. 51; Law Professors Br. 37. But even if the government were able to replace with public moneys all of the funds that are currently provided to universities and private companies through patent licensing fees, and even if government bureaucracies were as well-equipped as private actors to target funds to the most promising and valuable technologies, funding basic research alone would not provide the resources and incentives necessary to complete the full innovation life-cycle and "convert inventions that might otherwise exist only on paper into commercially viable products that improve the health and quality of life of the public." Roche Br. 13-14; *see also* BIO/University *Bilski* Br. 3-4. And the suggestion that innovation will nonetheless continue apace because doctors will perform the necessary research and development on their own, out of a sense

of duty or professional curiosity (Pet. Br. 44, 50-51), is shockingly naïve.

Mayo has not remotely demonstrated the wisdom of categorically eliminating patent incentives for private investment in this area. Although Mayo and its *amici* contend that patents like Prometheus's hinder innovation and degrade medical care, *see, e.g.*, Pet. Br. 40-45, 48-58; ACMG Br. 10-18, there is strong evidence to the contrary, *see* Roche Br. 19-25; Toneguzzo, 5 Expert Op. Med. Diag. at 274-75 (concluding that the real barriers are regulatory uncertainty and reimbursement by insurers); FTC, *Emerging Health Care Issues: Follow-up Biologic Drug Competition* 32 (2009).[23] Mayo's short-sighted approach seeks immediate savings in derogation of existing property interests and at the expense of great (and cost-effective) innovations over the long run.

Mayo's insistence (at 58) that enforcing patents like these "cannot be reconciled with the ethical duties of physicians" is even less persuasive. Prometheus's patents pose no unique threat to doctors' ethical obligations. Prometheus's test is widely available, and the fact that its price reflects a premium for innovation does not distinguish this invention from the thousands of patented drugs and medical instruments on which modern medicine also depends (and which physicians might also be duty-bound to employ). Despite its insistence that these patents are unethical, Mayo

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[23] Mayo's (and its *amici*'s) parade of horribles, such as a patent on weighing someone to determine their susceptibility to health risks, would as a practical matter be addressed under §§102 and 103. There is no reason to distort the threshold §101 inquiry based on such hypotheticals.

continues to this day to receive similar patents on methods of "monitoring" or "detecting" conditions in subjects, by "determining" and "detecting" characteristics in a sample, "wherein" the presence of those characteristics indicates a disease state. *See, e.g.* U.S. Pat. No. 7,998,670 (issued Aug. 16, 2011); U.S. Pat. No. 7,981,612 (issued July 19, 2011).

In any event, Congress has already considered these issues and, despite various invitations, has chosen not to restrict the patent-eligibility of medical processes. In 1995, Congress considered exempting certain medical methods from patent protection, but declined to do so. H.R. 1127, 104th Cong. (1995). And in 1996, Congress addressed the AMA's concerns about patent liability for doctors by providing a limited immunity from patent infringement liability for the performance of certain medical procedures—but Congress pointedly *did not* exempt such procedures from patent protection generally. 35 U.S.C. §287(c); *see* Pub. L. No. 104-208, §616, 110 Stat. 3009, 3009-67 (1996). Indeed, Congress declined to extend immunity to "the practice of a patented use of a composition of matter in violation of such patent," "the practice of a process in violation of a biotechnology patent," or the provision of "clinical laboratory services." 35 U.S.C. §287(c)(2)(A), (3). The legislative record demonstrates Congress's understanding that such methods are squarely within §101. *See Bilski*, 130 S. Ct. at 3228 (federal law "explicitly contemplates the existence" of business method patents); *J.E.M. Ag Supply, Inc., v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 145 (2001) (Congress "not only failed to pass legislation indicating that it disagrees with PTO's interpretation of §101, it has even recognized the availability of utility patents

for plants"); *accord* Duffy, 51 Wm. & Mary L. Rev. at 636-37 (noting that the new "statutory immunity … accomplishes [the AMA's] specific goal without completely foreclosing the possibility that the granting of patents for medical treatment could be socially worthwhile").

As the United States emphasizes, "[m]ethods of practicing the medical arts have long been viewed as [patent-eligible]"—indeed, "PTO has granted more than 150,000" such patents—and "Congress has recognized that longstanding practice." U.S. Br. 15, 16. This Court should not accept Mayo's invitation to upend settled expectations and interject a destructive uncertainty in the patentability of medical methods, particularly where Congress has expressly chosen another path. Having failed to get what they wanted from Congress, Mayo and its *amici* approach this Court as if it were a legislature of last resort. The Court should politely but firmly turn them away.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

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October 31, 2011

ADDENDUM

ADDENDUM

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35 U.S.C. § 100

§ 100. Definitions

When used in this title unless the context otherwise indicates—

* * *

(b) The term "process" means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.

* * *

35 U.S.C. § 101

§ 101. Inventions patentable

Whoever 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. § 287

§ 287. Limitation on damages and other remedies; marking and notice

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(c)(1) With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b), the provisions of sections 281, 283, 284, and 285 shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity.

(2) For the purposes of this subsection:

(A) the term "medical activity" means the performance of a medical or surgical procedure on a body, but shall not include (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent, (ii) the practice of a patented use of a composition of matter in violation of such patent, or (iii) the practice of a process in violation of a biotechnology patent.

(B) the term "medical practitioner" means any natural person who is licensed by a State to provide the medical activity described in subsection (c)(1) or who is acting under the direction of such person in the performance of the medical activity.

(C) the term "related health care entity" shall mean an entity with which a medical practitioner has a professional affiliation under which the medical practitioner performs the medical activity, including but not limited to a nursing home, hospital, university, medical school, health maintenance organization, group medical practice, or a medical clinic.

(D) the term "professional affiliation" shall mean staff privileges, medical staff membership, employment or contractual relationship, partnership or ownership interest, academic appointment, or other affiliation under which a medical practitioner provides the medical activity on behalf of, or in association with, the health care entity.

(E) the term "body" shall mean a human body, organ or cadaver, or a nonhuman animal used in medical research or instruction directly relating to the treatment of humans.

(F) the term "patented use of a composition of matter" does not include a claim for a method of performing a medical or surgical procedure on a body that recites the use of a composition of matter where the use of that composition of matter does not directly contribute to achievement of the objective of the claimed method.

(G) the term "State" shall mean any state or territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.

(3) This subsection does not apply to the activities of any person, or employee or agent of such person (regardless of whether such person is a tax exempt organization under section 501(c) of the Internal Revenue Code), who is engaged in the commercial development, manufacture, sale, importation, or distribution of a machine, manufacture, or composition of matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office), where such activities are:

(A) directly related to the commercial development, manufacture, sale, importation, or

distribution of a machine, manufacture, or composition of matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office), and

(B) regulated under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Clinical Laboratories Improvement Act.

(4) This subsection shall not apply to any patent issued based on an application the earliest effective filing date of which is prior to September 30, 1996.