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 PETITIONERS

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QUESTION PRESENTED

Prometheus's patents, which the district court invalidated but the Federal Circuit upheld, give Prometheus a sweeping monopoly on a biological correlation between drug administration and natural changes in blood chemistry. If these patents are sustained, health care providers, such as Mayo Clinic, cannot improve the numbers Prometheus has assigned to this correlation and provide more accurate drug monitoring services to patients at a lower cost, without permission from Prometheus.

The question presented is:

Whether 35 U.S.C. § 101 is satisfied by a patent claim that covers observed correlations between blood test results and patient health, so that the patent effectively preempts use of the naturally occurring correlations, simply because well-known methods used to administer prescription drugs and test blood may involve "transformations" of body chemistry.

RULES 24(b) AND 29.6 STATEMENT

All parties are identified in the caption of this brief. Petitioner Mayo Collaborative Services, a subsidiary of Mayo Clinic, is a for-profit Minnesota corporation that provides reference laboratory services under the name Mayo Medical Laboratories. Petitioner Mayo Clinic Rochester, a subsidiary of Mayo Clinic, is a charitable, nonprofit corporation located in Rochester, Minnesota. No publicly held company owns 10% or more of the stock of either petitioner.

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BRIEF FOR PETITIONERS

OPINIONS BELOW

The Federal Circuit's opinion following remand from this Court (Pet. App. 1a-23a) is reported at 628 F.3d 1347 (Fed. Cir. 2010). This Court's order granting certiorari, vacating, and remanding in light of *Bilski* v. *Kappos* (Pet. App. 24a) is reported at 130 S. Ct. 3218 (2010). The Federal Circuit's original opinion (Pet. App. 25a-49a) is reported at 581 F.3d 1336 (Fed. Cir. 2009). The district court's opinion holding Prometheus's patent claims invalid (Pet. App. 50a-83a) is reported at 2008 WL 878910 (S.D. Cal. Mar. 28, 2008).

JURISDICTION

The court of appeals entered its judgment on December 17, 2010, and this Court granted a timely petition for certiorari on June 20, 2011. The jurisdiction of this Court rests on 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

"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.

"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. § 100(b).

INTRODUCTION

For more than a century, this Court has made clear that a patent claim fails under 35 U.S.C. § 101 if it preempts all practical use of an abstract idea, natural phenomenon, or mathematical formula. The Court has explained that these fundamental tools of discovery must be available to all for use in developing new and better inventions.

Petitioners ask this Court to reaffirm that basic principle in the context of medical patents covering natural phenomena. The Prometheus patents claim a monopoly over consideration of a naturally occurring correlation between metabolites of a drug and the toxicity or efficacy of that drug, without specifying any concrete use of this correlation. As a result, the patents preempt all practical use of the naturally occurring correlation and are invalid under Section 101.

Justice Breyer has observed that broad and open-ended patents of this kind prevent "doctors from using their best medical judgment," "force doctors to spend unnecessary time and energy to enter into license agreements," "divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations," and "raise the cost of health care while inhibiting its effective delivery." *Laboratory Corp. of Am. Holdings* v. *Metabolite Labs.*, 548 U.S. 124, 138 (2006) ("*LabCorp*") (Breyer, Stevens, Souter, JJ., dissenting from dismissal of petition for certiorari). All these adverse effects are evident in this case. This Court should reverse the Federal Circuit's decision and invalidate Prometheus's patents under Section 101.

STATEMENT

A. Blood Testing For Metabolites.

All doctors know that a drug should be administered to a patient at a dose that is above an ineffective level but below a harmful level. Effective dosage ranges vary for each patient based on how a patient metabolizes the drug and on factors such as the patient's weight and medical condition.

Physicians often deal with these individual variations by analyzing blood samples for levels of "metabolites"—chemicals produced in the blood when a patient metabolizes a drug. The correlation between metabolites and patient condition is more consistent across a population than is the correlation between dosage levels and patient condition, so particular metabolite levels correlate generally with patient health. This is much like blood alcohol testing, where a certain blood alcohol level is a better indication of a person's condition, across a population, than the number of drinks the individual may have consumed.

Judgment plays a pivotal role in selecting the right correlation, as seen, by analogy, in the fact that many states initially set their acceptable blood alcohol level at 0.10, but adjusted it to 0.08 after further research. Case-by-case judgment also is needed because patient-to-patient variability cannot be removed entirely even by observing metabolite levels. The ability to question current wisdom, to develop better numbers, and to take into account relevant factors for each patient is critical to patient health and to our healthcare system. The *Wall Street Journal* recently reported that initial medical research is increasingly found to be wrong, and it

costs large amounts of money and many lives before such errors are corrected. Gautam Naik, *Mistakes in Scientific Studies Surge*, WALL ST. J., Aug. 10, 2011, available at http://tinyurl.com/43mf2ot. In making determinations about what metabolite numbers mean for patient health, the freedom to question old information and to improve on it is necessary to save lives.

B. The Patents At Issue.

The patents in this lawsuit involve blood testing after administration of a drug known as azathioprine, or thiopurine.[1] Thiopurine drugs have been administered for decades, and, as the patents admit, the appropriate levels of thiopurine metabolites in patients have been measured, studied, and discussed for many years. For example, English physicians studied them in the 1980s, and published articles about them relating to autoimmune diseases. See C.A. App. A12698-12701, A12705-12712, A12722-12727.

The inventors of the patents at issue here studied the correlations between thiopurine metabolite levels and the conditions of patients suffering

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[1] Azathioprine is the most commonly used thiopurine drug. It was sold under the brand name "Imuran" for years, and now is available in various generic forms. See FEDERAL DRUG ADMINISTRATION, ORANGE BOOK: APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Azathioprine "upon administration to a patient converts to 6-MP," which then "is broken down by the body into various 6-MP metabolites," including 6-TG (6-thioguanine) and 6-MMP (6-methyl-mercaptopurine). 6-TGN, referred to in many record documents, is a derivative of 6-TG. It is those metabolites that are covered by Prometheus's patents. Pet. App. 3a.

from gastrointestinal autoimmune diseases. They developed a database of pediatric patients with inflammatory bowel disease who had received thiopurine treatment. They used "methods well known in the art" to measure the metabolite levels in these patients. 2JA 11, at 9:13-14. Using these techniques, the inventors observed that patients seemed to get better when thiopurine's 6-TG (6-thioguanine) metabolite exceeded 230 picomoles per 800 million red blood cells and got worse when it exceeded 400 picomoles. The inventors also observed that patients got worse when thiopurine's 6-MMP (6-methyl-mercaptopurine) metabolite exceeded 7000 picomoles. They did not, however, "invent" these correlations between patient condition and metabolite levels, but merely recognized them as existing in the patient population that they studied. 1JA 15, 32.

The inventors worked at a teaching hospital in Montreal. There is no evidence that they ever considered patenting these natural correlations on their own. For example, well before the patents at issue were filed, the inventors freely disclosed in a paper in an academic journal the general association between thiopurine metabolites and the efficacy or toxicity of thiopurine therapy. Carmelo Cuffari *et al.*, *6-Mercaptopurine Metabolism in Crohn's Disease: Correlation with Efficacy and Toxicity*, 39 GUT 401 (1996). The patent acknowledges this prior work. See 2JA 10, at 8:37-46.

The inventors' publication apparently caught the eye of Prometheus. In 1998, Prometheus licensed the research from the inventors and their employer hospital, as recited in the complaint. C.A. App. A12597 ¶ 10. Apart from consulting fees, the inventors were

to be compensated only if Prometheus successfully commercialized their research. Within a few weeks of the execution of this license, Prometheus filed "provisional" patent applications on the inventors' research at the United States Patent and Trademark Office ("PTO"), from which the two patents at issue ultimately derived.[2]

Reflecting the academic background of the inventors, the Prometheus patents do not recite any real-world uses of the natural correlations between metabolite levels and patient health. Instead, they broadly encompass the mental recognition of the correlations by claiming (a) administering some undefined level of thiopurine to a person, and (b) considering whether that test dose is too small, within a therapeutic range, or too large based on observed metabolite levels, as exemplified by claim 1 of the '623 patent:

> 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

[2] The patents are U.S. Patents 6,355,623 ("the '623 patent") and 6,680,302 ("the '302 patent"), reproduced at 2JA 1-35.

> 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.

2JA 16, at 20:9-25; see Pet. App. 3a-5a (describing the patent claims). Other claims, such as claim 46 of the '623 patent, do not even require the "administering" step, reciting only the step of "determining" metabolite levels. 2JA 18, at 23:41-24:17; Pet. App. 5a. Despite preamble language stating that these steps "optimiz[e] therapeutic efficacy," none of the claims describes any patient treatment, any change in dosage, or any other real-world use of the physician-recognized natural correlations. They thus cover, and preempt, any and all uses of the correlations.

Based on these patents, Prometheus brought to market a blood test for thiopurine metabolites under the trade name Pro-Predict. Hospitals and laboratories send patient blood samples to Prometheus for analysis of metabolite levels. Prometheus provides the test results along with a form that contains information about the 6-TG metabolite correlation recited in its patents.[3] An example of a Prometheus test result form appears at 2JA 36.

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[3] Prometheus's form did not set forth any information regarding its patented "7000" 6-MMP correlation. See 2JA 36; Pet. App. 3a, 52a. In a vivid demonstration of why patenting naturally observed relationships should not be allowed, it turned out that Prometheus's "7000" 6-MMP correlation was unreliable when extended to a larger population than had been covered by the

C. Mayo Clinic's Improvement Of The Prometheus Blood Test.

Mayo Clinic is one of the world's leading medical institutions in both patient care and research. A not-for-profit organization, Mayo's mission is to provide the best possible care to its patients through integrated clinical practice, education, and research.

Mayo Medical Laboratories ("Mayo Labs") is a global reference laboratory operating within Mayo Clinic's Department of Laboratory Medicine and Pathology. Mayo Labs provides clinical laboratory services to Mayo patients, as well as to other hospitals and clinics. While Mayo Labs is a for-profit organization, any profits it earns go directly to support Mayo's patient care, education, and research activities.

Mayo has long been a leader in the research of gastrointestinal disorders. And its physicians and researchers have published extensively in the area of thiopurine metabolites, including in papers cited in Prometheus's patents. 2JA 1-3, 19-21; see William J. Sandborn *et al.*, *Lack of Effect of Intravenous Administration on Time to Respond to Azathioprine for Steroid-Treated Crohn's Disease*, 117 GASTRO-ENTEROLOGY 527 (1999). Mayo's gastroenterology practice is the largest in the United States. See http://www.mayoclinic.org/gi-rst. In any given year,

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inventors' original study. Accordingly, a "5700" 6-MMP correlation is widely used today. Indeed, even the "400" correlation for 6-TG has since been replaced by a "450" correlation, which itself is not a rigid cutoff. See 2JA 38-40.

Mayo physicians see over 30,000 gastroenterology patients. *Ibid.*[4]

For several years, Mayo Labs used Prometheus's Pro-Predict test, sending patient samples for testing to Prometheus. The results were accompanied by reports that included a description of Prometheus's patented 230-to-400 range. 2JA 36-37.

In 2003, Mayo Labs decided that it could improve upon the Pro-Predict test. In addition to developing better assays to measure metabolite levels, Mayo considered its own experience with thiopurine treatment and studied relevant literature to develop more detailed information to provide along with its test results. 2JA 38-39. See 1JA 10 (the improved, lower-priced Mayo test was designed to serve both "business" and "clinical" goals, the latter being "more important"); 1JA 8 (Mayo also aimed to provide faster service).

In June 2004, Mayo announced it would offer its own thiopurine metabolite test to compete with the Pro-Predict test. Like Prometheus, Mayo proposed to provide information with its test results. But unlike Prometheus, Mayo was not constrained by the need to conform to any patented invention, and provided more useful information with its test results. This information was to include the following (see 2 JA 38-39):

- A blood reading greater than 235 picomoles of 6-TGN is a "target therapeutic range," and a reading greater than 250

[4] U.S. News & World Report recently ranked Mayo as the #1 hospital in the country for gastroenterology. See http://health.usnews.com/best-hospitals/rankings.

picomoles of 6-TGN is associated with remission in adult patients; and

- A blood reading greater than 450 picomoles of 6-TGN indicates possible adverse health effects, but in some instances levels over 700 are associated with remission without significant toxicity, while a "clearly defined toxic level" has not been established; and
- A blood reading greater than 5700 picomoles of 6-MMP is possibly toxic to the liver. See p. 7, n.3, *supra*.

An example of the information Mayo proposed to provide with its test is provided at 2JA 38-39. For further background on the information reported on its form, Mayo cited scholarship from six different scientific journals, dating from 1989 to 2003. *Ibid.* Physicians ordering the test would have access to Mayo doctors if they had questions about test results. See 2JA 40; http://www.mayomedicallaboratories.com/customer-service/index.html.

Mayo proposed to offer its test at a substantially lower price than Prometheus's test. In 2004, the average selling price of Prometheus's test was $262. Mayo proposed to price its test 25 percent less, at $193. 1JA 28. As Prometheus's expert acknowledged, Prometheus's monopoly had enabled it to exact a "price premium." *Ibid.*

D. Prometheus's Lawsuit Against Mayo Clinic.

Despite the "different levels" of metabolites used in Mayo's test (Pet. App. 6a, 52a) and the different information provided, Prometheus sued Mayo Medi-

cal Laboratories days after its announcement of the test. As a result of this litigation, Mayo never launched its test and has withheld it from the market for more than seven years.

This lawsuit seeking to block Mayo's test showed the sweeping breadth of the Prometheus patents. In particular, while Mayo sought to limit the claims to require a real-world use of the correlation, such as a physician's raising or lowering a dosage, Prometheus successfully argued to the district court that the patents required no concrete implementation of the mental recognition. Pet. App. 107a-110a.

The breadth of Prometheus's claims was further revealed when Prometheus attacked different research in a different field than that studied by the physicians who developed Prometheus's ranges. After obtaining a broad claim construction from the district court, Prometheus filed an amended complaint accusing Mayo of infringement based on a study of dermatology patients conducted by Mayo physician and researcher Dr. Rokea el-Azhary. See Pet. App. 77a n.10. Prometheus asserted that Dr. el-Azhary's study infringed the patents even though Dr. el-Azhary was entirely unconcerned with metabolite ranges for gastrointestinal disorders; her patients suffered from disfiguring autoimmune diseases of the skin. After prescribing thiopurine to her patients for treatment of these disorders, she collected data on their metabolite levels to see if she could establish a therapeutic range for dermatological disorders. 1JA 17-18. While she had heard of prior research in the gastrointestinal area, she testified that Prometheus's gastrointestinal-related metabolite levels were "irrelevant to [her] study" because "there is no reason to extrapolate to dermatology." 1JA 19.

But because a Mayo-generated lab report that Dr. el-Azhary received mentioned the ranges in the patents, Prometheus accused Mayo of infringement through her work:

> The Biochemical Genetics Laboratory at Mayo Clinic Rochester sent a report of test results to Dr. el-Azhary, or someone working for Dr. el-Azhary. The test results described the "therapeutic range" as "235-400." The Biochemical Genetics Laboratory at Mayo Clinic Rochester did not subsequently advise Dr. el-Azhary that the "therapeutic range" was not "235-400."
>
> Such information informed Dr. el-Azhary, or someone working for Dr. el-Azhary (and thus "indicated a need"), that the next dose of azathioprine given to the patient should be increased in order to be within the "therapeutic range."

2JA 55, 71-72.

Prometheus demanded and received discovery of all Dr. el-Azhary's patients' confidential records. Prometheus also required Dr. el-Azhary to answer hours of questions in deposition about these patients and her treatment of them. 1JA 19. Prometheus even asserted infringement against Dr. el-Azhary's work when she subsequently received reports that did not list the patented "therapeutic range"—because the ranges were ***still in her memory***. 1JA 20-22, 36-42. Once she had seen the patented range one time, there was nothing Dr. el-Azhary could do, Prometheus maintained, to avoid infringement. Its expert testified that Dr. el-Azhary's receipt of a test report would lead to infringement "[w]hether she crumples

it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with." 1JA 42.

According to Prometheus, Dr. el-Azhary must stop her dermatological research until she purges her memory of the correlations—regardless of how she ultimately may use any test results—because Prometheus's claims preempt all possible uses of the natural correlations. Indeed, anyone who sees Prometheus's numbers and a patient test report of metabolite levels is a potential infringer—even someone who reads about those ranges in this brief.

Dr. el-Azhary ultimately completed her study and reported that, for dermatology patients, a therapeutic range of metabolites is 150 to 300 picomoles—substantially different from the range postulated by Prometheus based on gastroenterology data. But because of Prometheus's allegations and this lawsuit, Mayo was forced to hold up publication of Dr. el-Azhary's study until the district court ruled for Mayo in 2008, lest it risk claims by Prometheus that her study induced other dermatologists to infringe the patents. As a result, the field of dermatology and its patients lacked access to that information for several years. See Rokea A. el-Azhary, *et al.*, *Thioguanine Nucleotides and Thiopurine Methyl-transferase in Immunobullous Diseases: Optimal Levels as Adjunctive Tools for Azathioprine Monitoring*, 145 ARCH. DERMATOL. 644 (June 2009).

E. The District Court's Decision.

Mayo moved for summary judgment, asserting that the Prometheus claims were not patent-eligible under 35 U.S.C. § 101. See Pet. App. 52a-54a. The district court granted the motion, finding that

Prometheus's claims recite correlations between thiopurine drug metabolite levels and therapeutic efficacy or toxicity that are natural phenomena. Pet. App. 63a-71a. As Prometheus's expert admitted, "the key therapeutic aspect of such thiopurine drugs is that they are converted naturally by enzymes within the patient's body to form an agent that is therapeutically active." Pet. App. 65a. Accordingly, the district court concluded (Pet. App. 66a) that Prometheus

> did not "create" the correlation between thiopurine drug metabolite levels and therapeutic efficacy and toxicity. Instead, the correlation results from a natural body process, which as the inventors concede, was pre-existing in the patient population, and it exists in the patient population today.

The court also explained that the steps of the claim reciting "administering" a drug and "determining" metabolite levels were "merely data-gathering steps" that were necessary precursors for reviewing the claimed correlation. Pet. App. 63a. All "the inventors claim to have discovered is that particular concentrations of [thiopurine metabolites] correlate with therapeutic efficacy and toxicity in patients taking AZA drugs." *Ibid.*

The district court quoted approvingly from the *LabCorp* opinion of Justices Breyer, Stevens, and Souter, which explained that the similar claim there failed "the requirement that it not amount to a simple natural correlation, *i.e.*, a 'natural phenomenon'" (citing this Court's precedents):

> At most, respondents have simply described the natural law at issue in the

> abstract patent language of a "process." But they cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge. One might, of course, reduce the "process" to a series of steps, e.g., Step 1: gather data; Step 2: read a number; Step 3: compare the number with the norm; Step 4: act accordingly. The question is what those steps embody. And here, aside from the unpatented test, they embody only the correlation between homocysteine and vitamin deficiency that the researchers uncovered. In my view, that correlation is an unpatentable "natural phenomenon," and I can find nothing in [the claim] that adds anything more of significance.

LabCorp, 548 U.S. at 137-138 (citation omitted), quoted at Pet. App. 67a-68a.

In light of its review of Prometheus's broad claims and of this Court's preemption precedents, the district court concluded that these claims improperly preempt a natural phenomenon. Applying this Court's preemption standard in *Gottshalk* v. *Benson*, 409 U.S. 63 (1972), and *Parker* v. *Flook*, 437 U.S. 584 (1978), the court refused to apply a mechanical "transformation" test. Pet. App. 73a-74a. It explained that Prometheus's claims preempt all uses of the physician-recognized natural correlations, because every activity recited in the claims, other than recognition of the correlations themselves, was simply data gathering necessary to observe the natural correlation (Pet. App. 75a-78a):

> what the inventors claim to have discovered is that particular concentrations of 6-TG and

> 6-MMP correlate with therapeutic efficacy and/or toxicity in patients taking AZA drugs. Because the claims cover the correlations themselves, it follows that the claims "wholly pre-empt" the correlations.

F. The Federal Circuit's Decisions.

The Federal Circuit reversed. It applied its own "machine-or-transformation" test as a "definitive" standard, and in a footnote glossed over the analysis in Justice Breyer's *LabCorp* opinion. Pet. App. 33a-43a & n.3. Prometheus had invited that ruling by arguing that "a freestanding preemption inquiry is inappropriate" because the "machine or transformation test is the singular test for a process claim under § 101." Prometheus Reply Br. at 21 n.3 (Fed. Cir. Apr. 24, 2009).

Mayo sought review by this Court. While Mayo's petition for certiorari was pending, this Court decided *Bilski* v. *Kappos*, 130 S. Ct. 3218 (2010). *Bilski* included three opinions, which all agreed on certain key points: (1) they disapproved of the Federal Circuit's rote reliance on "machine or transformation" as a standard, demanding a more nuanced inquiry; (2) they affirmed that natural phenomena and abstract ideas lie outside Section 101, so that claims that have the practical effect of preempting all practical uses of a natural phenomenon are invalid; and (3) they reaffirmed the decisions in *Benson*, *Flook*, and *Diamond* v. *Diehr*, 450 U.S. 175 (1981), and pointedly declined to endorse any prior Federal Circuit approach. Moreover, the opinions by Justice Stevens (joined by Justices Ginsburg, Breyer, and Sotomayer) and Justice Breyer (joined in relevant part by Justice Scalia) each referenced *LabCorp* approvingly. And

the majority opinion emphasized the need to set the Section 101 bar high enough to avoid flooding courts "with claims that would put a chill on creative endeavor and dynamic change." 130 S. Ct. at 3229. After deciding *Bilski*, this Court granted certiorari, vacated, and remanded in the present case. Pet. App. 24a.

On remand, Mayo reiterated its preemption argument. Mayo Supp. Br. to Fed. Cir. on Remand, at 1-2. Prometheus argued that its claims involve transformations and machines, apply natural laws in a particular context, and do not preempt a general concept. Prometheus Supp. Br. to Fed. Cir. on Remand, at 1-3. Prometheus also argued that any claim that recites a machine or transformation necessarily passes the preemption standard. *Id.* at 2. Without hearing oral argument, the Federal Circuit affirmed its prior decision.

The Federal Circuit concluded that *Bilski* "did not undermine" its prior analysis—which had equated this Court's preemption standard with the Federal Circuit's "machine-or-transformation" test. Pet. App. 14a. Consistent with that view, the Federal Circuit again held that transformations of matter occur when a patient's body metabolizes a drug and when blood is tested for metabolites, and that these "transformations" made the claims patentable. Pet. App. 15a-21a. As for preemption, the Federal Circuit reasoned that "the claims do not preempt all uses of the natural correlations; they utilize them in a series of specific steps" (Pet. App. 15a)—failing to recognize that the steps recited in the claims that lead up to a physician's review of the correlations are *not* uses of the correlations, and failing to recognize that the claims cover and preempt anything that a physician

might do with the correlations. As it did before, the Federal Circuit dismissed *LabCorp* summarily, stating that it "decline[d] to discuss a dissent"—even though Justice Breyer's opinion was the only word by any Justice on the merits of this critical issue. Pet. App. 16a n.2.

SUMMARY OF ARGUMENT

A. Prometheus's patents purport to monopolize the field of blood testing for thiopurine metabolites, covering *anything* a physician might do with knowledge of the natural correlation between metabolite levels and health across autoimmune diseases of any description. This Court's precedents establish that such claims do not satisfy Section 101. A patent may not preempt "laws of nature, physical phenomena, and abstract ideas," which are "free to all men and reserved exclusively to none." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980). That principle bars not only a patent claim aimed directly at a natural phenomenon, but also one whose "practical effect would be a patent on the [phenomenon] itself." *Gottschalk* v. *Benson*, 409 U.S. 63, 71-72 (1972). And it bars patents that preempt a significant field of activity, even if some other uses are left in the public domain. See *Parker* v. *Flook*, 437 U.S. 584, 589-590 (1978). This Court consistently has applied that understanding, most recently in *Bilski*, where each member of this Court agreed that a patent may not confer a monopoly over an abstract idea in a broad field of use.

Under this settled principle, Prometheus's claims are invalid. Prometheus's patents recite a natural phenomenon—the biological correlation between metabolite levels and health—without describing what is to be done with that phenomenon beyond

considering whether a dosage adjustment may be necessary. Because Prometheus's claims culminate with this open-ended "mental step" (Pet. App. 21a), their "practical effect" is to "wholly pre-empt" use of the natural correlation with regard to any auto-immune disease. *Benson*, 409 U.S. at 71-72. This point is not debatable. Prometheus acknowledges that, if its patents are valid, physicians may not *consider* thiopurine metabolite correlations without a license, and they infringe the patents by determining that Prometheus's metabolite ranges are medically *inappropriate*.

B. Prometheus cannot defend its patents by embedding a natural correlation in a "process" that includes "token" and "conventional" data-gathering steps—administering a drug and testing blood for metabolites of the drug—that are "well known" and "long prevalent" in medical practice. *Flook*, 437 U.S. at 594; *Diamond* v. *Diehr*, 450 U.S. 175, 193 n.14 (1981); *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3231 (2010). These steps do nothing to narrow the scope of preemption of the biological phenomenon; any physician seeking to improve Prometheus's criteria would inevitably go through the same preliminary steps. As Justice Breyer explained in *LabCorp*, 548 U.S. at 137-138, any conduct can be described as a "process" with "a series of steps," but the key legal question is "what those steps embody." Here, they embody "a simple natural correlation" combined with well-known steps that do nothing to prevent the claims from wholly preempting physicians' practical use of that correlation. *Id.* at 136-137.

The Prometheus patents are not saved by application of the "machine-or-transformation" test invoked by the Federal Circuit. *Bilski* held that a

"transformation" is simply one "clue" to patent eligibility and does not override the principle that "laws of nature" must be free for all to use. 130 S. Ct. at 3225-3226. Here, the "transformations" held dispositive by the Federal Circuit—changes in the human body resulting from administration of drugs and changes in the blood when tested for metabolites—are incidental to data-gathering, have no limiting effect on the claimed monopoly, and lack any connection to the goal of the patent system to promote innovation. Because it does not require a transformation that narrows the field of preemption, the Federal Circuit's test is mechanical and easily manipulated, leaving courts and patent examiners prone to arbitrary line drawing.

C. The legal principle that a patent may not preempt laws of nature was well established before Congress enacted Section 101 in its current form in 1952. Congress never would have intended to allow sweeping patent claims like Prometheus's that chill research and speech and prevent institutions like Mayo Clinic from identifying better metabolite ranges or marketing more accurate and inexpensive tests. It is unthinkable that Congress intended the patent laws to embargo independent research and thought about a natural correlation based on Prometheus's suggestion of numbers that it deems relevant, but which others may reasonably reject.

D. The impact of a proposed patent on innovation and competition has an important bearing on the patent's validity: "The underlying policy of the patent system [is] that 'the things which are worth to the public the embarrassment of an exclusive patent'" must "'outweigh the restrictive effect of the limited patent monopoly.'" *Bilski*, 130 S.

Ct. at 3258 (Breyer, J., concurring in the judgment). Here, the Prometheus patents are far more likely to retard than to advance innovation, and thus to frustrate the broader goals of patent law.

Patent protection assuredly is unnecessary to encourage or fund basic research of the sort reflected in the Prometheus patents, which is now routinely undertaken by scientists and researchers without regard to filing patents. But patents like those obtained by Prometheus are certain to *inhibit* innovation and the improvement of patient care. Such patents on basic scientific principles deter the research that drives innovation. This problem is particularly acute in the medical field, where ready access to basic facts (such as the relationship between levels of metabolites and a drug's efficacy) is essential to research; where giving a patentee monopoly control over essential medical observations will adversely affect the quality of patient care, increasing costs and reducing the availability of medical services; and where physicians have an ethical obligation to spread knowledge and improve diagnostic criteria for the benefit of all. For these reasons, Prometheus's attempt to monopolize basic biological relationships is insupportable.

ARGUMENT

Thiopurine drugs, discovered over thirty years ago, are powerful medicine. Too much can be fatal. Too little can result in unsuccessful therapy. For decades, doctors have drawn blood after administering these drugs, tested for metabolite levels, and adjusted dosage in light of their best medical judgment.

The Prometheus patents seek to monopolize these metabolite numbers. They advise physicians to think about the need for a dosage adjustment when metabolites reach certain levels, but do not offer any specific change in therapy. Thinking about metabolite levels is exactly what doctors have long done, without any advice from Prometheus.

When Mayo Clinic examined its own patient records, it concluded that different numbers would better serve patient health and avoid injury. It also tried to offer a better test—with quicker blood testing, advice from its own expert staff, and specific reference to adverse side effects of thiopurine drugs. Mayo wanted to offer its service to doctors nationwide at a cost considerably less than Prometheus charged, offering savings to millions of people who take thiopurine drugs and require multiple blood tests while being treated over months or years for serious illness.

Mayo never had a chance to offer this improved test because Prometheus sued to block it. According to Prometheus, its patents preempt the entire field of blood testing for thiopurine metabolites for patients with any autoimmune disease, so that others may not improve on or disagree with its medical advice. The Federal Circuit agreed with Prometheus that this perverse result is required by federal patent law. Nothing could be further from Congress's intention, this Court's precedents, or ordinary common sense. This Court should put an end to the embargo that Prometheus has imposed on medical research and scholarly criticism of its medical advice. Doctors and patients should have the right to choose between the medical advice offered by Mayo Clinic and Prometheus, or whoever else wishes to weigh in.

I. PROMETHEUS'S CLAIMS DO NOT SATISFY SECTION 101 OF THE PATENT ACT.

A. Prometheus's Claims Monopolize All Uses Of A Natural Biological Relationship.

Prometheus's claims have broad preclusive reach over a natural biological phenomenon. Each claim consists either of the three steps of administering a thiopurine drug, determining metabolite levels produced by the body in natural reaction to that drug, and then considering a metabolite range that may "indicat[e] a need" to change dosage (*e.g.*, Claim 1, Pet. App. 4a), or the last two steps only. Claim 46, Pet. App. 5a. Prometheus successfully argued in the district court that the final step does not "requir[e] doctors to adjust dosage if the metabolite level reaches the specified level," but is satisfied when a physician or researcher is "warned" or "notified" that a dosage adjustment *may* be indicated. Pet. App. 108a-109a; see also Pet. App. 23a (Federal Circuit observed that the patent's result is "useful information for possible dosage adjustments").

The correlation between metabolite levels and patient health is dictated by natural enzymatic activity inside the human body. Prometheus's expert admitted that thiopurine drugs are "converted naturally by enzymes within the patient's body" into metabolites, as the district court found. Pet. App. 65a. And, confirming that the correlations are natural phenomena, the developers of the metabolite ranges admitted that they did not "invent" them, but "merely observed these natural correlations by studying a 'database of patien[t] information.'" *Ibid.*; see 1JA 15-16, 32. The Federal Circuit did not

disturb the district court findings to that effect, and agreed that the correlations are "naturally occurring." Pet. App. 15a.

Prometheus concedes, as it must, that it seeks to patent "a truth" about "the physical world," but asserts that its claims are nevertheless valid because they recite preliminary "process steps that require concrete human actions." Br. in Opp. 21-22. The "administering" and "determining" steps of Prometheus's claims are not, however, its inventions. The drugs involved and the method of blood testing for metabolites are well known and have been used by physicians and researchers for decades. And those preliminary steps—which the district court found are "merely necessary data-gathering steps for any use of the correlations" (Pet. App. 62a)—do nothing to confine the scope of Prometheus's claims. They impose no limit because the final mental step—the only one to which Prometheus made any contribution—preempts all practical uses of naturally occurring correlations between these drugs and metabolite levels across all types of autoimmune disease.[5]

Prometheus has confirmed the sweeping preclusive scope of its patents by suing to prevent Mayo from marketing a test it developed to achieve more

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[5] Prometheus's claims do not recite the administration of any amount of any drug to be given to any patient. Patent drafters know how to recite administration of "a therapeutically effective amount" of a drug for method of treatment claims. See, *e.g.*, *Geneva Pharms., Inc.* v. *GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-1384 (Fed. Cir. 2003) ("effective amount" is "a common and generally acceptable term" in claims covering pharmaceutical treatment methods); *Rapoport* v. *Dement*, 254 F.3d 1053, 1056 (Fed. Cir. 2001). Prometheus was careful not to do so here.

accurate results and improved patient care at a lower cost. Pet. App. 85a & n.2; 1JA 28. Prometheus insists that Mayo cannot develop a test with *different* criteria relating to *any* autoimmune disease unless it invents (needlessly) an entirely new way of examining the body for metabolites. Br. in Opp. 25, 27. And it maintains that a physician who knows of Prometheus's correlations cannot even decide *not* to use them without paying Prometheus. *Id.* at 24. Indeed, Prometheus's expert testified that a physician who receives test results referring to Prometheus's metabolite ranges infringes regardless whether she "crumples it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with." 1JA 40-42.

Prometheus thus asserts the power to prevent doctors and researchers—who considered metabolite levels on their own years before these patent claims were filed (see *supra*, p. 4)—from exercising independent medical judgment based on ordinary blood evaluations. That this is no exaggeration is shown by Prometheus's attack on Mayo researcher Dr. el-Azhary. Although Prometheus says that it "does not sue doctors" (Br. in Opp. 24), it sued her employer, deposed her for hours, examined her confidential patient records, and asserted that her study infringed Prometheus's patents because she administered drugs to dermatology patients with autoimmune diseases, tested their blood for metabolites, and investigated the optimal therapeutic range for dermatology patients. *Supra*, pp. 11-13. Dr. el-Azhary ultimately concluded—in a paper she dared not publish until the district court invalidated Prometheus's patents—that far different metabolite levels were necessary for dermatology patients. *Supra*, p. 13.

Similarly, a physician who seeks to investigate whether the appropriate metabolite ranges for patients with gastrointestinal disorders might vary with patient age, gender, presence of other diseases, or other relevant factors, could not do so without a license from Prometheus. It is clear, therefore, that Prometheus's claims monopolize the whole field, covering *anything* that a physician might do with her knowledge of the natural correlation between metabolite levels and health—even reject Prometheus's levels as detrimental to patient care.

B. This Court's Precedents Forbid Prometheus's Preemption Of A Natural Phenomenon.

This Court's precedents establish that claims like Prometheus's, which preempt all practical uses of a natural phenomenon across a broad field, do not satisfy Section 101.

1. Although Section 101 is expansive, "this is not to suggest that [it] has no limits" or "embraces every discovery." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980). The legislative background of the 1952 Patent Act makes clear that "'anything under the sun that is made by man'" is "not necessarily patentable under section 101": all "the conditions" for patent protection must first be met. S. Rep. No. 1979, 82d Cong., 2d Sess. 5 (1952); see *Bilski*, 130 S. Ct. at 3249 (Stevens, J., concurring). In particular, a patent cannot preempt "laws of nature, physical phenomena, or abstract ideas":

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor

> could Newton have patented the law of gravity. Such discoveries are 'manifestations of * * * nature, free to all men and reserved exclusively to none.'

Chakrabarty, 447 U.S. at 309 (quoting *Funk Brothers Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). This Court was therefore careful to explain that the "human-made, genetically engineered bacterium" it held patentable in *Chakrabarty* was "a product of human ingenuity," *not* a "natural phenomenon." 447 U.S. at 305, 309.

That this limitation on patentability is essential to promote innovation has long been understood. See *LeRoy* v. *Tatham*, 55 U.S. 156, 174-175 (1852) ("no one can appropriate * * * exclusively to himself, under the patent laws," a "principle," "fundamental truth," or "natural agenc[y]," because such monopolies "discourage arts and manufactures").[6] As this Court has explained, "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts" cannot support a patent monopoly because "they are the basic tools of scientific and technological work." *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972). As such they are "part of the storehouse of knowledge" and must be "free to all men." *Funk Brothers*, 333 U.S. at 130. That rule bars not only a patent claim aimed directly

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[6] The 1793 Patent Act defined patentable subject matter as "any new and useful art." Congress did not intend any substantive change when it replaced this phrase in 1952 with "any new and useful process" and defined "process" as "process, art, or method." See *Diehr*, 450 U.S. at 181-184; *Bilski*, 130 S. Ct. at 3248 (Stevens, J., concurring) ("the 1952 Act did not alter the nature of the then-existing limits").

at a natural phenomenon, but also one whose "*practical effect* would be a patent on the [phenomenon] itself," because such a claim also "wholly pre-empt[s]" use of the natural phenomenon. *Benson*, 409 U.S. at 71-72 (emphasis added). This Court's preemption decisions illustrate how these principles are applied, and show that Prometheus's claims fail the "natural phenomenon" standard.

2. In *Funk Brothers*, the inventor discovered that certain strains of bacteria that enable legume crops to thrive remained effective when combined. It patented a product of mixed bacteria cultures that would be more useful for growers than individual cultures. This Court held that although the inventor's steps applied a "law of nature" to a "new and useful end," they were not patentable because the essence of the product was a combination of natural biologic materials. 333 U.S. at 130.

The Court explained that the "qualities of these bacteria" are "manifestations of nature." 333 U.S. at 130. Even though the bacteria had been combined in a "new and different composition" that "contributed utility and economy," simply "aggregati[ng] species fell short of invention." *Id.* at 130-131. It was merely "an advance in the packaging" of the bacteria in which "[n]o species acquires a different use" and each "has the same effect it always had." That the combination was "an important commercial advance" did not satisfy the requirements of the Patent Act. "[O]nce nature's secret" that bacteria could be mixed without inhibiting their effectiveness was discovered, "the state of the art made the production of a mixed inoculant a simple step." *Id.* at 132. Attaching non-inventive production "steps" to a law of nature did not result in a patentable invention.

3. In *Benson*, this Court applied the same principles that governed the product claim in *Funk Brothers* to a "process" patent for the computer-based conversion of decimal numbers into binary numbers using generalized mathematical formulas. 409 U.S. at 64-65, 67-68. The method at issue introduced variations on "the ordinary arithmetic steps a human would use," employing an algorithm and existing computer technology. *Id.* at 67. Nevertheless, the Court held the patent invalid under Section 101 because it did not recite what was to be done with the numbers once they were converted. It used "[p]henomena of nature" and mathematical concepts in a "process" that was "so abstract and sweeping as to cover both known and unknown uses" of the conversion: any "end use" of the conversion was within its scope. *Id.* at 67-68. The "practical effect" was thus to "wholly preempt the mathematical formula," amounting to a patent on "the algorithm itself." *Id.* at 71-72.

4. This Court expanded upon these principles in *Parker* v. *Flook*, where the claims recited a process for updating an alarm limit for use in common chemical processes, employing a mathematical formula. The method consisted of three steps: measuring a variable in the chemical process, such as temperature, using an algorithm to calculate what the alarm limit should be, and adjusting the alarm limit to the new value. The algorithm was new, but the other steps were "well known." 437 U.S. at 585-586, 594.

The Court held that the claims failed to satisfy Section 101, even though they were narrower than the patents rejected in *Benson* in two ways. First, although the *Flook* claims covered "any use" of the

formula for updating alarm limits over a variety of chemical processes in particular industries, they left uses outside those industries in the public domain. 437 U.S. at 589-590, 592. Second, unlike the open-ended patent in *Benson*, they recited "useful, though conventional, post-solution applications" in the form of a final step that called for adjusting the alarm limit to the figure computed according to the formula. *Id.* at 585, 590.

These differences did not save the claims. To allow "conventional or obvious" post-solution activity to make a process based on natural laws patentable would "exal[t] form over substance." 437 U.S. at 590. A "competent draftsman" could make any mathematical formula patentable by attaching "post-solution activity." *Ibid.* Even the "Pythagorean theorem" could be patented by embedding it in a process containing "a final step indicating that the formula" could "be usefully applied to existing surveying techniques." *Ibid.* Because "the application, considered as a whole, contain[ed] no patentable invention" but consisted of "well known" steps plus a natural law, it did not satisfy Section 101. *Id.* at 594; see *ibid.* (a natural phenomenon "cannot support a patent" absent "some other inventive concept in its application").

5. Citing *Flook* and *Benson*, the Court in *Diamond* v. *Diehr*, 450 U.S. 175, 191-192 (1981), reaffirmed three important principles that govern analysis under Section 101: that "laws of nature" may not be claimed in the abstract, that this limitation "may not be circumvented" by focusing a claim on "a particular technological environment," and that "insignificant post-solution activity" cannot

"transform an unpatentable principle into a patentable process."

The claims in *Diehr*, in contrast to those in *Benson* and *Flook*, satisfied Section 101 because they narrowly confined use of the Arrhenius equation in a "process which, when considered as a whole, is performing a function which the patent laws were designed to protect"—transforming raw rubber into precision molded products. *Id.* at 184, 192. The claimant used the equation in a detailed step-by-step method that solved a significant industrial problem by continuously monitoring temperature inside a mold and using that data to open the mold only when the rubber was perfectly cured—"a result heretofore unknown in the art." *Id.* at 177-178, 184, 193 n.15. The claimant did not seek to preempt use of the equation generally, but only to foreclose its use "in conjunction with all of the other steps in their claimed process" in the particular application of molding raw rubber into finished products. *Id.* at 187.

6. *Bilski* reaffirmed the vitality of all these precedents. Although the process patent considered there made a contribution to knowledge by laying out a formula for risk arbitrage, applying the formula to specific industries, and then using random analysis techniques to establish inputs into the equation, this Court nonetheless disapproved it because it would "pre-empt use" of a "fundamental economic practice" that was "long prevalent" in the business world, and would "effectively grant a monopoly over an abstract idea." 130 S. Ct. at 3231. The patentee's efforts to "limit" the abstract formula to "one field of use" and add "token postsolution components" did not "make the concept patentable," or demonstrate that the

inventor created a "new and useful process" within the language of Section 101. *Id.* at 3225, 3231.

Justice Kennedy explained that this result strikes a balance that rewards "valuable inventions without transgressing the public domain." 130 S. Ct. at 3227. Care is especially necessary in considering method or process patents because they "raise special problems in terms of vagueness and suspect validity." *Id.* at 3229. "If a high enough bar is not set" for such patents, "patent examiners and courts could be flooded with claims that would put a chill on creative endeavor and dynamic change." *Ibid.* And Section 101's prohibition on patents that attempt to monopolize "abstract ideas" is particularly important in drawing the necessary line. *Id.* at 3229-3230.

Each of the Justices in *Bilski* agreed with these propositions. Justices Breyer and Scalia, concurring, observed that all members of the Court agree that incentives to innovation that "are worth to the public the embarrassment of an exclusive patent" must "outweigh the restrictive effect" of the patent monopoly. 130 S. Ct. at 3258. Federal courts must therefore exercise care "to determine not only what is protected, but also what is free for all to use." "Phenomena of nature, though just discovered," are "not patentable," and patentees may not "wholly pre-empt the public's access to the basic tools of scientific and technological work." *Ibid*; see *id.* at 3235 (Stevens, J., concurring). It is essential to consider whether a claimed process, "considered as a whole," is "performing a function which the patent laws were designed to protect." Courts must always reject overbroad and abstract patent claims that are "ridiculous" and "truly absurd," like patents on video

displays intended to teach the art of housekeeping. *Id.* at 3258-3259 (Breyer, J., concurring).

7. Under the settled principles described in *Funk Brothers*, *Benson*, *Flook*, *Diehr*, and *Bilski*, Prometheus's claims are invalid. See *Deepsouth Packing Co.* v. *Laitram Corp.*, 406 U.S. 518, 531 (1972) ("We would require a clear and certain signal from Congress before approving the position of a litigant" who "argues that the beachhead of privilege is wider, and the area of public use narrower, than courts had previously thought"). Like the claims disapproved in *Benson* and *Flook*, Prometheus's patents recite a natural phenomenon—the biological correlation between metabolite levels and health—without describing what is to be done with that phenomenon beyond considering whether a dosage adjustment may be necessary. Because Prometheus's claims culminate with this open-ended "mental step" (Pet. App. 21a), their "practical effect" is to "wholly preempt" use of the natural correlation across the entire spectrum of autoimmune diseases. *Benson*, 409 U.S. at 71-72. Prometheus concedes as much when it describes what others may and may not do without paying Prometheus:

- Physicians may freely use thiopurine metabolite correlations in patient care and research only if they take the impractical—and given the simplicity and ubiquitousness of blood tests, completely wasteful—step of developing "a method for measuring metabolite levels that does not require analysis of a bodily sample or a pre-treatment diagnostic test." Br. in Opp. 27.

- Mayo cannot consider the correlation—even if it "doesn't act on it"—in providing patient care or conducting research. 1JA 42.
- Mayo may not market its own less costly test based on improved metabolite ranges, which it believes enhances patient health and economy. *Supra*, pp. 8-10.
- Mayo researcher Dr. el-Azhary infringed when, knowing Prometheus's metabolite ranges, she determined that they were medically inappropriate for dermatology patients. *Supra*, pp. 11-13.

In contrast to *Diehr*, Prometheus did not recite a particular use of the correlation. As these examples show, its patents cover use of the correlation in every manner possible for *any* autoimmune disease. Its suggestion of certain metabolite ranges that it deems relevant should not preempt the right of others to think about the same biological correlation and form their own conclusions about the need for dosage changes. The abstract concepts Prometheus pre-empts are "part of the storehouse of knowledge of all men, free to all men and reserved exclusively to none." *Bilski*, 130 S. Ct. at 3225.

C. The Preemptive Effect Of The Patents Is Not Mitigated By The Token And Long-Prevalent Steps Recited By Prometheus.

For two independent reasons, Prometheus cannot defend its patents by dressing up this natural correlation as a "process" that includes additional steps that are "token," "conventional," long-prevalent," or "obvious." *Diehr*, 450 U.S. at 193 n.14; *Bilski*, 130 S. Ct. at 3231; *Flook*, 437 U.S. at 590.

First, the preparatory steps in some of Prometheus's claims—administering a drug and testing blood for metabolites of the drug—are "data-gathering" steps, as the district court found, and ordinary means of observing the natural correlation. Pet. App. 62a; see also *id.* at 23a (Federal Circuit acknowledged "prior steps" simply "provide useful information"); *In re Meyer*, 688 F.2d 789, 794 (C.C.P.A. 1982) (a "data gathering step" "cannot make an otherwise nonstatutory claim statutory"). Where "qualities are the work of nature," "packaging" them with steps that make no difference to the way the natural phenomenon operates is "not enough" to satisfy Section 101. *Funk Brothers*, 333 U.S. at 130-132.

Unlike the steps in the *Diehr* patent that narrowly confined the Arrhenius equation to use in a process for molding rubber, the data gathering steps in Prometheus's patents do *nothing* to narrow the range of preemption of the biological phenomenon. Any physician seeking to improve Prometheus's criteria inevitably would go through the same preliminary steps, which neither limit the scope of the claims nor prevent them from preempting all practical uses of the natural correlations. *Diehr* forbids the use of patent drafting that recites steps without confining the breadth of preemption of a law of nature. See 450 U.S. at 192.

A second defect in Prometheus's patents is that their administration and testing steps are "well known" and "long prevalent" in medical practice. *Flook*, 437 U.S. at 594; *Bilski*, 130 S. Ct. at 3231. Prometheus did not invent or make any contribution to either step. Nor was it the first to observe correlations between metabolite levels and dosage

adjustments, a concept familiar to physicians for decades. 2JA 1-3; *supra*, p. 4. Well-known, non-inventive steps cannot turn a natural phenomenon into patentable subject matter. See *Morton* v. *New York Eye Infirmary*, 17 F. Cas. 879, 882-883 (S.D.N.Y. 1862) (denying patent for the process of anesthetizing patients with ether because "[t]he effect discovered was produced by old agents, operating by old means upon old subjects. The effect alone was new," and as a law of nature "is not patentable"); *Flook*, 437 U.S. at 594-595 (combination of well-known chemical processes and monitoring practices with computer-applied algorithm "contains no claim of patentable invention").

These precedents do not improperly import novelty or obviousness analysis into Section 101 from Sections 102 and 103. Br. in Opp. 16; see *Flook*, 437 U.S. at 592 & n.14. Section 101 on its face limits patentable subject matter to a "new and useful process," making clear that if "the application, considered as a whole, contains no patentable invention" the provision is not satisfied. *Flook*, 437 U.S. at 591, 594. A "novel and useful structure" created by using a "scientific truth'" satisfies Section 101. But when, as here, "[t]he process itself" merely combines well-known steps with a law of nature and broadly preempts use of the latter, the result does not warrant a patent monopoly. *Id.* at 588, 591, 594. *Bilski* squarely holds that attaching "long prevalent" steps to an abstract idea or law of nature is insufficient. 130 S. Ct. at 3231.

Justice Breyer's dissent from the dismissal of *LabCorp* for procedural reasons (joined by Justices Stevens and Souter) illustrates the proper application of this Court's preemption precedents to

a patent like Prometheus's. The *LabCorp* patent involved several proposed "steps" to test a patient's body fluid to determine the level of amino acids and then correlate that level with a vitamin deficiency. As here, it sought to exert "control over doctors' efforts to use [a natural] correlation" through a "process" that the claimant urged was "useful, concrete, and tangible." 548 U.S. at 134, 136.

Justice Breyer explained, however, that the well-known testing steps in *LabCorp* were "nothing * * * that adds anything more of significance" to "an unpatentable 'natural phenomenon.'" 548 U.S. at 138. Embedding the correlation in a "process" was not enough to "avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge." *Id.* at 137-138. The process steps added nothing inventive. Nor did they limit the scope of the patent, which "any doctor" would "necessarily infring[e]" "merely by thinking about the relationship after looking at a test result." *Id.* at 132.

As Justice Breyer explained in *LabCorp*, any conduct can be described as a "process" with "a series of steps," but the key legal question is "what those steps embody." 548 U.S. at 137-138. Here, as in *LabCorp* and *Flook*, Prometheus's patents embody "a simple natural correlation" combined with well-known steps that do nothing to prevent the claims from wholly preempting physicians' use of that correlation. *Id.* at 136-137.[7]

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[7] In *LabCorp* the measured amino acids occurred naturally, while here the metabolites are the body's natural reaction to a drug. Prometheus did not invent the drug, and it concedes that

D. The Federal Circuit's Rote Reliance On The Machine-Or-Transformation Test Clashes With This Court's Precedents.

The Federal Circuit failed to follow this Court's precedents when it applied its "machine-or-transformation" test to uphold Prometheus's patents, reasoning that the administering and testing steps involve "transformations" of matter—*i.e.*, changes in the human body resulting from administration of drugs and changes in the blood when it is tested for metabolites. Pet. App. 17a-18a, 21a-23a. By making these well-known information-gathering steps into the touchstone of patent eligibility, the Federal Circuit misunderstood *Bilski*, which held that a "transformation" is a "clue" to patent eligibility—not a talisman—and does not override the principle that "laws of nature" must be free for all to use. 130 S. Ct. at 3225-3226.

Under this Court's preemption decisions, patentability is not an exercise in labeling. Recitations in a claim involving machines or transformations are relevant *if* they show that inventors have carved out a subset of real-world applications of a natural phenomenon, *e.g.*, by covering particular uses of the phenomenon on a particular machine (leaving open to the public other uses on other machines), or by using the phenomenon to transform something else (leaving open to the public other transformations). That is what happened in *Diehr*, where the patentee limited its claims to using the Arrhenius equation for a particular rubber molding process and left open its use in other applications. 450 U.S. at 187-188. The

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the difference between synthetic and natural promoters of a biologic change is immaterial. See Br. in Opp. 30 n.7.

transformations here, by contrast, are incidental to data-gathering, have no limiting effect on the claimed monopoly, and have no rational connection to the goals of the patent system.

Absent a focus on whether a machine or transformation narrows the field of preemption, the Federal Circuit's test is mechanical and easily manipulated, leaving courts and patent examiners without guidance and prone to arbitrary line drawing. The Federal Circuit's fractured decision in *Association for Molecular Pathology* v. *Myriad Genetics*, 2011 WL 3211513 (Fed. Cir. July 29, 2011), illustrates this point. Explaining in *Myriad* why it held that Prometheus's patents satisfy Section 101, the court observed that metabolite levels cannot be determined by inspection, only by "'extract[ing] metabolites from a bodily sample and determin[ing] their concentration'"—*i.e.*, testing blood as physicians long have done. *Id.* at *22. In denying the Myriad "method claims" directed to "'analyzing' or 'comparing'" a patient's BRCA gene sequence with the normal sequence to diagnose "the presence of cancer-predisposing mutations," the Federal Circuit contrasted the Prometheus "transformation" with Myriad's ability to compare genes "by mere inspection." *Id.* at *2, *22.

It is frankly absurd for the court to hold that the Myriad patents fail because they are "directed to the abstract mental process of comparing" two genes, while Prometheus's patents pass muster because considering the correlation between metabolites and patient health depends on conducting a blood test. BRCA genes cannot be inspected in the body. A segment of DNA must first be *extracted* from the patient and chemically isolated from its chromosom-

al environment. *Myriad*, 2011 WL 3211513, at *17, *20. That a physician's conclusions depend in one case on conducting standard blood tests and in the other on isolating and observing DNA extracted from the patient is a meaningless distinction. It says nothing at all about the scope of preclusion of a natural law, which is decisive under this Court's preemption decisions.

So arbitrary a test is no standard at all. Mayo's proposed approach, by contrast, explains how the machine-or-transformation inquiry identifies situations in which the patentee is not monopolizing all real-world applications of a natural phenomenon and will allow the PTO and courts to apply Section 101 consistently. See *Brenner* v. *Manson*, 383 U.S. 519, 532 (1966) (interpreting Section 101 "in light of the general intent of Congress, the purposes of the patent system, and the implications of a decision one way or the other").

E. Prometheus May Not Block Broad Areas Of Scientific Inquiry With Open-Ended Patents Built On A Narrow Discovery.

In addition to impermissibly preempting all uses of a natural phenomenon, Prometheus's patents violate Section 101 because they leverage a minimal contribution to medicine—attaching disputable numbers to a natural correlation—into a patent that blocks a broad area of scientific inquiry into the best way to treat a wide variety of serious diseases. The Act does not permit one who makes a narrow discovery to preempt future development in adjacent areas. See *Graham* v. *John Deere Co.*, 383 U.S. 1, 7-9 (1966) (Thomas Jefferson, author of the 1793 Patent Act "insist[ed] on a high level of patentability" that did not "gran[t] patents for small details").

Even Samuel Morse's monumental invention of electromagnetic telegraphy could not justify a broad patent precluding others from working on different forms of electronic communication, such as telephone and radio. *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 113-120 (1853). As Chief Justice Taney put it, "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" which is "less complicated—less liable to get out of order—less expensive in construction, and in its operation. But yet if it is covered by this patent the inventor could not use it, nor the public have the benefit of it without the permission of this patentee." *Id.* at 113. Stated otherwise, "indiscriminate creation of exclusive privileges tends rather to obstruct than to stimulate invention." *Atlantic Works* v. *Brady*, 107 U.S. 192, 200 (1883). It "creates a class of speculative schemers" who "watch the advancing wave of improvement, and gather its foam in the form of patented monopolies, which enable them to lay a heavy tax upon the industry of the country, without contributing anything to the real advancement of the art." *Ibid.*

In keeping with the need to avoid patent monopolies that interfere with the work of scientists beyond the scope of any specific invention, this Court in *Brennner* v. *Manson* denied a patent for a new chemical process for making steroids that were of scientific interest in the search for cancer therapy but that as yet had no known utility. 383 U.S. at 520-522, 529. In invalidating this process patent because it had not been "reduced to production of a product" that would "precise[ly] delineat[e]" the "metes and bounds of th[e] monopoly," the Court explained that patents may not

"engross a vast, unknown, and perhaps unknowable area," or "confer power to block off whole areas of scientific development without compensating benefit to the public." *Id.* at 534.

Like the patent rejected in *Brenner*, Prometheus's patents are vague and open-ended and do not set forth any real therapy—just an exhortation to consider a possible dosage change in the light of some numbers. But the monopoly effect of Prometheus's patents is sweeping. They prevent physicians and researchers from considering better metabolite ranges for different diseases or specific subsets of patients, or marketing a cheaper and more accurate test with different ranges. The patents would make Prometheus's metabolite ranges conclusive—"block[ing] off" "scientific development"—in a field where research is dynamic and ongoing. That result is not "clearly commanded by the statute" and should not be tolerated. *Brenner*, 383 U.S. at 534.

F. Upholding Prometheus's Patents Would Suppress Competition To The Detriment Of Patient Health.

Patent protection "reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance." *Bonito Boats* v. *Thunder Craft Boats*, 489 U.S. 141, 146 (1989). The challenge is to strike a "balance between protecting inventors and not granting monopolies over procedures" that foreclose "independent, creative application of general principles." *Bilski*, 130 S. Ct. at 3228 (Kennedy, J.). Open-ended patents like Prometheus's, which claim a broad monopoly with the drafting trick of embedding natural laws in a "process" that imposes no meaningful limitation on the claim, "decreas[e]

the range of ideas available as the building blocks of further innovation," in "conflict with the very purpose of the patent laws." *Bonito Boats*, 489 U.S. at 151.

Prometheus's patents must be considered "in light of this Nation's historical antipathy to monopoly and of repeated congressional efforts to preserve and foster competition." *Deepsouth Packing*, 406 U.S. at 530. The Federal Trade Commission has explained that careful gatekeeping in patent law is essential to foster the competition that is the goal of the Nation's antitrust laws. "Poor patent quality and legal standards"—including "claims that are likely overbroad"—have "anticompetitive effects," result in "unwarranted market power," and "unjustifiably increase costs," thereby "hamper[ing] competition that otherwise would stimulate innovation." FEDERAL TRADE COMMISSION, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY 5 (Oct. 2003) ("FTC 2003 REPORT"), available at http://ftc.gov/os/2003/10/innovationrpt.pdf.

To avoid these harms to consumers, it is important that "in interpreting the scope of patentable subject matter under Section 101," courts "ask whether granting patents on certain subject matter in fact will promote [scientific] progress" or instead "hinder competition that can effectively spur innovation." *Id.* at 15. See also FEDERAL TRADE COMMISSION, THE EVOLVING IP MARKETPLACE: ALIGNING PATENT NOTICE AND REMEDIES WITH COMPETITION 47-48 (Mar. 2011) ("FTC 2011 REPORT") ("questionable" patents "distort competition" and "inhibit innovation" by "discouraging firms from conducting R&D in areas the patent improperly

covers and raising costs through litigation and unnecessary licensing"; "[p]atent quality" is therefore "vitally important for achieving the balance of exclusivity and competition that best enhances consumer welfare"), available at http://ftc.gov/os/2011/03/110307patentreport.pdf.

"[C]ompetition from acceptable alternatives" limits a patentee's market power and "helps generate lower prices, more choices and higher quality products for consumers." FTC 2011 REPORT at 2. But when a claim is as vague and open-ended as Prometheus's that will never occur. Prometheus has squelched all competition to provide improved tests by claiming a monopoly on the correlation between thiopurine metabolites and health, as its suit against Mayo and attack on Dr. el-Azhary show. Far from "encourag[ing] investmen[t] in those inventions that are more likely to be valued by consumers," these patents distort competition by cutting off pro-consumer development of better and cheaper tests, including tests directed to other diseases. And no monopoly was necessary to incentivize the research that led to Prometheus's patents. Canadian physicians did what doctors always have done—looked at medical databases and reached conclusions about how to treat patients in light of them. Prometheus simply bought the right, after the fact, to patent their conclusions.

In short, Prometheus's patents have "commandeered the entire market" by monopolizing all thought about the health effects of the biologic fact, well known to physicians for many years, that thiopurine drugs produce metabolites that relate to the health of patients with autoimmune diseases. CHRISTINA BOHANNAN & HERBERT HOVENKAMP,

CREATION WITHOUT RESTRAINT: PROMOTING LIBERTY AND RIVALRY IN INNOVATION ch. 5, at 29 (forthcoming 2011); see *ibid.* ("Inventions that are nothing more than verbal assertions * * * cover as wide a market as human language allows"). By "creating a monopoly in a rather common mechanism" that physicians and researchers "have thought of entirely on their own," Prometheus's patents operate as "bottlenecks on innovation competition" that "prevent other firms from *independently* developing competing processes or products." *Id.* ch. 5, at 5, 27, 29.[8]

G. Prometheus's Patent Claims Are Not The Sort Of "Invention" Congress Meant To Protect.

Given the settled precedents and principles we have described, Prometheus's contention that it should be able to monopolize the natural correlation between thiopurine metabolites and health "should be addressed to the political branches of Government, the Congress and the Executive, and not to the courts." *Chakrabarty*, 447 U.S. at 317. If laws of nature long known to medical science "are to be patentable, considerable problems are raised" for medical research and patient care that "only committees of Congress can manage." *Benson*, 409 U.S. at 73; see *Flook*, 437 U.S. at 595-596 ("we must proceed cautiously when we are asked to extend patent rights into areas wholly unforeseen by Congress"; the "[d]ifficult questions of policy" involved must "be answered by Congress"). Far from

[8] With the authors' permission, petitioners have sought leave to lodge with the clerk page proofs of the cited chapter of this forthcoming book.

citing a "clear and certain signal from Congress" that expansion of patent protection is proper (*id.* at 596), Prometheus has offered no evidence whatsoever that its attempted patent on medical judgment is something "which the patent laws were designed to protect." *Diehr*, 450 U.S. at 192.

To begin with, the legal principles upon which we rely—that a patent may not preempt laws of nature or abstract ideas, and that it is not saved by embedding the law of nature in a well-known process that does not narrow the scope of the claim—were well established before Congress recodified the Patent Act and enacted Section 101 in its current form in 1952. Congress at that time intended no substantive change in the law. See *supra*, p. 27 & n.6.

Equally well established was the legal principle that federal legislation must be construed to avoid conflict with First Amendment freedoms whenever possible. See *Edward J. DeBartolo Corp.* v. *Florida Gulf Coast Bldg. & Constr. Trades Council*, 485 U.S. 568, 574-575 (1988) (observing that this "cardinal principle" has "for so long been applied by this Court that it is beyond debate"); *New York* v. *Ferber*, 458 U.S. 747, 769 n.24 (1982). Throughout our Nation's history, the freedom to think—to consider what one has seen, to reach mental conclusions based on those observations, and to change one's future plans in light of those conclusions—has been deemed sacrosanct. Reflecting that tradition, this Court held in *Ashcroft* v. *Free Speech Coalition*, 535 U.S. 234, 253 (2002), that speech is protected from government restriction because "[t]he right to think is the beginning of freedom, and speech must be protected

from the government because speech is the beginning of thought."

Prometheus's sweeping claims chill important research and speech in ways that Congress never would have intended. As the American Medical Association explained in urging review, patents like Prometheus's entangle physicians in "a vast thicket of exclusive rights" to "basic diagnostic information" that is "critical" to "providing sound medical care," to "the detriment of the nation's health." Am. Br. of American College of Medical Genetics, *et al.*, ("AMA Br."), at 5-6, 20-21. That chilling effect is obvious here, where Prometheus deposed Dr. el-Azhary, accusing her of infringement because she conducted research on the appropriate metabolite range for dermatology patients while aware of Prometheus's range, and where Dr. el-Azhary dared not publish her conclusion that Prometheus's range was defective for dermatology patients until after the district court invalidated Prometheus's patents. See ACLU Am. Br. in *Bilski*, No. 2007-1130 at 5-7, 14 (Fed. Cir. Apr. 3, 2008), available at http://www.aclu.org/pdfs/freespeech/in_re_bilski_aclu_amicus.pdf (patents like those here and in *LabCorp* amount "to a patent on pure thought or pure speech"; courts "should interpret patent law doctrines" to "avoid the difficult application of First Amendment doctrines").

Prometheus's patents, deferring to a physician's medical judgment, while demanding payment for exercising that judgment, are even more ridiculous than the example cited in *Bilski* of teaching good housekeeping. *Supra*, pp. 32-33. It is unthinkable that Congress intended the patent laws to embargo independent research and thought about a natural correlation based on someone's suggestion of

numbers that he deems relevant, but which others may reasonably reject. See *Microsoft Corp.* v. *i4i Ltd. P'ship*, 131 S. Ct. 2238, 2253 (2011) (Breyer, Scalia, Alito, JJ., concurring) (rigorous judicial scrutiny is required to assure "that discoveries or inventions will not receive legal protection where none is due"). This Court should not presume that Congress intended such a harmful result.

II. PATENTS ON MEDICAL CORRELATIONS WILL SUPPRESS RESEARCH AND INNOVATION, INTERFERE WITH PATIENT CARE, AND INCREASE COSTS.

The holding below that patents may be awarded on correlations between the administration of medication and the resulting biological reaction is flatly inconsistent with this Court's precedents. But more than that, such patents are far more likely to retard than to advance innovation, and thus to frustrate the broader goals of federal patent law. In fact, patents on natural medical correlations of the sort granted in this case can be expected to have a host of pernicious consequences: such patents will suppress both basic research and specific advances in medical treatment; interfere with patient care and the exercise of medical judgment by physicians; and raise consumer costs. These considerations confirm that the decision below should be reversed.

1. To begin with, the likely effect of a patent on innovation and competition has an important bearing on the patent's validity. The Court has repeatedly emphasized that the "Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Bonito*

Boats, 489 U.S. at 146. See *Bilski*, 130 S. Ct. at 3228 (Kennedy, J.); *id*. at 3252 (Stevens, J., concurring in the judgment). Thus, "[t]he underlying policy of the patent system [is] that 'the things which are worth to the public the embarrassment of an exclusive patent,' * * * must outweigh the restrictive effect of the limited patent monopoly." *Bilski*, 130 S. Ct. at 3258 (Breyer, J., concurring in the judgment).

In a comprehensive review of the patent process, the Federal Trade Commission concluded that, "properly interpreted," patent law awards patents "only when necessary to provide incentives for inventions, their commercial development, or their disclosure." FTC 2003 REPORT, at 4. "If the promise of patent protection is not necessary for those purposes, however, then the costs—which may include higher prices or retarded follow-on innovation—may cause unjustified injury to consumers." *Id*. at 8. Against this background, "a heavy burden of persuasion should be placed upon those who would extend such protection." Stephen Breyer, *The Uneasy Case for Copyright*, 84 HARV. L. REV. 281, 322-323 (1970) (citing research in patent and copyright fields). Prometheus cannot meet that burden here: its patents are certain to "impede rather than 'promote the Progress of Science and useful Arts.'" *LabCorp*, 548 U.S. at 126-127 (Breyer, J., dissenting).

2. Patent protection assuredly is unnecessary to encourage research and innovation of the sort reflected in the Prometheus patents. Patents doubtless serve an important purpose "when the original innovator's efforts entail substantial fixed costs, and the imitators can copy the innovation cheaply." FTC 2003 REPORT, at 4. An example is the development of a new pharmaceutical or medical

device, which must be invented, tested, and approved, typically all at great expense. See *Bilski*, 130 S. Ct. at 3253 (Stevens, J., concurring in the judgment); Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 505 (2009).[9] But as the American Medical Association and other leading groups of physicians and medical colleges observed in supporting the grant of certiorari here, "[p]atents on scientific observations underlying medical care" lack "these salutary effects." AMA Br. at 9. "Development costs for these diagnostic tests" are "low, in part because approval of such tests does not involve the high regulatory costs involved in the development of pharmaceuticals and medical devices." *Id*. at 15. And the simple observation of medical correlations plainly "does not entail the same kinds of risk as does more traditional, technological innovation. It generally does not require the same enormous costs in terms of time, research, and development." *Bilski*, 130 S. Ct. at 3254 (Stevens, J., concurring in the judgment).

Moreover, as the Secretary of Health and Human Services' Advisory Committee on Genetics, Health, and Society ("the Secretary's Advisory Committee")

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[9] "Empirical analysis of the patent system is, at best, ambiguous as to the importance of this incentive except in certain specific industries, such as pharmaceutical products." John H. Barton, *Patents and Antitrust: A Rethinking in light of Patent Breadth and Sequential Innovation*, 65 ANTITRUST L.J. 449, 453 (1997). "[I]n most industries, patenting is among the less important mechanisms for protecting the results of innovation." BOHANNAN & HOVENKAMP, *supra*, ch. 5, at 4; see *id*. at 3 ("Time and first mover-advantage often provide greater or more predictable returns to innovation than patenting does").

recently noted in the area of genetic research, "[t]he prospect of patent protection" does not play a significant role in motivating scientists to conduct medical research. "Scientists typically are driven instead by factors such as the desire to advance understanding, the hope of improving patient care through new discoveries, and concerns for their own career advancement." GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS 1 (April 2010) ("ADVISORY COMMITTEE REPORT"), available at hhtp://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf.

Nor is the prospect of obtaining a patent necessary to support such work financially: the federal government "is likely the major funder" for basic research. *Id.* at 2; see John H. Barton, *supra*, 65 ANTITRUST L.J. at 453-454 ("nations have usually encouraged such research by direct support rather than by use of the patent system"). Similarly, patents "are not needed to stimulate the disclosure of research discoveries," because "[t]he norms of academic science encourage disclosure of research results, and scientists have strong incentives to publish and present their discoveries." ADVISORY COMMITTEE REPORT 2; see *id.* at 90.

These observations about the limited role of patents in encouraging medical research are not theoretical. The Secretary's Advisory Committee "found *no* cases in which possession of exclusive rights was necessary for the development of a particular genetic test, including test kits and tests for both common and rare genetic diseases." ADVISORY COMMITTEE REPORT 2 (emphasis added). And "exclusive rights do not result in faster test

development. In none of the cases studied was a patent-protected test the first to market." *Ibid*.

In the particular context here, the AMA and other medical groups have explained that "patents are not needed to incentivize physicians and researchers to study the kinds of clinical correlations at issue." AMA Br. 14-15. Indeed, the work behind Prometheus's patents was done by physicians who only later sold the right to patent their research to Prometheus at a minimal price. It is no exaggeration to say that Prometheus invested in litigation, not research. Given the certainty that such research will proceed without the promise of monopoly profits, the Prometheus patents "have not furthered innovation one bit but have only created a power to exclude from an otherwise competitive market." BOHANNAN & HOVENKAMP, *supra*, ch. 5, at 1.

3. That such patents are unnecessary is only half the problem; patents like those issued to Prometheus are certain to *inhibit* innovation and the improvement of patient care. That is true in several respects.

First, as a general matter, allowing patents to preempt important fields of research will retard innovation and increase costs. The rule against patenting fundamental scientific principles reflects both "'the enormous potential for rent seeking that would be created if property rights could be obtained'" in these basic principles and "'the enormous transaction costs that would be imposed on would-be users.'" *LabCorp*, 548 U.S. at 127 (Breyer, J., dissenting) (quoting WILLIAM LANDES & RICHARD POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 305 (2003)). When such patents are claimed—and this surely is true of the

Prometheus patents—the "monopoly breadth is a function of [the patent's] *lack* of technical specification." BOHANNAN & HOVENKAMP, *supra*, ch. 5, at 27. Unlike "[t]actile inventions," which "generally have alternatives," it is impossible to invent around "[i]nventions that are nothing more than verbal assertions" like those at issue here. *Id*. at 29.

This reality has significant real-world consequences. The holder of such a patent on a scientific principle or correlation "may be able to use it to threaten litigation and to bully competitors." *Bilski*, 130 S. Ct. at 3257 (Stevens, J., concurring in the judgment). This may lead other researchers "to forgo R&D in the areas that the patent improperly covers. * * * Such effects deter market entry and follow-on innovation by competitors and increase the potential for the holder of a questionable patent to suppress competition." FTC 2003 REPORT, at 5-6; see *id*. at 20 (such patents "create a 'significant drag' on competition" and "have a 'chilling effect on both public and private sector research'"). Academic commentary confirms that "use of a patent to prevent future research turns the research encouragement goal of the patent system on its head, and seems inherently anticompetitive as well." Barton, *supra*, 65 ANTITRUST L.J. at 454.[10]

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[10] See, *e.g.*, JAMES BESSEN & MICHAEL MEURER, PATENT FAILURE 8-9, 17, 27 (2008) (patents on "mental correlations" make it "very difficult to know [the patents'] boundaries," creating the "nee[d] to check a very large number of patents," inviting "disputes and litigation," and encouraging "patent trolls" to "opportunistically take advantage of poor patent notice to assert patents against unsuspecting firms"); DAN BURK & MARK LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT 123-124 (2009) (innovators must be able to work out

Second, these limiting effects on research and innovation are especially acute in the medical field, for reasons made apparent by the Prometheus patents themselves. It is fundamental that "[r]eady access to basic facts, such as a relationship between levels of drug metabolites and the drug's efficacy and toxicity, is essential to medical research," as knowledge about the effectiveness of specific treatment "accumulates through medical practice and is shared throughout the medical community." AMA Br. 13-14. But under the Prometheus patents, as the AMA and other medical groups explained, a physician or researcher "would become an infringer if he or she *merely considered what to do about the results [of a test of metabolite levels] in light of relevant scientific information*," while a laboratory would induce infringement simply "by publishing articles or brochures discussing the correlation" between those levels and drug efficacy. *Id.* at 11 (emphasis added). If these patents are valid, others can, and surely will, claim patent monopolies on scientific observations

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new uses of abstractions and natural phenomena "without fear of patent liability" because patents "cove[r] entire concepts"); LAWRENCE LESSIG, THE FUTURE OF IDEAS 205-217 (2001) (describing negative impact of broad patent protection on innovation; "we should be most concerned when existing interests use the legal system to protect themselves against innovation"); Robert Merges & Richard Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 915 (1990) ("[T]he real threat of a patent like this stems from the industry's close ties to science. * * * The Patent Office and courts should not permit the over-privatization of the scientific knowledge that makes the industry possible"); Andrew Torrance & Bill Tomlinson, *Patents and the Regress of Useful Arts*, 10 COLUM. SCI. & TECH. L. REV. 130, 138, 162-167 (2009) (collecting economic research showing lack of stimulus to innovation from broad patent grants).

underlying proper diagnosis and treatment of a host of medical conditions.

As we have explained, patents on scientific correlations "often claim (or come close to claiming) fundamental principles of nature; therefore, it is frequently not possible to invent around these patents to produce materials of equivalent diagnostic and research value." ADVISORY COMMITTEE REPORT 90. Necessarily, such patents

> discourage research by impeding the free exchange of information, for example by forcing researchers to avoid the use of potentially patented ideas, by leading them to conduct costly and time-consuming searches of existing or pending patents, by requiring complex licensing arrangements, and by raising the costs of using the patented information, sometimes prohibitively so.

LabCorp, 548 U.S. at 127 (Breyer, J., dissenting)

Here, too, as the Secretary's Advisory Committee explained in detail, "[t]hese concerns are more than hypothetical. Patents are already hindering the development" of genetic tests and laboratories "are already choosing not to report medically significant results * * * for fear of liability." ADVISORY COMMITTEE REPORT 3. There also "is evidence to suggest that patents on genes discourage follow-on research." *Id.* at 2. See *id.* at 89; Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Non-problem? Rethinking the Anticommons in Biomedical Research*, 45 HOUS. L. REV. 1059, 1071 (2008) ("Empirical evidence in the United States suggests that patents on genes have impeded both the provision of genetic testing services and the

development of new tests by diagnostic laboratories"). Indeed, the Prometheus patents have had precisely that effect in this case, precluding Mayo researchers from developing improved metabolite ranges and interfering with Dr. el-Azhary's effort to establish therapeutic ranges for skin disorders that are not addressed by the research underlying the Prometheus patents. Patents that have such an effect are demonstrably "less an incentive to basic research than a barrier to applied research." Barton, *supra*, 65 ANTITRUST L.J. at 454.[11]

Third, in addition to undermining medical research, the Prometheus patents (and the many others like them that would follow if these patents are upheld) will have an immediate adverse effect on the quality of patient care, increasing the cost and reducing the availability of medical service. "It is a routine part of the practice of medicine—indeed, it is essential to meet appropriate medical standards of care—for physicians to monitor metabolite levels and to use those levels along with other laboratory and clinical parameters to guide dosage adjustments." AMA Br. 10. That being so, allowing a single patent

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[11] The point is confirmed by Prometheus's own defense of its patents, which asserts that they will not freeze research because scientists remain free to develop "a method for measuring metabolite levels that does not require analysis of a bodily sample." Br. in Opp. 27. Even assuming that such an unlikely, hands-free metabolite measurement method could be developed (and it is hard to imagine what such a method would entail; see 1JA 42-43), Prometheus recognizes that, at a minimum, its patents will require researchers to forgo use of the ordinary tools of medical testing and instead develop what would otherwise be a novel and wholly unnecessary alternative test, a process that would be inordinately expensive and inefficient.

holder to control the use that is made of such basic and essential medical observations will "raise the cost of medical care prohibitively without compensating benefits to medical research." *Id*. at 20.

Again, that effect is visible in this case: the Prometheus patents will bar Mayo physicians from offering a test of metabolite levels that is much less expensive than Prometheus's test and provides a more accurate and helpful correlation range to guide treatment. See Aaron S. Kesselheim & Michelle M. Mello, *Medical-Process Patents—Monopolizing the Delivery of Health Care*, 355 NEW ENG. J. MED. 2036, 2036 (2006) ("Medical-process patents threaten to complicate medical practice, increase costs, and restrict access to therapeutic and diagnostic procedures"); Lori Andrews, *et al.*, *When Patents Threaten Science*, 314 SCIENCE 1395, 1396 (2006) ("Although the discoveries of natural phenomenon may be necessary precursors to invention, improperly tying up these discoveries with patent rights will only drive up the costs of such subsequent innovations, if not thwart them altogether").

This case is hardly unique. Patient care and "access to tests" have "suffered in a number of ways" from patents that purport to control natural phenomena. ADVISORY COMMITTEE REPORT at 3. The sharply increased costs produced by giving monopoly control over a basic medical methodology has caused patients to "forgo testing because they cannot afford the test," or forgo "second-opinion testing from an independent laboratory." *Ibid*. And control of the use that can be made of medical correlations by a patent-protected sole provider raises "significant concerns about the quality" of test results because "[t]he most robust method for assuring quality in laboratory

testing is through the comparison of results obtained on samples shared between different labs." *Id*. at 4. In all, as Justice Breyer observed in *LabCorp*, 548 U.S. at 138, patents like those in this case

> may inhibit doctors from using their best medical judgment; they may force doctors to spend unnecessary time and energy to enter into license agreements; they may divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations; they may raise the cost of health care while inhibiting its effective delivery.

For these same reasons, the decision below cannot be reconciled with the ethical duties of physicians. As explained by the AMA and other medical organizations (AMA Br. 9-11), patent protection of Prometheus's claims conflicts with ethical standards that require physicians to spread knowledge—and improve diagnostic criteria—for the benefit of all. Prometheus acknowledges as much, agreeing that "physicians in the course of patient care are less able to avoid patent infringement than professionals in other fields, because avoiding the patented method may be inconsistent with the physician's ethical obligations." Br. in Opp. 34. Prometheus would solve this ethical dilemma by requiring physicians and patients "to pay inventors" —which is to say, Prometheus. *Id*. at 35. The better solution, and the one compelled by fundamental principles of patent law, is to hold that a putative patentee may not monopolize basic biological relationships at all.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

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