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 OF *AMICI CURIAE* THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN MEDICAL ASSOCIATION, THE AMERICAN HOSPITAL ASSOCIATION, THE AMERICAN SOCIETY OF HUMAN GENETICS, THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES, THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE ASSOCIATION OF PROFESSORS OF HUMAN AND MEDICAL GENETICS, THE COLLEGE OF AMERICAN PATHOLOGISTS, THE FLORIDA HOSPITAL ASSOCIATION, THE MINNESOTA HOSPITAL ASSOCIATION, AND THE MINNESOTA MEDICAL ASSOCIATION IN SUPPORT OF PETITIONERS

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INTEREST OF THE *AMICI CURIAE*

Amici curiae submit this brief in support of petitioners Mayo Collaborative Services (d/b/a Mayo Medical Laboratories) and Mayo Clinic Rochester (collectively "Mayo") because the judgment of the Federal Circuit in this case stems from an interpretation of patentable subject matter that is inconsistent with this Court's constitutionally grounded precedent and with public policy regarding both innovation and health care.[1]

Amici are associations of physicians, researchers, medical educators, and other providers of healthcare-related services. *Amici* are concerned with the potential impact of patent claims covering natural phenomena, such as the correlations covered by Prometheus's patents. Such patents have great potential to impede the development and practice of medicine and raise health care costs.

The American College of Medical Genetics (ACMG) is a private, non-profit, voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral-level medical geneticists and other physicians involved in the practice of medical genetics. With more than 1,500 members, the

[1] The parties have consented to the filing of this brief. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* and their members or their counsel made a monetary contribution to its preparation or submission.

ACMG's mission is to improve health through the practice of Medical Genetics. In order to fulfill this mission, the ACMG strives to 1) define and promote excellence in medical genetics practice and the integration of translational research into practice; 2) promote and provide medical genetics education; 3) increase access to medical genetics services and integrate genetics into patient care; and 4) advocate for and represent providers of medical genetics services and their patients. The position of the ACMG is that observations of naturally occurring correlations should not be patentable.

The American Medical Association (AMA) is the largest professional association of physicians, residents and medical students in the United States. Additionally, through state and specialty medical societies and other physician groups seated in its House of Delegates, substantially all U.S. physicians, residents and medical students are represented in the AMA's policy making process. The objectives of the AMA are to promote the science and art of medicine and the betterment of public health. The AMA joins this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies. The Litigation Center is a coalition among the AMA and the medical societies of each state, plus the District of Columbia, whose purpose is to represent the viewpoint of organized medicine in the courts.

The American Hospital Association (AHA) represents nearly 5,000 hospitals, health care systems,

and networks, plus 37,000 individual members. AHA members are committed to improving the health of communities they serve and to helping ensure that care is available to, and affordable for, all Americans. The AHA educates its members about health care issues and advocates to ensure that their perspectives are considered in formulating health care policy.

The American Society of Human Genetics (ASHG) is a non-profit, tax-exempt organization that consists of more than 7,200 professionals in human genetics including researchers, clinicians, academicians, ethicists, counselors and other medical professionals. ASHG serves members by providing forums to share study results (the annual meeting and the Society journal); enhancing genetics education by preparing future professionals and the public; and promoting genetic services. As ASHG members transfer new knowledge to the next generation of genetics professionals and the public, new ideas will be translated into improved clinical practice. ASHG is concerned that claims covering patenting of natural phenomena will impede research and the development of improved medical practice, particularly in genomic or personalized medicine.

The Association of American Medical Colleges (AAMC) is a non-profit organization representing all 135 allopathic medical schools in the United States, about 400 major teaching hospitals and health systems, and about 90 academic and professional societies representing nearly 110,000 faculty members. AAMC's member institutions are at the forefront of

medical education, research and research training, and health care innovation and delivery. AAMC members perform nearly 55% of the extramural research sponsored by the National Institutes of Health, and they partner with industry in discovering new and better approaches to the diagnosis, treatment, and prevention of human diseases. The AAMC is committed to the continuing improvement of health care and the Continuing Medical Education of physician practitioners based on sound scientific evidence.

The Association for Molecular Pathology (AMP) is an international medical professional association representing approximately 1,900 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. AMP dedicates itself to the development and implementation of molecular diagnostic testing, which includes molecular genetic testing in all its definitions, in a manner consistent with the highest standards established by CLIA, the College of American Pathologists, the American College of Medical Genetics, and the FDA. AMP members work in widely diverse settings: academic medical centers, independent medical laboratories, community hospitals, public health laboratories, government agencies, and the *in vitro* diagnostics industry. AMP members are involved in every aspect of molecular diagnostics: research and development, administration and interpretation of molecular tests, policy and regulation, and education.

The Association of Professors of Human and Medical Genetics (APHMG) is a non-profit organization that promotes human and medical genetics educational programs in North American medical and graduate schools. Currently more than 90 medical and graduate schools are members. The APHMG represents the faculty members that teach human and medical genetics to virtually all medical students in North America. As educators, they teach medical students to think about, diagnose and treat genetic diseases. It is the APHMG's position that all physicians must be free to think broadly, creatively, analytically and without fear that they risk infringing a patent merely by *thinking* about the relationship between certain treatments and their potential metabolic and clinical sequelae.

The College of American Pathologists (CAP) is the world's largest medical society composed exclusively of pathologists, with nearly 18,000 members. Pathologists are physicians who examine tissues, blood, and other body fluids for the purposes of medical diagnosis and patient care. Through its accreditation and proficiency testing programs, the CAP is also a leader in assuring the quality of laboratory testing. More than 7,000 laboratories are accredited by the CAP, and approximately 23,000 laboratories are enrolled in the College's proficiency testing programs.

The Florida Hospital Association (FHA) is a voluntary association comprised of 185 hospitals and health systems, and 16 Professional Membership Groups that include 1,300 professional members from

across the state of Florida. The FHA has a common goal of providing the highest quality of care to the patients served by its members. Through effective and proactive advocacy, FHA demonstrates the community value of hospitals, builds consensus with other groups, and secures necessary resources so its members can continue to provide needed critical care to their communities.

The Minnesota Hospital Association (MHA) represents the interests of hospitals in the State of Minnesota, including 146 community-based hospitals and 16 health systems. MHA assists Minnesota hospitals – and their employed and affiliated health care providers – in carrying out their responsibilities to provide quality health care services to their communities; promote universal health care coverage, access, and value; and coordinate development of innovative health care delivery systems.

The Minnesota Medical Association (MMA) is a professional association representing approximately 11,000 physicians, residents, and medical students in the State of Minnesota. The MMA seeks to promote excellence in health care, to insure a healthy practice environment, and to preserve the professionalism of medicine through advocacy, education, information and leadership. For more than 150 years, the MMA and its members have worked together to safeguard the quality of medical care in Minnesota as well as the future of medical professionalism.

SUMMARY OF ARGUMENT

New drugs and new tools for diagnosing illness and monitoring treatment are critical to the advancement of medicine. The patents at issue in this case, however, do not claim innovative drugs or new diagnostic tools. Instead, these patents grant exclusive rights over the mere observation of natural, statistical correlations between certain metabolite levels in the body, as measured by well-known means, and the potential toxicity and effectiveness of well-known drugs. If these patents remain in force, any physician who measures those metabolite levels and knows about the observed correlations will unavoidably become an infringer. Thus, these patents convert routine, sound medical practice into prohibited infringement.

If such claims to exclusive rights over the body's natural responses to illness and medical treatment are permitted to stand, the result will be a vast thicket of exclusive rights over the use of critical scientific data that must remain widely available if physicians are to provide sound medical care. Conscientious physicians will be unwilling and unable to avoid considering all relevant scientific information when reviewing test results. Thus, as medical knowledge accumulates, patent licenses increasingly will be required for physicians to conduct even well-established diagnostic tests. Laboratories will risk indirect infringement merely by educating doctors about advances in scientific understanding. It is hard to imagine how the clinical diagnostic community will

continue to provide quality patient care and how physicians will continue to practice medicine in an ethical and effective manner under such a regime.

Moreover, the claims at issue run afoul of this Court's longstanding ban on patenting "laws of nature, physical phenomena, and abstract ideas," *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)). That prohibition implements the constitutionally grounded policy that patents may be granted only to "Inventors" so as to "promote Progress in . . . the useful Arts." U.S. Const. art. I, § 8, cl. 8.

The patentable subject matter inquiry therefore must consider whether an applicant who has discovered a natural phenomenon or come up with an abstract idea is the *inventor* of a patentable application of the phenomenon or idea, rather than the competent draftsman of a merely conventional application. *Parker v. Flook*, 437 U.S. 584, 590 (1978). Thus, in evaluating whether claim terms such as Prometheus's "administering" and "determining" steps are "insignificant" additions to claimed natural phenomena or abstract ideas, *Bilski*, 130 S. Ct. at 3230 (quoting *Diamond v. Diehr*, 450 U.S. 175, 191-92 (1981)), courts must determine whether incorporating such steps involved "an exercise of the inventive faculty." *Dann v. Johnston,* 425 U.S. 219, 225 (1976). Yet the Federal Circuit failed to implement this constitutionally grounded requirement. Prometheus's claims, which involve utterly conventional applications of unpatentable natural phenomena, scientific conclusions,

and mental processes, are not the work of an inventor.

The Federal Circuit also has erred twice in its analysis of the additional requirement that claims involving natural phenomena or abstract ideas not inappropriately preempt their use. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 581 F.3d 1336 (Fed. Cir. 2009); *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347 (Fed. Cir. 2010). First, the court relied heavily on a transformation of matter analysis. While the transformation of matter test provides a "useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101," *Bilski*, 130 S. Ct. at 3227, it is inapposite for assessing the patentability of claims applying newly-discovered natural phenomena, which nearly always involve transformations of matter. Second, the court ignored the fact that the claims at issue preempt virtually all practical uses of the particular natural correlations they cover, holding them patentable under § 101 because they do not encompass correlations involving other drugs and diseases.

In sum, the Federal Circuit failed even to ask whether the claimed applications of natural phenomena reflect inventive activity, which they do not, and erred in applying this Court's preemption standard. The claims at issue do not meet either requirement and therefore are unpatentable.

ARGUMENT

I. Health Care Will Be Undermined If Conventional Medical Applications of Scientific Observations of Naturally-Occurring Bodily Processes Can Be Patented

The scope of patentable subject matter established by Congress in the Patent Act, 35 U.S.C. § 101, although quite broad, does not extend to scientific facts or observations of natural phenomena. *See Bilski,* 130 S. Ct. at 3225 (citing *Le Roy v. Tatham*, 55 U.S. 156 (1853)); *Diehr*, 450 U.S. at 185 (citing *Flook*, 437 U.S. at 593; and *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). The patents at issue here give Prometheus exclusive private ownership not of a new drug, a new diagnostic test, or even a new method of diagnosing a particular disease. Rather, the patents at issue effectively award Prometheus exclusive ownership of a pre-existing diagnostic test based on the mere *observation* of a naturally-occurring phenomenon: the correlation between the levels of certain metabolites produced naturally in the human body in response to administration of thiopurine drugs and the efficacy and toxicity of those drugs.

Amici medical associations recognize that health-care-related patents can enhance the provision of high-quality and cost-effective medical care. The financial incentive that patents offer supports the expensive and uncertain research required to identify, test, and gain approval for new pharmaceuticals, medical devices, diagnostic testing kits, and other products. In this respect, the patent system has

served patients and the medical profession well, drawing investment into the development of important new treatments.

Patents on scientific observations underlying medical care, however, do not have these salutary effects. Such patents erode the quality of patient care by limiting use of the very knowledge on which physicians must rely to diagnose and treat their patients, threaten to stifle innovation and the development of personalized medicine, and raise ethical concerns for physicians.

A. Patents on Scientific Observations Burden Physicians' Use of Pre-Existing Laboratory Tests and Erode Their Ability to Provide Quality Patient Care

A doctor who administers thiopurine drugs and tests metabolite levels infringes the claims at issue *merely by considering what to do about the results in light of relevant scientific information* about the correlation between dosage and efficacy or toxicity. This is the case even if he or she had a pre-existing practice of testing levels of the same metabolites and adjusting dosages of thiopurine drugs based on the test results.

The potential ramifications of the Federal Circuit's ruling that claims of this sort are patentable are profound and sobering. By uncovering a correlation between obesity and a particular illness, for

example, a researcher could obtain a patent on the process of having a patient step on a scale and then considering that natural correlation in deciding whether to recommend that the patient diet to lose weight. Any entity that made or sold scales and that dared to mention the correlation in a brochure might then be liable for intentionally inducing infringement. An observation that some patients tend to run a particularly high fever if given too much of a particular drug could lead to a patent on taking a patient's temperature and considering whether to raise or lower the dosage with that natural response in mind. Patients, physicians, and thermometer manufacturers might directly or indirectly infringe because a thermometer reading "indicates" that it might be advisable to adjust dosage of the drug. Such results are unthinkable, yet are eminently plausible applications of the Federal Circuit's analysis in this case.

There can be no design around a scientific fact. A physician who learns, from the medical literature, colleagues, continuing medical education, or elsewhere, of the natural correlation between metabolite levels and drug efficacy and toxicity cannot—and should not—put that knowledge out of mind. Quality patient care demands that a physician make treatment decisions in light of current medical knowledge. If natural correlations, such as those claimed here, are patented, physicians considering how to personalize their patients' care in light of the full and evolving scope of available scientific information will become mired in a thicket of exclusive rights. Not only might

a doctor infringe multiple patents by considering the results of a battery of diagnostic tests, but each test might be the subject of multiple, overlapping, patented guidelines.

In addition, if the claims at issue here were properly patentable, a laboratory such as Mayo might induce infringement simply by informing a doctor of the correlation in conjunction with delivery of test results or perhaps even by merely publishing articles or brochures discussing the correlation. Indeed, confronting very similar facts in *Metabolite Labs., Inc. v. Lab. Corp. of America Holdings*, 370 F.3d 1354 (Fed. Cir. 2004), the Federal Circuit found that the defendant laboratory had induced infringement through the publication of medical articles. *Id.* at 1365. To avoid inducement liability, laboratories would be forced to negotiate and pay license fees to multiple holders of such diagnostic correlation patents and might well decide to forego offering some tests. Moreover, patentees might decide to license their patents only to selected laboratories and physicians, restricting test availability and driving up costs.

If patent licenses are required for physicians merely to *consider* newly-discovered implications of well-established diagnostic tests and laboratories become indirect infringers merely by educating doctors about those implications, it is hard to imagine how quality patient care can result. Laboratories and physicians will expend time and resources tracking, interpreting, and licensing such patents, rather than

on improving patient care. Higher-priced medical care is the inevitable result.

B. Patents on Scientific Observations Threaten to Stifle Innovation, Including the Development of Personalized Medicine

Basic scientific facts 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 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 130 (1948). To promote medical innovation, basic facts, such as the relationship between levels of drug metabolites and the drug's efficacy and toxicity, must be freely accessible and widely disseminated. These patentees are neither the first nor the last to study the implications of these particular metabolite levels for human health. Physicians' understanding of the body's natural responses to treatment, such as the correlations involved here, accumulates over time through clinical practice and research, often leading to revisions of treatment guidelines and adaptation of those guidelines to reflect distinct recommendations for patients with particular illnesses or personal characteristics.

Patents are not needed to incentivize this study of clinical correlations and would stifle rather than incentivize developments in the practice of personalized medicine. The Secretary's Advisory Committee on Genetics, Health, and Society conducted an

extensive investigation into the need for patents in the closely-related context of genetic diagnostic testing and found:

> [P]atents do not appear to be necessary to stimulate research and genetic test development. . . . [S]cientists are principally motivated to conduct research by their curiosity, career ambitions, and desire to advance understanding of health and disease. . . . Similarly, laboratories have sufficient non-patent incentives to develop genetic tests: clinical need and demand drive development, and development costs are minimal.[2]

Patents are even less necessary to motivate academic researchers and clinicians to uncover correlations such as those claimed here. To improve existing treatment regimens, laboratories such as Mayo continually strive to develop more accurate standards for the clinical interpretation of metabolite levels. Researchers seek to study how these metabolite levels correlate with efficacy and toxicity in different clinical contexts and to develop appropriately tailored clinical approaches. The need for time-consuming, costly, and risky patent clearing and licensing, coupled with the possibility that patentees will simply refuse to license, will chill such research and raise its costs. Patent

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[2] SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, DEP'T OF HEALTH & HUMAN SERVS., GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS (2010) at 90, available at http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf (last visited Sept. 6, 2011).

claims such as those at issue here impermissibly burden medical research, effectively "shut[ting] the door" to scientific progress. *O'Reilly v. Morse*, 56 U.S. 62, 113 (1853).

C. Patents on Scientific Observations Raise Ethical Concerns for Physicians

Physicians have longstanding ethical obligations to advance and share useful medical knowledge with patients and other physicians. Principle V of the AMA's Principles of Medical Ethics states, "[a] physician shall continue to study, apply, and advance scientific knowledge," and "make relevant information available to patients, colleagues, and the public. . . ."[3] Opinion 9.095 of the Code of Medical Ethics of the AMA, reaffirmed in 2008, elaborates upon this basic principle:

> Physicians have ethical responsibilities not only to learn from but also, when possible, to contribute to the total store of scientific knowledge. Physicians should strive to advance medical science and make their achievements known through publication or other means of disseminating such information. This encourages physicians to innovate and to share ensuing advances. The use of patents, trade secrets, confidentiality

[3] Available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/principles-medical-ethics.shtml (last visited Sept. 6, 2011).

> agreements, or other means to limit the availability of medical procedures places significant limitation on the dissemination of medical knowledge, and is therefore unethical.[4]

Basic scientific observations that could be useful in reaching diagnoses and treating patients or in devising medical innovations are quintessential examples of the kinds of knowledge that physicians are obliged to share freely.[5]

Physicians also have ethical obligations to consider the most up-to-date scientific information available when treating their patients. Measurements and observations such as those at issue here are part of the broader clinical evaluation that physicians must undertake when treating patients. 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

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[4] Available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion9095.page# (last visited Sept. 6, 2011).

[5] *See* Opinion 9.08 ("Physicians have an obligation . . . to report the results of clinical and laboratory research. . . . The intentional withholding of new medical knowledge, skills, and techniques from colleagues for reasons of personal gain is detrimental to the medical profession and to society and is to be condemned."), available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion908.shtml (last visited Sept. 6, 2011).

parameters to guide dosage adjustments, thereby providing necessary and appropriate medical care for their patients. In sum, to interpret the patent laws so as to make scientific observations eligible for patent protection threatens to undermine, rather than promote, the ethical practice of medicine.

II. The Claims at Issue Are Conventional, Rather than Inventive, Applications of Natural Phenomena and Mental Steps and Hence Are Unpatentable

Prometheus's patent claims run afoul of the long-standing ban on patenting "laws of nature, physical phenomena, and abstract ideas." *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 309). While patents are available for inventive applications of natural phenomena and abstract ideas, they may not be granted for merely conventional applications. *Bilski*, 130 S. Ct. at 3230 (quoting *Flook*, 437 U.S. at 590).

The claims at issue consist at most of the following steps: (a) administering a thiopurine drug that is broken down by the body into a particular metabolite (6-TG or 6-MMP); and (b) determining the level of the metabolite, "wherein" metabolite levels above or below certain specified levels provide "a warning that an adjustment in dosage may be required." *Prometheus*, 628 F.3d at 1351 (quoting *Prometheus Labs., Inc. v. Mayo Collaborative Servs.,* No. 04-CV-1200,

2008 WL 878910 at *1 (S.D. Cal. Mar. 28, 2008) (hereinafter "Dist. Ct. Op.").

Long before the patentee drafted his claims, physicians treating autoimmune disorders administered thiopurine drugs, measured their patients' resulting levels of 6-TG and 6-MMP metabolites, and recognized the relationship between metabolite levels and optimal dosage. The patentee's only contribution is encapsulated in the "wherein" clauses: he analyzed statistical correlations between the metabolite levels and the therapeutic efficacy and toxicity of the drugs, and inferred dosage adjustment guidelines from those studies. U.S. Patent No. 6,355,523 col.8 ll.43-46 (filed Apr. 8, 1999) ("the '523 Patent"); U.S. Patent No. 6,680,302 col.8 ll.48-51 (filed Dec. 27, 2001) ("the '302 Patent"). The "wherein" clauses merely report these unpatentable scientific conclusions, which are based on observations of unpatentable natural phenomena. To the extent the "wherein" clauses require anything from physicians, they require only the unpatentable abstract mental state of being "warned."

The Federal Circuit found that the claims as a whole were patentable only because the patentee included the steps of "determining" the metabolite levels and, in some claims, "administering" the drugs. *Prometheus*, 628 F.3d at 1355. However, the incorporation of these utterly conventional steps does not meet the constitutionally grounded requirement that a patentee be an *inventor* of a patentable application of a newly-discovered law of nature, physical phenomenon or abstract idea, rather than merely a

competent draftsman of claims covering entirely conventional applications of the phenomenon or idea.

A. Constitutionally Grounded Precedent Requires that Patentable Applications of Natural Phenomena and Mental Steps Reflect Inventive Activity

1. One Who Applies a Natural Phenomenon or Abstract Idea in a Conventional Manner Is Not an Inventor

The Constitution grants Congress the power "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const., art. I, § 8, cl. 8. The limitations of this grant have long informed this Court's interpretation of the patent statutes. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 6 (1966) ("Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must 'promote the Progress of . . . useful Arts.' This is the *standard* expressed in the Constitution and it may not be ignored.") (emphasis in original).

A patent may be awarded only to an *inventor of an application* of a natural phenomenon or abstract idea. *See, e.g.*, *Le Roy*, 55 U.S. at 175 ("The elements of the power exist; the invention is not in discovering them, but in applying them to useful objects."); *MacKay Radio Co. v. Radio Corp. Am.*, 306 U.S. 86, 94

(1939) ("While a scientific truth, or the mathematical expression of it, is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be."); *Dann*, 425 U.S. at 225 ("Invention – *i.e.*, an exercise of the inventive faculty . . . has long been regarded as an absolute prerequisite to patentability.") (internal quotation marks omitted); *cf. Feist Publ'ns, Inc. v. Rural Tel. Serv. Co.*, 499 U.S. 340, 346 (1991) (interpreting U.S. Const. art. I, § 8, cl. 8, to permit copyright protection only for "Authors").

Neither the mere application of "skill," *Funk Bros.*, 333 U.S. at 132, nor the addition of "conventional or obvious" activity, *Bilski,* 130 S. Ct. at 3230 (quoting *Flook*, 437 U.S. at 590), nor competent claim drafting, *Flook*, 437 U.S. at 590, is sufficient to transform the discoverer of a natural phenomenon or scientific principle into an inventor of a patentable application of that principle. To be eligible for a patent, the applicant must invent and claim an *application* of the natural phenomenon or abstract idea that reflects human ingenuity and is not wholly conventional. *Bilski*, 130 S. Ct. at 3230 (quoting *Flook*, 437 U.S. at 590, 594); *Flook*, 437 U.S. at 593-95; *Funk Bros.*, 333 U.S. at 132; *see also Chakrabarty*, 447 U.S. at 309-10, (holding patentable a nonnaturally occurring composition of matter deemed "a product of human ingenuity having a distinctive name, character and use" (quotations omitted)).

In *Funk Bros*., decided shortly before the enactment of the 1952 Patent Act, this Court considered a

claim to an "inoculant" made up of a combination of natural bacterial strains that assist plants in nitrogen-fixing by forming nodules on their roots. 333 U.S. at 130. Though a variety of such bacteria had been identified, they were used and sold separately because they inhibited one another's activity. The patentee "discovered" the scientific fact "that there are strains of each species of root-nodule bacteria which do not exert a mutually inhibitive effect on each other," *id.*, and claimed an inoculant combining mutually-non-inhibitive species. Despite the fact that the inventor had "made a new and different composition of non-inhibitive strains which contributed utility and economy to the manufacture and distribution of commercial inoculants," this Court deemed the claim unpatentable:

> [H]owever ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants. . . . [O]nce nature's secret of the non-inhibitive quality of certain strains of the species of [bacteria] was discovered, the state of the art made the production of a mixed inoculant a simple step. Even though it may have been the product of skill, it was not the product of invention.

Id. at 131. Though the patentee was the discoverer of a natural phenomenon, he was not the inventor of a patentable application of that phenomenon.

The requirement that a patentee be an *inventor* of an application of a law of nature, physical phenomenon, or abstract idea did not disappear when Congress enacted the 1952 Patent Act. Thus, for example, in *Parker v. Flook* the applicant had claimed a "Method for Updating Alarm Limits" during catalytic conversion, which employed a formula. *Flook*, 437 U.S. at 585. This Court assumed, for purposes of analysis, that the formula was "novel and useful and that [the applicant] discovered it." *Id.* at 588. After posing the question "whether the discovery of this feature makes an otherwise conventional method eligible for patent protection," *id.,* the Court concluded:

> The notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process exalts form over substance. A competent draftsman could attach some form of post-solution activity to almost any mathematical formula; the Pythagorean theorem would not have been patentable, or partially patentable, because a patent application contained a final step indicating that the formula, when solved, could be usefully applied to existing surveying techniques.

Id. at 590. The presumed originality of Flook's formula did not make him an inventor. "Whether the algorithm was in fact known or unknown at the time of the claimed invention, as one of the 'basic tools of scientific and technological work,' it is treated as though it were a familiar part of the prior art." *Id.* at 591 (quoting *Benson*, 409 U.S. at 67).

In *Chakrabarty*, on the other hand, this Court affirmed the patentability of a "man-made" genetically engineered bacterium, because the claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity." *Chakrabarty*, 447 U.S. at 309. The Chakrabarty bacterium was "not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101." *Id.* at 310. Having applied "human ingenuity" to invent a nonnaturally occurring bacterium, Chakrabarty was eligible for patent protection (assuming he could meet the other requirements of the Patent Act). *Id.* at 310.

Diehr did not change this fundamental requirement. There, this Court considered a patent claim to a "process for molding raw, uncured synthetic rubber into cured precision products," which employed the Arrhenius equation. *Diehr*, 450 U.S. at 177. Unlike *Funk Bros.*, *Flook*, and the present case, *Diehr* did not concern an applicant who claimed to have discovered a new natural phenomenon or devised a new formula. The applicant did not (and could not) claim to have invented the Arrhenius equation, which, among its many uses, had "long been used to calculate the cure time in rubber-molding presses." *Id.* at 178, n.2. The issue in *Diehr* was whether the *mere inclusion* of a formula rendered the applicant's claims to an industrial rubber molding process unpatentable. This Court rejected an approach that would "dissect the claims into old and new elements and then [ ] ignore the presence of the old elements in the analysis,"

confirming the longstanding rule that combinations that include unpatentable elements may constitute patentable inventions. *Id.* at 188. Because the Arrhenius equation was a well-established part of the prior art, which would contribute to the evaluation of nonobviousness under 35 U.S.C. § 103, the Court did not confront the central issue in the present case, which involves an allegedly new scientific observation.

Where, as in *Funk Bros.*, *Flook*, and the present case, patent claims call out a purportedly new natural phenomenon or abstract idea, the requirement that patents issue only to "Inventors," U.S. Const. art. I, § 8, cl. 8, constrains patentability under Section 101. Claim limitations that do no more than apply a natural phenomenon or abstract idea in a conventional way are "insignificant," *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 191-92), because the claim "as a whole," *Diehr*, 450 U.S. at 188, does not reflect inventive activity. A patent may not be granted for a scientific discovery simply because the discoverer is a "competent draftsman." *Flook*, 437 U.S. at 590.

2. The Inventor Requirement Must Be Enforced Under Section 101 and Is Not Wholly Subsumed by Section 103's Nonobviousness Requirement

The nonobviousness requirement, 35 U.S.C. § 103, "comports with [ ] constitutional strictures," by ensuring that patents issue only for claims that are sufficiently inventive in comparison to "the prior art."

Graham, 383 U.S. at 10-12, 16. "The prior art," as defined by 35 U.S.C. § 102,[6] encompasses only "art" previously known, used, published, or invented by human beings. Section 103's nonobviousness analysis therefore cannot subsume the inventor requirement where, as here, a patentee claims to have discovered natural phenomena or devised abstract ideas. In such cases, the inquiry into whether the patentee is an inventor properly takes place under the auspices of Section 101. *See Flook*, 437 U.S. at 590; *Chakrabarty*, 447 U.S. at 310.

B. Prometheus's Claims Are Unpatentable Conventional Applications of Natural Phenomena and Do Not Reflect Inventive Activity

1. Correlations Between Metabolite Levels and Drug Efficacy and Toxicity Are Unpatentable Natural Phenomena

The Federal Circuit did not disturb the District Court's correct findings (1) that the observed correlations between metabolite levels and drug toxicity "were natural phenomena, not patent-eligible inventions because the correlations resulted from a natural

[6] *See* DONALD S. CHISUM, CHISUM ON PATENTS § 5.03[3], ("Section 103 does not expressly define what sources might be looked to as 'prior art' to determine obviousness. However, the opening phrase clearly implies that the provisions of Section 102 are to be the guide.").

body process," (2) that the patentee "did not 'invent' the claimed correlation; rather '6-TG and 6-MMP are products of the natural metabolizing of thiopurine drugs,'" and (3) that the patentee "'merely observed the relationship between these naturally produced metabolites and therapeutic efficacy and toxicity.'" *Prometheus*, 628 F.3d at 1352 (quoting Dist. Ct. Op. at *7). It is true, of course, that the metabolites are produced when the body reacts to human administration of a drug. But the body's reaction is a natural phenomenon nonetheless. In patent law, "natural" means "nature's handiwork" as generally juxtaposed with the products of human agency and ingenuity. *See Chakrabarty*, 447 U.S. at 310; *Flook*, 437 U.S. at 591-94.

In *Funk Brothers*, for example, the newly-discovered mutual non-inhibition of the bacterial strains was a natural phenomenon even though they displayed that property when combined by human action into an inoculant. *Funk Bros.*, 333 U.S. at 131 (the bacteria "act[ed] quite independently of any effort of the patentee").

Similarly, this Court, in discussing the English case, *Neilson v. Harford*, 151 Eng. Rep. 1266 (1841), distinguished between the unpatentable "principle that hot air will promote the ignition of fuel better than cold" and the patentable invention of a mechanical apparatus for supplying hot air to a furnace. *O'Reilly*, 56 U.S. at 114-16. The fact that burning fuel in a furnace is a human activity did not render the fuel's natural response to a supply of hot air

patentable. Nor did the fact that printing characters at a distance is a human endeavor save Morse's claim to the basic scientific concept of using "the motive power of the electric or galvanic current" to make such characters. *Id.* at 119. Conversely, Bell's claim to the use of undulatory current for transmitting speech was patentable because it was "not for the use of a current of electricity *in its natural state as it comes from the battery*. . . ." *Dolbear v. American Tel. Cases*, 126 U.S. 1, 534 (1888) (emphasis added). Clearly, the electricity flow produced by a battery occurs only because of human activity, yet this Court rightly deemed that flow "natural."

To comport with longstanding case law, a phenomenon must be deemed natural when it proceeds without direct human agency, even if in response to a human stimulus. Indeed, Prometheus's own expert displayed this understanding, testifying that "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." Dist. Ct. Op. at *7. Any other understanding of "natural phenomenon" would lead to absurd results: the process of digestion would be non-natural when digesting synthetic foods and natural when digesting wild berries, the process of sunburning would be non-natural when it occurred in tanning booths and natural when it happened on a beach, and so forth.

The Federal Circuit rightly concluded that Prometheus's claims involve "naturally occurring correlations

between metabolite levels and efficacy or toxicity." *Prometheus*, 628 F.3d at 1355.

2. The Claimed Metabolite Levels at Which Physicians Should Consider Revising Dosage Are Unpatentable Scientific Conclusions

The claimed metabolite levels at which physicians should consider raising or lowering dosage are unpatentable scientific conclusions. To arrive at the claimed levels, the patentee analyzed clinical data concerning the responses of a group of patients with inflammatory bowel disease to the administration of thiopurine drugs. *See* '302 Patent at cols.16-20; '623 Patent at cols.16-20. He observed, for example, that in a group of 93 pediatric patients with inflammatory bowel disease, 78% of those with 6-TG levels above 230 pmol/$8x10^8$ red blood cells responded well to the drug, while only about 40% of those with levels below that value responded well. '302 Patent at col.17 l.26-col.18 l.54, fig. 3; '623 Patent at col.17 l.26-col.18 l.54, fig. 3. He then used statistical methods to infer from such observations the claimed guideline of 230 pmol/$8x10^8$ red blood cells for increasing drug dosage. *See, e.g.*, '302 Patent, claim 1; '623 Patent, claim 1. Similarly, the patentee inferred a guideline for decreasing dosage from observations of patients who experienced toxic reactions to the drugs.

Such guidelines are merely scientific conclusions based on observing the underlying natural phenomena. This Court recognized long ago that "a scientific

truth, or the mathematical expression of it, is not a patentable invention." *MacKay Radio*, 306 U.S. at 94.

3. The "Wherein" Clauses Cover Mere Thought About Natural Phenomena and Scientific Conclusions

The final "wherein" clauses of the claims at issue rely on the unpatentable metabolite level guidelines inferred from observing the natural correlations between metabolite levels and efficacy and toxicity to "indicate a need" to adjust dosage. *Prometheus*, 628 F.3d at 1350. The claim language "indicates a need" was construed to mean only that the test results provide "'a warning that an adjustment in dosage may be required.'" *Id.* at 1351 (quoting Dist. Ct. Op. at *1). Notably, "[t]his construction did not require doctors to adjust drug dosage if the metabolite level reached the specified levels; rather, the court found the two 'wherein' phrases to mean 'that when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required, if the doctor believes that is the proper procedure.'" *Id.*

The "wherein" clauses thus do not require any volitional action by physicians beyond reviewing the results of a test. A doctor who merely orders a measurement of a patient's metabolite levels, reviews the results, and is aware of the relationships among metabolite levels and efficacy and toxicity reflected in the claims is an infringer. The Federal Circuit

correctly "agree[d] with the district court that the final 'wherein' clauses are mental steps and thus not patent-eligible per se." *Id.*

4. The Claims as a Whole Are Unpatentable Conventional Applications of the Observed Natural Correlations

In this case, the patentee administered a conventional drug, performed conventional tests to measure a natural bodily response to the drug, analyzed and interpreted the data, and suggested that physicians should think about the results when treating their patients. The claims at issue reflect nothing more. There is nothing unconventional in the "administering" and "determining" limitations of the claim. Nor is the combination of elements as a whole anything but conventional medical application of the observed natural correlations. The Federal Circuit thus erred in holding that these limitations transformed unpatentable natural phenomena and abstract ideas into patentable subject matter. *Prometheus*, 628 F.3d at 1355-56. While the Federal Circuit gave lip service to the importance of "the critical question, 'What did the applicant invent?'," it never seriously addressed this fundamental issue. *Id*. at 1359.

Enforcement of the requirement that a patentee *invent an application* of any natural phenomenon or abstract idea incorporated in a claim is critical for innovation in medicine and other fields dependent on scientific advances. Moreover, when, as here, courts

ignore this requirement, patentees have incentives to engage in gamesmanship in claim drafting. As Judge Rader very recently emphasized, "[w]hen careful claim drafting or new claim formats avoid eligibility restrictions, [patentable subject matter] doctrine becomes very hollow." *Classen Immunotherapies, Inc. v. Biogen IDEC*, 2011 WL 3835409 at *16 (Fed. Cir. Aug. 31, 2011) (Rader, J., additional views).

While he correctly diagnoses the problem, Judge Rader's conclusion that courts should "decline to accept invitations to restrict subject matter eligibility" sweeps too broadly. *Id.* at *15. In *Classen*, for example, the Federal Circuit held that the unpatentable observation that one immunization schedule results in fewer side effects than another became patentable subject matter when the conventional step of following the less risky schedule was added to the claims. *Id.* at *10 (majority opinion). As Judge Moore emphasized in dissent, "Classen's claims readily illustrate that linking a natural phenomenon or abstract idea to a useful or practical result is no barrier for a competent patent drafter attempting to monopolize unpatentable subject matter." *Id.* at *23 (Moore, J., dissenting).

Enforcing the requirement of inventive activity, on the other hand, would address such attempts to draft around the ban on patenting natural phenomena and abstract ideas. In the present case, the question of whether Prometheus's claims reflect "an exercise of the inventive faculty," *Dann*, 425 U.S. at 225, is easily answered: the patentee in this case is a physician, a

medical researcher, and a competent claim draftsman, but not, as least with regard to the claims at issue here, an inventor. The claims are therefore unpatentable under § 101.

III. The Federal Circuit Also Erred in its Transformation of Matter and Preemption Analyses

The Federal Circuit's patentable subject matter analysis focused on the requirement that patent claims not be overly preemptive of uses of natural phenomena and abstract ideas. *Prometheus*, 628 F.3d at 1355. The court concluded that the addition of the "administering" and "determining" steps met this requirement because those steps rendered the claims "sufficiently definite to confine the patent monopoly to within rather definite bounds," *id.* at 1357, involved a "transformation of matter," *id.* at 1355-56, and did not constitute "insignificant extra-solution activity." *Id.* at 1357-58. The Federal Circuit's heavy reliance on the transformation of matter test is misplaced, however, because that test is inapposite to claims based on natural phenomena. The court's preemption analysis, moreover, failed to focus on the particular correlations recited in the claims and therefore did not recognize the substantial burden that the claims place on downstream research.

A. The Transformation of Matter Test Is Inapposite to Natural-Phenomenon-Based Claims

Both before and after the remand for reconsideration in light of this Court's opinion in *Bilski*, the Federal Circuit focused the bulk of its attention in this case on applying the transformation of matter test. *Prometheus*, 628 F.3d at 1355-56; *Prometheus*, 581 F.3d at 1345-46. As this Court held in *Bilski*, that test is "a useful and important clue, an investigative tool, for determining whether *some* claimed inventions are processes under § 101." 130 S. Ct. at 3227 (emphasis added).

The machine or transformation test is inapposite, however, to determining whether a claim preempts a natural phenomenon. Photosynthesis, the freezing of water into ice and its evaporation into steam, and the rusting of iron – all involve transformations of matter, but are unpatentable unless they are part of an inventive application of the phenomenon. Similarly, the measurement or use of a natural phenomenon will ordinarily involve a physical transformation. As Justice Breyer explained in his dissent to dismissal of *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, "to use virtually any natural phenomenon for virtually any useful purpose could well involve the use of empirical information obtained through an unpatented means that might have involved transforming matter." 548 U.S. 124, 136 (2006) (Breyer, J., dissenting). Whatever the usefulness of the transformation of matter test in determining the patentability of processes

similar to the abstract hedging methods in *Bilski*, 130 S. Ct. at 3227-28, the fact that a natural phenomenon, or a method of observing or measuring the phenomenon, involves a transformation of matter has little bearing on whether a patent claim preempts that phenomenon.

Moreover, the transformation of matter test is highly manipulable in cases involving scientific observations of natural phenomena. Where, as here, the claim simply requires "determining" the level of a natural phenomenon, the outcome may depend on whether the court chooses to infer that the measurement requires a transformation of matter. Thus, in *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989), the Federal Circuit determined that a claim step requiring "performing . . . clinical laboratory tests," *id.* at 836, was unpatentable because it "did not require the performing of clinical tests on individuals that were transformative . . . because the tests were just to 'obtain data.'" *Prometheus*, 628 F.3d at 1358 (explaining *Grams*). In *Prometheus*, however, the court assumed that the "determining" step of the claims involved "[s]ome form of manipulation . . . or some other modification of the substances to be measured [] to extract the metabolites from a bodily sample and determine their concentration," *Prometheus*, 628 F.3d at 1357, and, as a result, concluded that Prometheus's claims were patentable. *Id.*

The Federal Circuit's attempt to distinguish the claims at issue here from those in *Grams* based on the extent to which the claims involve transformations of

matter makes little sense because the transformation of matter test is simply inapposite to the real issues at hand – whether the claims apply a natural phenomenon to make a patentable contribution to the "useful Arts" and whether they improperly preempt downstream uses of the phenomenon.

B. The Federal Circuit Failed to Recognize that the Claims at Issue Preempt Virtually All Practical Uses of the Covered Correlations

The Federal Circuit's analysis of the preemption issue stumbles at the outset by focusing on whether the claims "wholly preempt all uses of the recited correlations." *See Prometheus*, 628 F.3d at 1355. This Court's precedents do not demand that claims "wholly preempt all uses" of a natural phenomenon or abstract idea to be unpatentable. *See Bilski*, 130 S. Ct. at 3230 ("the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment' or adding 'insignificant postsolution activity'") (quoting *Diehr*, 450 U.S. at 191-92); *Flook*, 437 U.S. at 589-90 (claims were unpatentable under § 101 even though applicant "does not seek to 'wholly preempt the mathematical formula'") (quoting *Benson*, 409 U.S. at 71-72).

Moreover, the Federal Circuit erred by failing to focus its inquiry on preemption of uses of the *correlations recited in the claims*. The court reasoned that:

> [T]he claims recite specific treatment steps, not just the correlations themselves. And the steps involve a particular application of the natural correlations: the treatment of a specific disease by administering specific drugs and measuring specific metabolites. As such . . . the claims do not preempt all uses of the natural correlations; they utilize them in a series of specific steps. . . . The [claims'] inventive nature stems not from preemption of all use of these natural processes, but from the application of a natural phenomenon in a series of steps comprising particular methods of treatment. Other drugs might be administered to optimize the therapeutic efficacy of the claimed treatment.

Prometheus, 628 F.3d at 1355. This reasoning simply does not address whether the claims preempt "the recited correlations," even though it may purport to do so. *Id.* The claims recite no "specific treatment steps" other than the administration of the drug that triggers the body's creation of the metabolites and the measurements necessary to observe those correlations. There can be few, if any, practical uses of the "recited correlations" that would not be preempted by these claims.

In the end, the Federal Circuit appears to be convinced that the claims are not preemptive solely because they are confined to administering one of a specific group of drugs and measuring one of a specific group of metabolites and are thus "sufficiently

definite to confine the patent monopoly to within rather definite bounds." *Prometheus*, 628 F.3d at 1357.

This conclusion is incorrect. Though two particular metabolites are specified in the claims, the claims cover all autoimmune disorders in all contexts. Because of this broad coverage, the claims preempt a wide swath of scientific study of responses to treatment for different diseases. As an example, Prometheus contended that dermatologist Dr. el-Azhary infringed the patents while studying autoimmune disorders far removed from the inflammatory bowel disease studies from which the claims were derived, Brief for Petitioners at 11-13, and for which she eventually discovered efficacy ranges for the measured metabolites quite different from those in the patent claims.[7] Even a claim limited to a specific disease, however, significantly preempts research into whether treatment of that disease should be personalized based on individual patient characteristics, such as age or gender, or on the results of complementary tests. The Federal Circuit's preemption analysis simply ignored these downstream effects.

[7] Rokea A. el-Azhary, *et al*., *Thioguanine Nucleotides and Thiopurine Methyltransferase in Immunobullous Diseases: Optimal Levels as Adjunctive Tools for Azathioprine Monitoring*, 145 ARCH. DERMATOL. 644 (June 2009).

CONCLUSION

For the foregoing reasons, this Court should clarify that patents may issue only for applications of natural phenomena and abstract ideas that reflect use of the "inventive faculty" and are not merely conventional and that the transformation of matter test is inapposite to the patentable subject matter analysis for claims directed at natural phenomena and scientific conclusions. Because the claims at issue are unpatentable under 35 U.S.C. § 101, the Federal Circuit's ruling in this case should be reversed.

Respectfully submitted,

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