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 THE BIOTECHNOLOGY INDUSTRY ORGANIZATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF THE *AMICUS CURIAE*

The Biotechnology Industry Organization (BIO) is a trade association representing over 1,100 companies, academic institutions, and biotechnology centers. BIO members are involved in researching and developing healthcare, agricultural, environmental, and industrial products.[1] The biotechnology industry currently has more than 370 products in clinical trials for treating more than 200 diseases. The vast majority of BIO members are small companies that have not yet brought a product to market or attained profitability.

The biotechnology industry is uniquely dependent on predictable and effective patent protection for the development of new technologies. This is because investors such as venture capitalists in large measure base their decisions whether to invest in early-stage companies—thereby funding the research and development that eventually will bring new products to market—on the availability of patent protection for an asset that can be commercialized. Innovation in our industry thus depends upon predictability and transparency in the procurement and enforcement of patent rights. BIO therefore promotes the adoption and application of standards for patent eligibility that will ensure appropriate and consistent protection for inventions in the biotechnology sector.

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[1] Pursuant to Supreme Court Rule 37.6, *amicus curiae* states that no counsel for a party authored this brief in whole or in part, and no entity or person other than *amicus curiae*, its members, and its counsel, made any monetary contribution toward the preparation or submission of this brief. Mayo Clinic is a member of BIO but did not participate in the consideration or preparation of this brief. Letters from the parties consenting to the filing of this brief are on file with the Clerk.

SUMMARY OF THE ARGUMENT

To exclude categories of inventions from patent eligibility under 35 U.S.C. § 101 has the potential to do tremendous damage to innovation affecting entire sectors of the economy. This is because, unlike a measured and focused inquiry into the merits of a particular invention—such as whether it is sufficiently new and useful—a rule of patent-eligibility concerning classes of inventions simply eliminates the patent incentive for that class of technology. This Court previously has recognized the danger inherent in "adopting categorical rules that might have wide-ranging and unforeseen impacts." *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3229 (2010).

That danger is present in this case. Announcing a broad rule of ineligibility concerning diagnostic and therapeutic methods that exploit knowledge gained from the study of biological systems would threaten harm to the biotechnology industry, and devastation to the nascent field of "personalized medicine," which promises substantial benefits to patients through its capacity to match focused and appropriate treatments and improved diagnostic methods.

In a time when health-care costs continue to increase, personalized medicine promises to yield substantial savings. *See* BIO, *Guide to Biotechnology 2008*, at 35 (2008), *available at* http://www.bio.org/sites/default/files/BiotechGuide2008.pdf ("*Guide to Biotechnology*"). Personalized medicine, also called targeted therapy, entails the use of individual genetic information to select medicines and treatments that precisely match the needs of a patient. *Id.* Personalized medicine therefore saves health-care dollars by targeting treatments to those patients most likely to respond to them. And medicines that have been abandoned because they may have shown low efficacy

rates on the population as a whole may be put to effective use in treating a particular subpopulation of patients in which those drugs can be shown to be effective. But this important and growing field is threatened by the arguments advocated by Petitioners, and BIO therefore urges that the Court take a cautious approach in applying § 101 to the field.

Like inventions in many other fields of technology, inventions in the field of personalized medicine often exploit known elements and discoveries. They do so, however, in the service of new and useful ways of diagnosing and treating patients. The inventive spark—a spark that is lit by extensive funding and research—occurs when a scientist connects the dots between these known and unknown elements, such as by using biomarkers to devise a new way of selecting patients, identifying symptoms that can be associated with a disease or using a drug to treat those patients, or selecting a drug that does not trigger adverse reactions in the patient. The result of these insights—a novel and useful method or treatment—is and should remain patent-eligible.

To be sure, every invention must satisfy each of the requirements of patentability to warrant the grant of a patent. If the invention is anticipated by some prior art, see 35 U.S.C. § 102, or obvious in view of that prior art, *id.* § 103, it should not be awarded a patent. Similarly, if the breadth of the rights awarded by a patent claim are not in proportion to the disclosure made by the inventor in the patent, that may warrant holding the patent claim invalid. *Id.* § 112. Indeed, much of the thrust of Petitioners' complaint is that the patents at issue in this case encompass elements that were commonly known to researchers or clinicians. But if true, that fact may render the patent claims invalid for reasons entirely unrelated

to § 101. The question whether these claims meet the requirements of §§ 102, 103, and 112, however, is not presently before the Court, and the Court should not use patent-eligibility as a surrogate for addressing questions properly addressed under those separate statutory provisions.

Rather than adopt the broad holding under § 101 that Petitioners advocate, this Court should reiterate two fundamental principles that it has applied for decades, and under which the claims at issue in this case define inventions that are patent-eligible, regardless whether they ultimately are determined to be valid.

First, the Court should emphasize that in reviewing a claim under § 101, courts must consider the claim *as a whole*. Courts should not, as Petitioners request, dissect the claims into discrete elements and then ignore any individual claim element deemed to be known or "insignificant." The settled rule against doing so is particularly important to personalized medicine for the reasons just set forth—a personalized medicine process may and often will draw upon known steps or components to yield an overall process that is important, valuable, and deserving of patent protection. The claim-dissection approach advocated by Petitioners would plunge the patent system into a standardless, "eye of the beholder" system for measuring an invention's merit. This would fundamentally erode the patent incentive for all innovators by making it impossible for inventors to know in advance whether they can secure patent rights in their inventions. Moreover, this approach would run counter to decades of guidance from this Court, which long ago recognized that claim-dissection distorts the invention during its evaluation for patent entitlement.

Second, the Court should reaffirm that, although a law of nature, natural phenomenon, or abstract idea is not itself patentable subject matter, a particular *application* of that law of nature, natural phenomenon, or idea is. It is well-established and has been long understood that an invention is not excluded from patent-eligibility under § 101 merely because it harnesses natural or biological processes. But Petitioners seem to advance a rule whereby not only natural phenomena and laws of nature would be excluded from patent-eligibility, but also some ill-defined subset of applications of those laws of nature or natural phenonema. The Court should squarely reject this rule, and reaffirm its prior precedents. Holding otherwise would interpose insurmountable obstacles to securing patent protection in the field of life sciences, as virtually all inventions in this field draw upon biological systems, or seek to exploit or affect their function.

The progress of the biotechnology industry over the 30 years of its existence has demonstrated that patent protection is an essential driver of innovation. The role that patents have played for this industry, and which they must play to encourage innovation in the field of personalized medicine, is exactly the role that Patent Clause envisions. See U.S. Const. art. I, § 8, cl. 8; *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989). Using § 101 to broadly exclude entire categories of new and useful inventions from patent eligibility would be antithetical to this basic purpose. BIO urges the Court to deploy § 101 cautiously, because the danger of unforeseen consequences is great.

ARGUMENT

THE COURT SHOULD HEED THE FUNDAMENTAL PRINCIPLES IT HAS PREVIOUSLY APPLIED IN DETERMINING PATENT ELIGIBILITY.

A hallmark of our patent law is that it protects, and thereby fosters, emerging technologies whose commercial potential may not yet be fully understood or appreciated. This feature of the patent system is critical to economic growth,[2] which is precisely why the provisions of the Patent Act concerning the threshold question of patent eligibility were framed in such broad terms: "The subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts' with all that means for the social and economic benefits envisioned by Jefferson." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 315 (1980).[3] A contrary rule—"that unanticipated inventions are without protection"—"would conflict with the core concept of

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[2] *See* H.R. Rep. No. 112-98, pt. 1, at 73 (2011) (purpose of the America Invents Act, the recent patent-reform bill, is to "spur innovation as a means to create American jobs and raise standards of living"); Fed. Trade Comm'n, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy* 1 (Oct. 2003), *available at* http://www.ftc.gov/os/2003/10/innovationrpt.pdf ("Innovation benefits consumers through the development of new and improved goods, services, and processes. An economy's capacity for invention and innovation helps drive its economic growth and the degree to which standards of living increase.").

[3] *See also Chakrabarty*, 447 U.S. at 308 ("In choosing such expansive terms" in the definition of patentable subject matter "modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope.").

the patent law that anticipation undermines patentability." *Id.* at 316.

For this basic reason, the Court repeatedly has recognized the need to exercise caution before excluding some domain of inventive activity from the protection of the patent laws. Unlike defects with particular patents, which may be dealt with on a case-by-case basis in a court or the Patent & Trademark Office, sweeping determinations of patent-ineligibility amount to policy determinations that generally are not well suited to judicial resolution on a categorical basis:

> Should certain classes of invention be treated in one way and other classes differently? These are not legal questions, which courts are competent to answer. They are practical questions, and the decision as to what will accomplish the greatest good for the inventor, the government, and the public rests with the Congress. We should not read into the patent laws limitations and conditions which the Legislature has not expressed.

United States v. *Dubilier Condenser Corp.*, 289 U.S. 178, 198-99 (1933); accord *Diamond* v. *Diehr*, 450 U.S. 175, 182 (1981) (the Court has "more than once cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed" (internal quotation marks omitted)).

Against this backdrop, the Court has recognized only three exceptions to patent-eligibility—namely, claims that define natural phenomena, laws of nature, and abstract ideas. *Chakrabarty*, 447 U.S. at 309. But, the existence of these "well-established exceptions" does not "give[] the Judiciary *carte blanche* to impose other limitations that are incon-

sistent with the text and the statute's purpose and design." *Bilski*, 130 S. Ct. at 3226. This is because "[t]he § 101 patent-eligibility inquiry is only a threshold test." *Id*. at 3225. It is, as the PTO has explained, a "coarse filter." U.S. Patent & Trademark Office, *Interim Guidance for Determining Subject Matter Eligibility for Process Claims in View of* Bilski v. Kappos, 75 Fed. Reg. 43922, 43926 (July 27, 2010).[4]

The capacity of the patent system to foster development of new technology is proven by the history of the biotechnology industry. The inventions that have led to the growth and success of biotechnology, both as a scientific and engineering discipline and as an industry, could not have been imagined when the Patent Act was rewritten in 1952. An inclusive standard for patent eligibility has proven essential to the successful development and commercialization of over 200 biotechnology therapies and vaccines, hundreds of diagnostic tests, and pest- and herbicide-

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[4] The patent claims at issue in this case plainly satisfy this inquiry. They do not disclose a natural phenomenon, as there is nothing "natural" about the processes claimed here. A man-made drug that does not exist in nature is administered to a patient through artificial means. Pharmacologically potent active metabolites that do not occur under natural conditions are then analyzed through sophisticated laboratory processes. The patents also do not claim a law of nature, like the law of gravity or $E=mc^2$. Whereas those laws operate universally and independently of human endeavor, the claimed invention is a human-devised way of interfering with the natural course of a human disease that, if untreated, would get only progressively worse. And, the patents do not claim an abstract idea. The claims recite concrete steps—administering a drug and determining the levels of particular metabolites in plasma—taken to reach a specific result. Whether or not the claims are anticipated or obvious in light of prior art, they define a patent-*eligible* process.

resistant crops. See *Guide to Biotechnology* at 2. This is particularly true because "[b]iotechnology is one of the most research-intensive industries in the world." *Id.* U.S. publicly traded biotech companies spent $22.8 billion on research and development in 2010. Ernst & Young, *Beyond Borders: Global Biotechnology Report 2011*, at 37 (2011), *available at* http://tinyurl.com/5u9o5bd.

But, just as the patent system may encourage innovation, it carries the converse danger that court-adopted rules trimming away patent eligibility may hinder such technological advance. This concern is particularly great where personalized medicine is concerned. BIO therefore urges the Court to reaffirm two basic principles, both of which are critically important to the biotechnology industry generally, and personalized medicine specifically, and which BIO discusses in greater detail below. Specifically, the Court should reaffirm that "claim dissection" is not an appropriate way to evaluate patent claims for eligibility. *Infra* Section A. A rule which calls for courts or the PTO to pick apart an invention in the way Petitioners advocate, disregarding the old and focusing only on the new or "significant" elements, will inherently diminish and distort the importance of every invention—and especially inventions that build upon prior knowledge or discoveries but which do so through important, patentable leaps of inventive genius.

In addition, the Court should reaffirm that although natural phenomena and laws of nature are not patentable, *applications* of them certainly are. *Infra* Section B. Certain of Petitioners' arguments seem to call into question this basic rule, and any decision of the Court accepting Petitioners' invitation

will have highly detrimental consequences in the biotechnology industry.

A. Patent-Eligibility Must Be Determined By Considering The Claim As A Whole.

1. Petitioners suggest repeatedly that in evaluating the patent-eligibility of the claims, the Court may disregard aspects of the invention that are non-novel. In effect, Petitioners urge whittling away the invention, leaving what it claims is a non-patent-*eligible* core. *E.g.*, Pet. Br. 24 ("The drugs involved and the method of blood testing for metabolites are well known and have been used by physicians and researchers for decades."); *id.* at 35 (asking the Court to ignore steps in the claimed process that are "preparatory" or "'data-gathering'" steps, or "ordinary means of observing the natural correlation").

The Court should reject this argument, which has no place in analyzing patent eligibility. The Court has previously and properly criticized the use of a "claim dissection" approach when reviewing a claim for patentability. Instead, it has explained,

> claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made. The "novelty" of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter.

Diehr, 450 U.S. at 188-89; *accord Bilski*, 130 S. Ct. at 3230 (describing and relying upon *Diehr*); *Application of Chatfield*, 545 F.2d 152, 158 (C.C.P.A. 1976) ("We have thus specifically rejected the broad notion that if a portion of a claim be non-statutory the whole claim is ipso facto non-statutory. The requirement is that the invention set forth in a claim be construed as a whole").

The dangers inherent in a contrary approach are manifest. An analysis of patent-eligibility that starts by dissecting a claim into pieces invites litigants to focus on process steps that appear to be algorithms, decision-points, or that otherwise make use of data—i.e., "solution" steps that appear central to the claimed process. But once the analysis is thus focused, preceding and subsequent claim steps naturally will appear to be no more than pre- and post-solution activity, and proper focus on the claim as a whole will be lost, and with it a proper understanding of what the inventor actually invented. This is why, even in the context of evaluating whether an invention is obvious—a fact-intensive inquiry that is necessarily more searching than the "coarse filter" of patentability—the Court has recognized the danger of picking apart inventions in the fashion Petitioners advocate:

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the

> elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR Int'l Co. v. *Teleflex Inc.*, 550 U.S. 398, 418-19 (2007).

2. Applying the basic rule against claim dissection is particularly important in the domain of personalized medicine, where, in the language of *Diehr*, "a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made." 450 U.S. at 188. Taken to its logical conclusion, claim-dissection could call into question many process claims that use data generated from a biological system. Such claims will frequently require the gathering of information and so, as we discuss next, individual steps in a treatment protocol or diagnostic process may be familiar, using known testing techniques or isolating known compounds. But although certain of this knowledge may be familiar, the technique for applying the knowledge through treatment or diagnosis will not be. The results are new and useful diagnostic or therapeutic procedures, which the patent laws should properly recognize as patentable subject matter.

An example demonstrates the point. The anticancer drug irinotecan first received conditional marketing authorization by the FDA in 1996, and full approval as second-line therapy for patients with metastatic colorectal cancer in September 1998.[5] Irinotecan,

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[5] *See* Pfizer, *Background Document on the UGT1A1 Polymorphisms and Irinotecan Toxicity* 3 (2004), *available at* http://

however, was found to cause severe adverse effects in certain patients. Those effects were unpredictable, and the inability to predict which patients would suffer these potentially fatal toxicities became an important factor for physicians who considered adopting this important new drug in clinical practice.

Subsequent studies suggested that interpatient variability in the toxicity of irinotecan might be related to genetic factors. Scientists homed in on a particular mutation of the UGT1A1 gene that had long been known to be associated with Gilbert's syndrome, an inherited metabolic disease unrelated to colon cancer.[6] It was found that the presence of this particular mutation explains not only the metabolic symptoms of Gilbert's syndrome, but also predicts the risk of severe irinotecan side effects in the completely different context of colon cancer therapy.[7] This finding triggered repeated revisions of the drug's label to warn that reduced dosing of irinotecan is recommended in patients who carry certain forms of the UGT1A1 gene.[8] The use of

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www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079B1_07_Pfizer-UGT1A1.pdf.

[6] *See* Piter J. Bosma et al., *The Genetic Basis of the Reduced Expression of Bilirubin UDP-Glucuronosyltransferase 1 in Gilbert's Syndrome*, 333 New England J. Med. 1171 (1995).

[7] L. Iyer et al., *UGT1A1*28 Polymorphism as a Determinant of Irinotecan Disposition and Toxicity*, 2 Pharmacogenomics J. 43 (2002); Federico Innocenti et al., *Genetic Variants in the UDP-Glucuronosyltransferase 1A1 Gene Predict the Risk of Severe Neutropenia of Irinotecan*, 22 J. Clinical Oncology 1382 (2004).

[8] Yael Waknine, *FDA Safety Labeling Changes: Camptosar, Keppra, Prempro/Premphase*, Medscape News (Sept. 21, 2005), http://www.medscape.com/viewarticle/513175; *Camptosar (iriotecan HCL) injection*, FDA Safety (May 2010), http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm215480.htm

UGT1A1 testing for predicting irinotecan toxicity was patented by researchers at the University of Chicago[9] and exclusively licensed to Mayo Clinic, which sublicensed the rights to clinical laboratories and uses the revenues to support research and education.[10]

Today, UGT1A1 testing is an important part of personalized colon cancer therapy with irinotecan. And, importantly for present purposes, the Gilbert's Syndrome mutation, irinotecan, and its toxicity were all individually known at the time costly clinical research established the connection between the three. The invention was in connecting the dots, and developing a patentable process for commercializing that invention. Doing so created a substantial and novel benefit to numerous colon cancer patients.

3. The claim-dissection approach urged by Petitioners is particularly ill-advised because the patent law already contains more focused mechanisms for evaluating the patentability of particular claims. If a piece of prior art describes each limitation of the asserted claim, then the claim may be held invalid as anticipated. 35 U.S.C. § 102. If an asserted claim is obvious—that is, if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious"—then it may be invalidated on

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[9] U.S. Patent No. 6,395,481 (claim 62).

[10] Press Release, Univ. of Chi. Med. Ctr., University of Chicago researchers license pharmacogenomics test for patients with colorectal cancer to Mayo Clinic (Dec. 21, 2005), http://www.uchospitals.edu/news/2005/20051221-ugt1a1.html; Press Release, Univ. of Chi., Gene screen patent leads to 'Deal of Distinction' for University of Chicago (Oct. 29, 2007), http://www-news.uchicago.edu/releases/07/071029.licensing.shtml.

that basis. *Id.* § 103. And if a claim confers an imprecise or excessive scope of rights relative to what the inventor has taught and disclosed in the patent, the claims may be refused or held invalid. See *BJ Servs. Co.* v. *Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1371 (Fed. Cir. 2003) (claim invalid if description does not "enable" one of ordinary skill in the art to practice the full scope of the invention); *Source Search Techs., LLC* v. *LendingTree, LLC*, 588 F.3d 1063, 1076 (Fed. Cir. 2009) (claim invalid as indefinite if it cannot be construed); *Ariad Pharm., Inc.* v. *Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (en banc) (claim invalid if patent does not contain adequate "written description" of what is claimed).

It is telling, indeed, that Petitioners depend repeatedly on the considerations relevant to these other criteria of patentability to advance their attack on the claims under § 101. Petitioners insinuate repeatedly that aspects of Respondent's asserted claims are known in the art. See, *e.g.*, Question Presented ("well-known methods"); Pet. Br. 3 ("[a]ll doctors know"), 4 ("Thiopurine drugs have been administered for decades, and … the appropriate levels of thiopurine metabolites in patients have been measured, studied, and discussed for many years."), 5 ("the inventors freely disclosed"), 21 ("discovered over thirty years ago"), 21 ("For decades"), 22 ("have long done"), 24 ("The drugs involved and the method of blood testing for metabolites are well known and have been used by physicians and researchers for decades."), 25 ("doctors and researchers … considered metabolite levels on their own years before these patent claims were filed"), 36 ("Well-known, non-inventive steps cannot turn a natural phenomenon into patentable subject matter."), 39 ("as physicians long have done"), 44 ("well known to physicians for many years").

If Petitioners wish to argue that the asserted claims are anticipated by prior art, that they are so well-known that the claims are obvious, or that the claims omit limitations that make them correspond to the disclosure provided by the patentee, then Petitioners may raise those objections in due course. *Cf.* U.S. Br. 26-33.[11] But it is those requirements of patentability that provide the proper conduit for Petitioners' objections, not least of all because those doctrines have a significant advantage over consideration of patent-eligibility: They cut narrowly, rather than sweep broadly.

Anticipation, for instance, requires a comparison between the asserted claim and the purportedly prior-art reference to see whether the prior art describes "each and every claim limitation." *Iovate Health Scis., Inc.* v. *Bio-Engineered Supplements & Nutrition, Inc.*, 586 F.3d 1376, 1380 (Fed. Cir. 2009). It is a factual determination, and thereby is litigated as such. *Finisar Corp.* v. *DirecTV Grp., Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). Obviousness, while considering the invention "as a whole," 35 U.S.C. § 103, of necessity focuses on the elements of the claim to determine whether, both individually and in combination, they would have been considered obvious from the prior art to a person of ordinary skill. *E.g.*, *Unigene Labs., Inc.* v. *Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011); *Princeton Biochemicals, Inc.* v. *Beckman Coulter, Inc.*, 411 F.3d

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[11] It would be particularly inadvisable to announce broad rules concerning patent-eligibility, with the concomitant adverse consequences, merely because of the fortuity that this case arises in an interlocutory posture. The district court held the claims patent-ineligible under § 101 without addressing anticipation or obviousness, and the Federal Circuit reversed the § 101 determination. *See* Pet. App. 7a-8a, 23a, 83a.

1332, 1337-38 (Fed. Cir. 2005). The numerous inquiries underlying an obviousness determination are questions of fact. *Graham* v. *John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). The inquiries mandated by § 112 similarly are focused on the claims, demanding a proper correspondence between what has been taught and described by the inventor and what the claims encompass. *E.g.*, *AK Steel Corp.* v. *Sollac*, 344 F.3d 1234, 1242-44 (Fed. Cir. 2003); *Exxon Research & Eng'g Co.* v. *United States*, 265 F.3d 1371, 1380-81 (Fed. Cir. 2001); *Ariad*, 598 F.3d at 1347. In short, the analysis compelled by these conditions of patentability is fact- and patent-specific, with the consequence that finding one particular invention undeserving of patent protection does not create risks for an industry as a whole. By contrast, an interpretation of § 101 that excludes a class of invention from the realm of patent law altogether necessarily will have widespread effects.

4. While asking the Court to ignore certain elements of the claims, Petitioners also attack the claims for "not recit[ing] the administration of any amount of any drug to be given to any patient." Pet. Br. 24 n.5; see also *id.* at 22 (claims "do not offer any specific change in therapy"). But inventors in the field of personalized medicine must be able to protect their inventions in a commercially effective manner, and the example of irinotecan toxicity proves the impracticability of imposing such a requirement. Discovering the correlation between the UGT1A1 gene and irinotecan toxicity required substantial investment and produced substantial benefits. As a practical matter, it permits use of the correlation to increase treatment effectiveness, including by determining the presence or absence of the relevant mutation, and deciding to act on that diagnostic inform-

ation. But requiring an administration step whereby the dose is adjusted—much less as a condition of patentability—would sap the invention's commercial value.

If, for instance, only one in ten patients has the mutation, then the drug dose would be adjusted in only one out of ten applications of the process, and the process as patented would be practiced in only 10% of applications. The value of the invention, however, lies in the determination of whether an adjustment is needed in advance of administration of the agent. A contrary rule would enable a competing laboratory to extract 90% of the test's real commercial value without facing infringement liability.[12] The patentee, on the other hand, who through his efforts created a market for a laboratory service where none had existed before, would be able to realize no more than 10% of the invention's commercial value.[13]

If biotechnology inventions are deemed patent-eligible only to the extent that they include limitations that render their invention nearly commercially irrelevant, then patent protection will

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[12] Indeed, in the irinotecan example, only about 10% of patients carry two copies of the mutation that predisposes them to irinotecan toxicity, placing them at a high risk of side effects. Accordingly, the University of Chicago's patent on a "method for optimizing [irinotecan] dosages" requires only a determination of certain polymorphisms in the UGT1 gene; like Prometheus's claim, the claim does not require the actual administration of an optimized dose. *See* U.S. Patent No. 6,395,481 (claim 62).

[13] Nor would the patentee be able to capture the remaining commercial value through a claim that comprises the steps of assaying for the biomarker and "not adjusting the dose if the biomarker is not present." Negative claim elements are normally improper and not allowable in the PTO, because they add no limitation to the claim.

be worth very little. The law does not support such a result. *See* Resp. Br. 34-36 (explaining that "Section 101 does not categorically exclude processes that end by providing useful information" rather than a physical step) (capitalization omitted). The plain result of any such rule would be less research, less discovery, and less "promot[ion of] the Progress of Science." U.S. Const. art. I, § 8, cl. 8. Biotechnology inventions are driven by expensive clinical trials, complicated laboratory tests, and computerized analysis of large amounts of data under complex algorithms. As other amici have explained, such investments can be significant, and often would not occur without the patent incentive. Br. for Amici Curiae Roche Molecular Systems, Inc., et al. ("Roche/Abbott Br.") 13-19.

The danger of these profoundly negative consequences for public health is the reason Petitioners feel compelled to argue that government and academia will step in. Pet. Br. 51. This is cold comfort. In a recessionary era of steep budget cutbacks, speculation about government support is worth very little. And, more importantly, this is not the system the Framers envisioned. Petitioners point to no support for the notion that patent protection should be obviated because of the potential for alternate funding sources for research. This is because the basic premise of the patent system, from the time of Thomas Jefferson forward, is that the best way to "promote the Progress of Science" is by "securing for limited Times to … Inventors the exclusive Right to their … Discoveries." U.S. Const. art. I, § 8, cl. 8; see *Graham*, 383 U.S. at 9 n.2 ("'Society may give an exclusive right to the profits arising from [inventions], as an encouragement to men to pursue ideas which may produce utility….'") (quoting Letter from Thomas Jefferson to Isaac McPherson (Aug. 13, 1813) *in* 6

Writings of Thomas Jefferson 181 (Henry Augustine Washington ed., 1853)).

Moreover, academic and government-focused research commonly focuses on early-stage research, while research funding from the private sector often emphasizes paths of research that will yield new products and services. Indeed, the federal government's inability to commercialize inventions was a major purpose of the University and Small Business Patent Procedures Act of 1980, 35 U.S.C. §§ 200 *et seq*.: the sponsors of that legislation recognized that "[i]f the results of federally sponsored research were to be rescued from oblivion and successfully developed into commercial products, they would have to be patented and offered up for private appropriation." Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 Va. L. Rev. 1663, 1664 (1996). Here, eliminating the patent incentive will be particularly harmful to the focused research and development efforts that are needed to bring innovative new products and services to market to benefit patients.

If this Court adopts the broad theory urged by Petitioners, the impact on investment in personalized medicine products is likely to be profound.

B. While Natural Phenomena Are Not Eligible For Patenting, New And Useful Applications Of Them Always Have Been And Should Remain So.

The law has long recognized "the true distinction between a mere principle, as the subject of a patent, and a process by which a principle is applied to effect a useful result." *Tilghman* v. *Proctor,* 102 U.S. 707, 724 (1880); see also*, e.g., Mackay Radio & Tel. Co.* v.

Radio Corp. of 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."). Thus, even if a natural phenomenon or principle is itself ineligible for patenting, a method, article, composition or machine that makes use of such a phenomenon or principle to achieve a concrete, useful end remains patentable. See, *e.g.*, *Diehr*, 450 U.S. at 187 (process that "admittedly employs a well-known mathematical equation" to cure synthetic rubber is patentable subject matter).

The analysis that Petitioners ask the Court to adopt would call this fundamental principle into question. The premise of Petitioners' argument is that "Prometheus's patents recite a natural phenomenon—the biological correlation between metabolite levels and health." Pet. Br. 18.[14] On Petitioners' view, it seems, the Court should ignore the transformative steps in the asserted patent and examine only whether the correlation itself can be patented. To accept Petitioners' premise would seriously undermine the longstanding tenet that an *application* of a natural phenomenon is patent-eligible. Any decision that calls into question this basic principle, either expressly or by implication, will have drastic consequences

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[14] *See also* Pet. Br. Question Presented (patent grants a "sweeping monopoly on a biological correlation between drug administration and natural changes in blood chemistry"); *id.* at 33 ("Prometheus's patents recite a natural phenomenon—the biological correlation between metabolite levels and health"), 44 (patent "monopoliz[es] all thought about the health effects of the biologic fact … that thiopurine drugs produce metabolites that relate to the health of patients with autoimmune diseases").

for the biotechnology industry, and particularly for the types of technologies described in this brief.

Again, an example demonstrates why this is so. The study and use of "biomarkers" is essential to the treatment approaches required for personalized medicine. Biomarkers typically are naturally occurring proteins, genes, or gene transcripts that provide a "readout" on, for instance, specific disease processes within the body.[15] The presence or altered level of a particular biomarker (or relative levels of some combination of biomarkers) may be correlated with the status of a disease; an application of that correlation then may be used to diagnose patients, select appropriate therapeutic interventions, and evaluate the effect of a treatment on the course of the disease. See, *e.g.,* N. Rifai et al.*, Protein biomarker discovery and validation: the long and uncertain path to clinical utility*, 24 Nature Biotechnology 971 (2006).

Using a biomarker to monitor therapy, instead of relying on traditional assessments of a patient's clinical status, offers important advantages. Among these are a much earlier indication of the therapy's effectiveness, as well as freedom from "interference" due to the progression of other diseases in the patient. Such advantages allow doctors to more effectively tailor therapeutic approaches to individual patients. In addition to the use of biomarkers to detect the presence of, or susceptibility to, certain diseases or toxins, biomarkers also may be used to

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[15] *See, e.g.*, Food & Drug Admin., *Challenge and Opportunity on the Critical Path to New Medical Products* 23 (Mar. 2004), *available at* http://tinyurl.com/6ykodwv (defining "biomarkers" as "quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness").

explain the response of individual patients to certain drugs, and to identify classes of patients who are more or less likely to benefit when treated. These technologies have implications for global public health; the United Nations, for example, has recognized that prevention and early screening, both of which can be improved through personalized medicine technologies, are key components in global strategies to lessen the rate of non-communicable diseases. See G.A. Draft Res. 66/1, ¶¶ 1-3, 17, 34, 45(k), (l), (p), (q), U.N. Doc. A/RES/66/1 (Sept. 16, 2011).

Thus, it is expected that the use of biomarkers will allow drug developers to conduct clinical trials of new medicines more quickly, more economically, and with smaller numbers of patients than are now required. Moreover, biomarker technology may enable drug developers to explain seemingly inconclusive or negative results from past clinical studies, and to identify valuable uses for some of the hundreds of investigative drugs whose clinical testing has been discontinued due to inconsistent efficacy or toxicity. Biomarker technology therefore offers hope that at least some "failed" drugs may be developed into the "right drug for the right patient," and that past investments made by patient volunteers, physicians, academic scientists and drug developers may come to fruition after all. See Roche/Abbott Br. 7-13 (discussing examples of innovations in personalized medicine that make use of biomarkers).

Biomarkers and their use in diagnosis or treatment, however, necessarily are linked to the human body's biological processes. In other words, any form of human intervention and activity that makes use of biomarkers necessarily will make use of the response of a biological system. A rule of patent law that holds these applications to be natural phenomena or

principles *per se*, and thus non-patent-eligible at the threshold, will obviate patent protection in this domain—contrary to well-settled law. As the Court explained in *Chakrabarty*, the "relevant distinction" between patent-eligible subject matter and ineligible subject matter is "not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions." 447 U.S. at 313. Thus, an invention that exploits a biological response—that, for example, involves the identification and use of biomarkers for a particular treatment or diagnostic purpose—is patentable so long as the biological response is used in the context of a broader process, with transformative steps that provides a treatment, diagnosis, or other medical function. See *Chatfield*, 545 F.2d at 158 ("We should not penalize the inventor who makes his invention by discovering new and unobvious mathematical relationships which he then utilizes in a machine, as against the inventor who makes the same machine by trial and error and does not disclose the laws by which it operates.").

The proper distinction between patent-eligible and -ineligible uses of biomarkers and biological responses was illustrated well by the Federal Circuit's analysis in the recent *Myriad* case. See *Ass'n for Molecular Pathology* v. *USPTO*, 653 F.3d 1329 (Fed. Cir. 2011) ("*Myriad*"). In *Myriad*, the Federal Circuit held to be unpatentable subject matter a claimed "method for screening a tumor sample" by "comparing" a first BRCA1 sequence from a tumor sample and a second BRCA1 sequence from a non-tumor sample, wherein a difference indicates an alteration in the tumor sample. The claim did not include the steps of extracting DNA from a human sample or sequencing the BRCA DNA molecule; instead, the

claim recited only "comparing" the tumor and non-tumor samples. *Id.* at 1356-57. The Federal Circuit therefore held the claim unpatentable: "This claim thus recites nothing more than the abstract mental steps necessary to compare two different nucleotide sequences." *Id.* at 1356.

By contrast, a claim directed to a method for screening potential cancer therapeutics via changes in cell growth rates was patentable, because the claimed method included the steps of "growing" host cells transformed with an altered BRCA1 gene in the presence or absence of a potential cancer therapeutic, "'determining' the growth rate of the host cells with or without the therapeutic," and "'comparing' the growth rate of the host cells." *Id.* at 1357-58. Because these steps involved a "physical manipulation of the cells"—i.e., a tangible transformation rather than a mere observation, as in the claim held unpatentable—they satisfied § 101. *Id.*

Similarly, in *In re Grams*, the applicant claimed a process that involved (1) performing any generic clinical test on individuals and (2) based on the data from that test, determining if an abnormality existed and determining possible causes of any abnormality by using an algorithm. 888 F.2d 835 (Fed. Cir. 1989). The Federal Circuit found that this process was not drawn to patentable subject matter because the essence of the claimed process was the mathematical algorithm, rather than any transformation of the tested individuals. *Id.* at 839-41. In particular, the *Grams* process was no more than an algorithm performed on collected data; although gathering the relevant data was a step in the claimed process, the claims did not require the performing of a specific clinical test that was shown to be transformative. As these examples illustrate, where a claimed process

does include tangible, transformative steps that limit the claim to a particular application, as the asserted claims at issue here do, the claim is patent-eligible subject matter.

Here, Petitioners seek to avoid the impact of these principles by focusing solely on the reference in the claim to the deduced relationship between 6-TG and 6-MMP following administration of the agent that creates these metabolites. But Petitioners can make this argument only by ignoring the key process steps of "administering a drug providing 6-thioguanine to a subject" and "determining the level of 6-thioguanine in said subject." These steps "are part of a treatment protocol, and they are transformative." Pet. App. 20a; see also U.S. Br. 14 ("The claim recites a series of acts in the physical world that achieve a useful end (treatment of auto-immune disorders) by transforming the body chemistry of the patient."). Once these steps are taken into consideration, it is apparent that the asserted claims recite an application of the correlation between 6-TG and 6-MMP—not the correlation itself. And, for this reason, the process for determining the plasma concentrations of metabolites produced after the administration of a manmade medication is not a "natural phenomenon." It is instead the product of human intervention, the result of administering a foreign agent (*i.e.,* the drug) and undertaking a transformative test to determine the resulting level of metabolites. A process that determines and makes practical use of these non-natural metabolite levels is not a patent-ineligible natural phenomenon.[16]

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[16] Notably, the "administering" step, entailing active transformation of both the patient and the drug and giving rise to a non-naturally occurring correlation, distinguishes the Prometheus claims from those at issue in *Laboratory Corp. of*

To accept Petitioners' argument would require ignoring these essential, non-"natural" aspects of the claimed process—eliminating the "trees" (*i.e.*, steps) of the asserted claims in a manner that would substantially transform the forest. Such an approach is inconsistent with this Court's precedents, and it poses grave risks to the biotechnology industry and the future of personalized medicine, in which known biomarkers and known correlations are frequently used in novel processes for beneficial treatment or diagnostic purposes. This Court should reiterate that "a process by which a principle is applied to effect a useful result" is patentable subject matter. *Tilghman*, 102 U.S. at 724.

America Holdings v. *Metabolite Laboratories Inc.*, 548 U.S. 124 (2006) (per curiam). The claim at issue in that case involved no more than a correlation between a naturally occurring vitamin deficiency with an elevated level of homocysteine. That claim involved no transformative steps of any kind and is thus materially distinguishable from the claims at issue here.

CONCLUSION

For the foregoing reasons, and those stated in Respondent's Brief, the judgment of the court of appeals should be affirmed.

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