No. 09-490

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 Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF QUEST DIAGNOSTICS INCORPORATED, LABORATORY CORPORATION OF AMERICA HOLDINGS (D/B/A LABCORP), ARUP LABORATORIES, INC., AND TRICORE REFERENCE LABORATORIES AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICI CURIAE*[1]

Amici are leading clinical laboratory companies. Like petitioner Mayo Collaborative Services, d/b/a Mayo Medical Laboratories (together with its co-petitioner, "Mayo" or the "Mayo Clinic"), *amici* are in the business of analyzing specimens to aid in the diagnosis, treatment, and prevention of disease. Like Mayo, *amici* also have active research programs through which they develop new, cutting-edge assays and diagnostic techniques.

Amicus Quest Diagnostics Incorporated ("Quest"), a publicly traded, Fortune 500 company, is the leading independent clinical laboratory company in the United States. Quest's network of laboratory facilities performs tests for up to approximately half a million patients each day, and offers testing and consultation in, among other areas, genetics, oncology, hematology, cardiovascular disease, endocrinology, infectious disease, and toxicology. Quest has also pioneered advances in anatomic pathology and gene-based testing. In addition, Quest is one of the world's largest providers of laboratory services used in connection with research trials of new drugs.

Amicus Laboratory Corporation of America Holdings ("LabCorp"), the country's second-largest

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[1] No counsel for a party has written this brief in whole or in part, and no counsel for a party or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity other than *amici curiae* and their counsel has made a monetary contribution to this brief's preparation or submission. Counsel of record for both petitioners and respondent received timely notice of *amici*'s intent to file the brief, and consented to it.

independent clinical laboratory company, is an S&P 500 company whose 28,000 employees serve 220,000 clients and perform more than one million tests on approximately 400,000 patient samples every day. LabCorp is a pioneer in applying advances in medicine and science to laboratory testing. LabCorp was the petitioner in *Laboratory Corporation of America Holdings* v. *Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) ("*LabCorp*"), which concerned the validity of a patent claim for a "method" for detecting certain vitamin deficiencies. The "method" consisted entirely of these two steps: (1) measure the levels of a particular amino acid in the body, and (2) recognize that elevated levels of the amino acid are correlated with the vitamin deficiencies. LabCorp was accused of inducing infringement every time a doctor ordered the company's amino acid assay (even though the assay itself was not covered by the patent claim) because doctors would automatically recognize that elevated levels of the amino acid signified the existence of one of the vitamin deficiencies.

Amicus ARUP Laboratories, Inc. ("ARUP") is a nationally renowned medical reference laboratory owned by the University of Utah. Formerly known as Associated Regional and University Pathologists Inc., ARUP offers more than 2,000 clinical tests and test combinations, many of them developed by ARUP researchers. ARUP's test menu ranges from routine screenings to highly esoteric molecular and genetic assays, and includes the areas of allergy and immunology, chemistry, cytogenetics, endocrinology, fetal risk assessment, genetics, hematology, hepatitis and HIV, infectious diseases, neurology, oncology, and pathology. With more than 2,600 employees,

ARUP processes between 30,000 and 35,000 tissue and fluid specimens every day.

Amicus TriCore Reference Laboratories ("TriCore") is a leading not-for-profit medical reference laboratory that serves doctors and patients across the Southwestern United States. TriCore's 1,000 employees perform a full range of tests under the direction of more than 30 pathologists and scientific directors.

Amici have a compelling interest in this case. Just as in *LabCorp*, the Federal Circuit has once again allowed a patent-holder to claim ownership of basic scientific facts: in this case, the clinical significance of levels in the human body of certain substances. *Amici*'s research activities, as well as the diagnostic services that they offer to hospitals, physicians, and managed-care organizations, depend on precisely that kind of knowledge. The Federal Circuit's decision therefore allows patentees and litigants to frustrate *amici*'s mission of advancing medical science and delivering the highest level of clinical service. *Amici* agree with petitioners' arguments, but submit this brief to explain that medicine in general and clinical chemistry in particular vitally depend on the availability of just the kind of knowledge that the Federal Circuit has allowed respondent ("Prometheus") to monopolize.

INTRODUCTION AND SUMMARY OF ARGUMENT

The Federal Circuit's decision cannot be reconciled with this Court's longstanding prohibition on patenting "scientific truths." Examined closely, the patents that Prometheus controls teach nothing more than a statistical association between (on the one

hand) particular levels of particular substances in the human body and (on the other) particular clinical effects. This is the kind of knowledge on which an entire branch of medicine, known as therapeutic drug monitoring, rests. Excluding such knowledge from the public domain seriously interferes with the provision of medical care, and with research, innovation, and quality control in the field of clinical chemistry. Prometheus's assertions that a ruling for the Mayo Clinic would somehow destroy "personalized medicine" are utterly unfounded; medical progress is stifled, not advanced, by patents like these.

The Federal Circuit's endorsement of the increasingly common practice of privatizing fundamental medical knowledge urgently calls for review by this Court. That practice was at issue in *LabCorp*, but there the eight-Member Court ultimately felt compelled, over the dissent of three Justices, to dismiss the writ as improvidently granted given that petitioner did not "refer in the lower courts to § 101 of the Patent Act," 548 U.S. at 132. Similarly, this Term's case about the patentability of an abstract business method, *Bilski* v. *Kappos*, No. 08-964 (argued Nov. 9, 2009), does not involve patents on medical therapies or diagnostic techniques and appears likely to be decided without resolving questions about such subject matter.[2]

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[2] As the government explained at oral argument, *Bilski* is an "unsuitable vehicle" for determining when "medical diagnostic techniques . . . would and would not be patent eligible, because the case really doesn't present . . . any question regarding those technologies." Oral Arg. Tr., No. 08-964, at 36, 47 (U.S. Nov. 9, 2009).

Here, by contrast, the 35 U.S.C. § 101 issues were fully aired, preserved, litigated, analyzed, and decided in the lower courts. And the fact pattern is highly representative of one discrete but extraordinarily consequential form of patent-system abuse. Accordingly, this case is an ideal vehicle for addressing matters that are of critical importance to *amici*, the health-care industry *amici* serve, and patients in need of access to quality medical diagnosis and treatment.

ARGUMENT

I. The Federal Circuit Has Authorized a Raid on the "Storehouse of Knowledge"

This Court has said many times that "'a scientific truth . . . is not a patentable invention,'" *Diamond* v. *Diehr*, 450 U.S. 175, 188 (1981) (quoting *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939)); accord *Parker* v. *Flook*, 437 U.S. 584, 591 (1978); *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972). Such "manifestations of laws of nature" form part of humanity's "storehouse of knowledge" and therefore are "free to all men and reserved exclusively to none." *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). The reason patents should be unavailable for such discoveries is not that they are "easy" or "not useful," but that "protection in such cases, despite its potentially positive incentive effects, would too often severely interfere with, or discourage, development and the further spread of useful knowledge itself." *LabCorp*, 548 U.S. at 126, 128 (Breyer, J., dissenting from dismissal of writ). The Federal Circuit's decision flies in the face of those sound and longstanding principles.

A. The patents in this case are as far-reaching as they are basic. (Most of their combined 35 pages merely discuss prior knowledge and paraphrase the claims in boilerplate fashion.) A drug known as 6-mercaptopurine, or 6-MP, and its close relative azathioprine (AZA), have long been used to treat inflammatory bowel disease (IBD), a type of autoimmune disorder that includes Crohn's disease. See, *e.g.*, C.A. App. 10007. 6-MP drugs (as we shall refer to 6-MP and AZA) are "prodrugs," meaning that the drug itself is inactive but is converted through natural processes in the human body into substances – metabolites – that in turn are responsible for the desired therapeutic effects or undesired toxic effects. See *ibid.*; TABER'S CYCLOPEDIC MEDICAL DICTIONARY 1898 (21st ed. 2009).

As the patents explain (*e.g.*, C.A. App. 10008-10010), it was common medical knowledge that the metabolites of 6-MP drugs include 6-thioguanine (6-TG) and 6-methyl-mercaptopurine (6-MMP), and also that the effectiveness and toxicity of 6-MP drugs are a function of the concentration in the bloodstream of the drugs' metabolites. (The reason for that association is that the metabolites, not the prodrug, are immediately responsible for the therapeutic and toxic effects.) According to the patents, what science did not yet know was precisely "what concentrations of 6-MP metabolites correlated with optimized therapeutic efficacy or with toxicity." C.A. App. 10010.

So the named inventors – actually two clinical researchers at a hospital center in Montreal whose patent applications were assisted or sponsored by Prometheus, see page 20, *infra* – conducted several observational studies of IBD patients on a regimen of

6-MP drugs. The researchers observed whether and to what extent the patients were responding to the drugs, and also measured the levels of 6-TG and 6-MMP in their bloodstreams. The researchers discerned two basic associations: (1) in general, patients who responded most favorably to the drug tended to have a concentration of 6-TG in their bloodstream that was at least 230 picomoles per $8x10^8$ red blood cells; and (2) in general, patients who reacted adversely tended to have a concentration of 6-TG in their bloodstream above 400 picomoles per $8x10^8$ red blood cells, or a concentration of 6-MMP above 7000 picomoles per $8x10^8$ red blood cells. C.A. App. 10014-10016.

That is all. The Federal Circuit's repeated references to "transformative" steps notwithstanding, the patents disclose nothing new apart from those observable statistical correlations. Indeed, the only "transformations" that the Federal Circuit actually identified are (1) the changes in the body produced by a 6-MP drug, Pet. App. 17a ("When administering a drug such as AZA or 6-MP, the human body necessarily undergoes a transformation"), and (2) the manipulation involved in an (unspecified and unpatented) assay necessary to measure the levels of 6-TG and 6-MMP, Pet. App. 19a ("[D]etermining metabolite levels in the clinical samples taken from patients is transformative."). The court of appeals did *not* say that there was anything "transformative" about the ultimate understanding, which is the whole point of the claims, that certain levels "indicate a need" to adjust dosage. See Pet. App. 15a-19a.

In dissecting the patent claims to tease out something that would satisfy a supposed criterion of pat-

entability, the Federal Circuit disregarded this Court's important command that a patent claim must be "considered as a whole," *Diehr*, 450 U.S. at 188. As Justice Breyer (joined by Justices Souter and Stevens) explained in *LabCorp*:

> [T]he process is no more than an instruction to read some numbers in light of medical knowledge. . . . One might, of course, reduce the "process" to a series of steps . . . . But one can reduce *any* process to a series of steps. The question is what those steps embody.

548 U.S. at 137 (dissent from dismissal of writ). Here the steps embody only the knowledge that concentrations of two metabolites above and below certain levels have been correlated with certain clinical effects.

B. Under the Federal Circuit's rule, huge swaths of basic medical knowledge can be removed from the public domain. Every day, thousands of clinical researchers are at work trying to derive the precise kind of information that the Federal Circuit has said can be patented. One of medicine's major advances in recent decades has been the development of therapeutic drug monitoring, a sub-field of clinical chemistry concerned with measuring the levels of a medication (or its metabolites) in the bloodstream in order to keep those levels in a therapeutic range. (The alternatives to therapeutic drug monitoring are simply to administer a pre-determined dosage, or to adjust dosing based on a patient's clinical reaction.) Not surprisingly, therapeutic drug monitoring is used with drugs that can easily be overdosed or underdosed.

A real-world – but unpatented – example should help illustrate how therapeutic drug monitoring works and why patents on the field's foundational

knowledge are potentially so damaging. Our example – which is just one of many that could be marshaled – concerns a drug known as mycophenolate mofetil, or MMF, and its metabolite mycophenolic acid, or MPA.

Recipients of transplanted organs are prescribed drugs to suppress their immune systems. It is essential to get the dosage right: too little drug in the body, and the transplanted organ may be rejected because the immune system is not sufficiently repressed; too much drug, and the immune system could become so weak that the patient develops opportunistic infections. See generally Grant W. Cannon, *Immunosuppressing Drugs Including Corticosteroids*, *in* CECIL MEDICINE 182-189 (23d ed. 2008). Accordingly, physicians attempt to ensure that the concentration of the drug in the bloodstream is within certain target ranges (sometimes referred to as "reference ranges") established through research. See, *e.g.*, Teun van Gelder et al., *Therapeutic Drug Monitoring of Mycophenolate Mofetil in Transplantation*, 28 THERAPEUTIC DRUG MONITORING 145, 145 (2006).

MMF (marketed as CellCept® and Myfortic®) is one of the drugs that can be used to suppress transplant recipients' immune systems. Like the 6-MP drugs at issue in this case, MMF is a prodrug; the body processes it into its active metabolite – MPA. *E.g.*, Leslie M. Shaw et al., *Therapeutic Drug Monitoring of Mycophenolic Acid*, 2 CLINICAL J. AM. SOC. OF NEPHROLOGY 1062, 1062 (2007). Physicians have previously administered MMF at a fixed dose. *Ibid.*; van Gelder et al., *supra*, at 145. Different individuals, however, produce significantly different levels of MPA in response to the same dose of MMF. See van Gelder et al., *supra*, at 146.

Researchers have therefore set out to determine the optimal therapeutic levels of MPA. The result of that research is the knowledge that (for patients on a particular drug regimen) a "trough"[3] MPA concentration below about 1 mg/L represents an underdose and above about 3.5 mg/L represents an overdose. See Shaw et al., *supra*, at 1070. Physicians regularly use that knowledge to treat post-transplant patients. Specifically, physicians monitor such patients' MPA levels, and conduct the following analysis: a trough MPA concentration below 1 mg/L suggests that the MMF dosage needs to be increased, and a trough MPA concentration above 3.5 mg/L suggests that the amount needs to be decreased. It is the level of MPA that the human body produces when it processes MMF, not the level of MMF itself, that helps physicians optimize dosage.

That is exactly the same kind of analysis claimed by the patents that Prometheus controls. In fact, one could describe the MMF analysis using the language of those patents: a physician "determine[s]" the trough concentration of MPA, and recognizes that a "level of [MPA] less than about [1 mg/L] indicates a need to increase the amount of [MMF] subsequently administered to said subject," and a "level of [MPA] greater than about [3.5 mg/L] indicates a need to decrease the amount of [MMF] subsequently administered to said subject," C.A. App. 10016. And, under the decision below, one could defend the patentability of that analysis by referring to the supposedly "trans-

[3] "Trough" is to be distinguished from "peak." Drug or metabolite levels typically undergo cycles in patients on a regular dosing regime.

formative" steps of (a) administering MMF and (b) determining the resulting concentration of MPA.

There are literally hundreds of other (unpatented) examples of the use of therapeutic drug monitoring to optimize the concentration in the body of a therapeutic substance,[4] and as medicine advances there will doubtless be many more. The court of appeals' decision means that reference ranges for any such drugs (or their metabolites) are potentially patentable.

C. In authorizing Prometheus broadly to exclude practitioners and researchers from applying knowledge of reference ranges, the Federal Circuit regarded the *LabCorp* dissent – the *only* opinion from this Court that addressed the merits of that case – as entirely undeserving of attention. Even though the district court "[found] Justice Breyer's reasoning persuasive" and relied heavily on it, see Pet. App. 42a-45a, the Federal Circuit's entire analysis of *LabCorp* was that it "is not controlling law and also involved different claims from the one at issue here." Pet. App. 16a n.3. In fact, at oral argument, the judge

[4] See, *e.g.*, Svein I. Johannessen et al., *Therapeutic Drug Monitoring of the Newer Antiepileptic Drugs*, 25 THERAPEUTIC DRUG MONITORING 347 (2003) (assessing tentative target ranges for a variety of anti-epilepsy drugs, including oxcarbazepine (trade name Trileptal), a prodrug whose effectiveness is a function of the concentration of its active metabolite); Buster Mannheimer et al., *Impact of Multiple Inhibitors or Substrates of Cytochrome P450 2D6 on Plasma Risperidone Levels in Patients on Polypharmacy*, 30 THERAPEUTIC DRUG MONITORING 565 (2008) (reporting on research into concentrations of risperidone, an antipsychotic marketed as Risperdal, and its active metabolite); RxKinetics, Aminoglycoside Dosing, *at* http://www.rxkinetics.com/amino.html (last visited Nov. 17, 2009) (listing target "peak" and "trough" concentrations for aminoglycoside antibiotics).

who would later become the author of the decision below expressed the view that the *LabCorp* opinion somehow carries less persuasive weight because one of the Justices who joined it has retired.[5] Cf. EUGENE GRESSMAN ET AL., SUPREME COURT PRACTICE 252 (9th ed. 2007) ("where the court of appeals deliberately refuses to follow the applicable Supreme Court decisions in the belief that . . . the current personnel of the Court might change the trend of decisions," this Court often grants review).

What the Federal Circuit overlooked is that the issues in *LabCorp* were important enough for this Court to invite the views of the United States and eventually to grant certiorari. See 543 U.S. 1185 (2005); 546 U.S. 999 (2005). The Court ultimately dismissed the writ for a procedural reason, not a substantive one. See 548 U.S. at 132.

There was, moreover, essentially no mainstream support for the proposition that the subject matter at

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[5] The following exchange with Prometheus' counsel took place during oral argument in the Federal Circuit:

> MR. BRESS: . . . I do think that reliance, too heavy reliance on a three judge – justice dissent in *LabCorp* is not where I'd go, particularly where Justice Stevens, who was one of the three judges –
>
> JUDGE LOURIE: Souter.
>
> MR. BRESS: – disagreed with –
>
> JUDGE LOURIE: Souter's not there any more.
>
> MR. BRESS: Souter's not there any more and Justice Stevens of course disagreed with *Diehr* to begin with and agrees with *Flook*.

Audio recording: Oral Arg., No. 2008-1403 (Aug. 5, 2009), *available at* http://oralarguments.cafc.uscourts.gov/mp3/2008-1403-1.mp3).

issue in *LabCorp* was patentable. Respondents' only *amici* with reasonably broad-based membership refused to defend respondents' patent claim, instead calling for a remand or for the writ to be dismissed. See Am. Intell. Prop. L. Ass'n Br., No. 04-607, at 4 (U.S. Feb. 6, 2006); Fed. Cir. Bar Ass'n Br., No. 04-607, at 1-2 (U.S. Feb. 6, 2006). The United States did not defend the claim, and the claim was forcefully criticized by a slew of organizations that included the American Medical Association, the American Heart Association, AARP, and many other medical and industry associations. See U.S. Br., No. 04-606, at 17 (U.S. Dec. 23, 2005); Am. Med. Ass'n et al. Br., No. 04-606 (U.S. Dec. 23, 2005); Am. Heart Ass'n Br., No. 04-606 (U.S. Dec. 23, 2005); Am. Clinical Lab. Ass'n Br., No. 04-606 (U.S. Dec. 23, 2005); AARP Br., No. 04-606 (U.S. Dec. 23, 2005). Those organizations understood that allowing overbroad patenting of laws of nature, dressed up as a series of "steps" that only take laws of nature into account, impedes both scientific advancement and patient care.

The only *amici* to defend the patent claim in *LabCorp* were a pair of biotechnology ventures, one city's association of patent lawyers, and a law school that went so far as to ask the Court to overrule the prohibition on patenting laws of nature. See Perlegen Sciences et al. Br., No. 04-607 (U.S. Feb. 6, 2006); Boston Patent L. Ass'n Br., No. 04-607 (U.S. Feb. 6, 2006); Franklin Pierce L. Ctr. Br., No. 04-607 (U.S. Feb. 6, 2006). Tellingly, however, after its own patents were invalidated by the district court, Prometheus went on record in support of the validity of the *LabCorp* patent claim. Prometheus Br., *Bilski* v. *Kappos*, No. 08-964, at 14 (U.S. Aug. 6, 2009) ("Prometheus *Bilski* Br."). Prometheus correctly perceives that, were the

position of the three Justices who expressed any view on the merits in *LabCorp* to command a majority of this Court, its own patents would be in deep trouble.

D. Prometheus nevertheless may argue here, as it did below, see Prometheus C.A. Br. 38 & n.12, that the patents it controls do not raise the same concerns as the *LabCorp* patent claim because these patents involve a *synthetic* substance and metabolites that do not occur in nature. As an initial matter, the *LabCorp* correlations also appear to have involved synthetic substances – most forms of cobalamin, one of the vitamins whose deficiency was associated with elevated levels of the amino acid homocysteine, do *not* occur in nature. See, *e.g.*, Victor Herbert, *Vitamin B-12: Plant Sources, Requirements, and Assay*, 48 AM J. CLINICAL NUTRITION 852, 852-853, 857 (1988). The whole point of that claim was to identify situations in which it is necessary to administer a (man-made) tablet containing cobalamin, see *Metabolite Labs., Inc.* v. *Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1358 (Fed. Cir. 2004), just as the whole point of the claims here is to identify situations in which it is necessary to administer more or less 6-MP.

In any event, the prohibition on patenting "manifestations of laws of nature," *Funk Bros.*, 333 U.S. at 130, has never applied only to phenomena occurring literally in the state of nature and involving no human intervention. The invention in *Funk Brothers*, for example, was a particular mix of bacterial strains that decidedly does *not* occur in nature. See *ibid.* Nevertheless, because the bacteria's *qualities*, which the inventor did not create, were the "handiwork of nature," *id.* at 131, the patent was invalid.

In this case, the 6-MP drugs are not naturally occurring, but the patents do not claim 6-MP drugs. The metabolites of 6-MP are not naturally occurring, but the patents do not claim those, either. What the patents *do* claim is the *effects* on the human body of those metabolites. And those effects result from chemical processes that most definitely *are* naturally occurring. Human beings are *designed* to process foreign substances. Indeed, "xenobiotic"[6] metabolism accounts for the body's ability to process countless substances that are not "naturally" found within it, including most pharmaceutical products and alcohol in beverages. The observable clinical effects of that metabolism are certainly "manifestations of laws of nature."

II. The Federal Circuit's Decision Will Impede Medical Research, Treatment, and Quality Control

A. The court of appeals' decision threatens major harm to the health-care system. First of all, patents like these stymie research. The nature of scientific research in general, and clinical chemistry in particular, is that it builds on itself, adding incrementally to the "storehouse of knowledge." Suppose that a clinical researcher seeks to refine the science covered by the Prometheus-controlled patents. Perhaps she thinks she can obtain a more precise reference range for 6-TG or 6-MMP, or she discovers other metabolites whose levels correlate with those of 6-TG and 6-MMP but can be measured more precisely. Those investigations would be impossible, or at least strong-

[6] The term comes from a Greek word for "foreigner" or "stranger." See, *e.g.*, STEDMAN'S MEDICAL DICTIONARY 2158 (28th ed. 2006).

ly deterred, without permission from Prometheus. In fact, Prometheus has *already* asserted its patents against a Mayo Clinic researcher who sought to do further research into therapeutic ranges of 6-MP metabolite levels. See C.A. App. 12787-12790, 12848-12850, 12852-12854.

Relatedly, these patents interfere with medical treatment. One of *amicus* ARUP's most frequently ordered tests is for the levels of MPA in the bloodstream of patients taking MMF to suppress their immune systems. If there were a patent on the knowledge that, as discussed above, the optimal trough concentration of MPA is between 1 and 3.5 mg/L, the owner of that patent would be able to control whether and when ARUP and other laboratories could conduct tests for MPA levels – or, for that matter, when physicians could even order them. Therapeutic drug monitoring of MMF would thus be entirely at the mercy of the patent-holder.

Again, the problem is not hypothetical. This lawsuit arose when the Mayo Clinic announced plans to conduct its own testing for 6-MP metabolite levels. See Pet. App. 4a, 28a. Because the clinical significance of the test *results* arguably would have depended on some of the same science covered by the Prometheus-controlled patents, Prometheus was able to block Mayo's test, even though Mayo was planning to use different reference ranges from the ones specified in those patents. See Pet. App. 4a-5a. Mayo's plans, however, were not at all unusual. Laboratories frequently introduce new tests and improvements on existing tests. The Federal Circuit's ruling ensures that improvements like the one Mayo sought to introduce will simply remain unavailable.

Three Justices, drawing on the experience of *amici*, referred to precisely these types of problems in *LabCorp*, observing that restrictions imposed by the kind of patent upheld below

> may inhibit doctors from using their best medical judgment; they may force doctors to spend unnecessary time and energy to enter into license agreements; they may divert resources from the medical task of health care to the legal task of searching patent files . . . ; they may raise the cost of health care while inhibiting its effective delivery. See Brief for American Clinical Laboratory Association as *Amicus Curiae* 8-13.

LabCorp., 548 U.S. at 138 (dissent from dismissal of writ).

Finally, and again relatedly, patents like those here can make independent validation of a laboratory's test results impossible. In the field of clinical chemistry, it is important to ensure the accuracy and reliability of a laboratory's assays. Accordingly, Congress has mandated that federal regulators, or an approved professional organization, conduct quarterly inspections of a laboratory's performance of most tests. See Clinical Laboratory Improvement Amendments of 1988, Pub. L. No. 100-578, § 2, 102 Stat. 2903 (1988), codified in relevant part at 42 U.S.C. § 263a(f)(3); 42 C.F.R. § 493.801. The College of American Pathologists ("CAP") accomplishes this by using, among other techniques, comparisons between results of participating laboratories. See CAP, What is Proficiency Testing, *at* http://tinyurl.com/dkoncq (last visited Nov. 19, 2009). No such "peer comparisons," however, are available for Prometheus's assays for 6-TG and 6-MMP because Prometheus has ex-

cluded all competition. It is now impossible to validate Prometheus's work in this area – and that will become true of more and more tests if the Federal Circuit's decision is left in place.

B. As if to counter all of the harmful consequences of restricting the use of elementary knowledge, Prometheus (along with its *amici* in the Federal Circuit) has trumpeted the importance of fostering advances in the field of "personalized medicine" (*e.g.*, Prometheus C.A. Br. 48-50; Patent L. Profs. C.A. Br. 15-16), which Prometheus contends would be "crush[ed] in its infancy" if the patents it controls were invalidated. Prometheus C.A. Br. 18; see also Prometheus *Bilski* Br. 4; Myriad Genetics C.A. Br. 14 (a ruling for Mayo would have "threaten[ed] to destroy the personalized medicine industry in its infancy"). The truth is the exact opposite.

Personalized medicine seeks to use genetic markers to predict, among other things, an individual's response to a particular therapy. See, *e.g.*, TABER'S CYCLOPEDIC MEDICAL DICTIONARY 1759, 2302 (21st ed. 2009). That field would be *stifled*, not advanced, if "the basic tools of scientific . . . work," *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972), could be removed from the public domain.

Suppose, for example, that a clinical researcher wants to gain the ability to predict any given patient's sensitivity to a 6-MP drug. So the researcher goes searching for a genetic marker linked to one of the naturally occurring enzymes that break 6-MP drugs down into their active metabolites. Individuals without the type of marker she is looking for naturally produce less of the enzyme and so will break the prodrug down slowly. Individuals with such a mark-

er, on the other hand, will have more of the enzyme and so will break the prodrug down more quickly – in other words, those individuals will be more sensitive to the drug. The researcher's ultimate goal is to refine the use of 6-MP drugs to treat Crohn's disease, but she cannot possibly assess the clinical significance of a possible marker if, as Prometheus would have it, she is forbidden from using the knowledge captured by the patents in this case. And, again, it is not at all hypothetical to fear that the holder of such a patent will assert it against researchers trying to refine or apply the findings reported in the patent. See C.A. App. 12787-12790, 12848-12850, 12852-12854.

Not surprisingly, Prometheus and its *amici* in the Federal Circuit never provided a coherent, much less persuasive, account of how advances in medicine in general, or "personalized medicine" in particular, would be promoted, rather than inhibited, by a ruling upholding these patents. In this Court, in another case, Prometheus has argued that the incentives created by the patent system "are critical to promoting technological innovation in the field of personalized medicine, where development costs are high and costs of imitation are often low." Prometheus *Bilski* Br. 16. But Prometheus completely failed to support that assertion. The secondary literature cited by Prometheus referred to the *pharmaceutical* industry (where there are in fact good reasons to believe that patent incentives play a valuable role), *not* to personalized medicine. See *id*. at 16-18 & n.4.

Indeed, the incentives created by the patent system may be important for *some* technologies, but there is no reason to believe that those incentives ap-

ply to the kind of discovery at issue in *this* case. That is, there is no reason to believe that the determination of basic physiological relationships – as opposed to the development of new therapies and technologies *based on* such discoveries – depends on the existence of patent-related incentives. The history of the patents in this very case illustrates the point. What happened here is that the scientists in Montreal were *already* researching and publishing in the area covered by the patents. See C.A. App. 13201. Prometheus then helped the scientists to apply for patents of which Prometheus of course became the exclusive licensee. See U.S. Patent App. Serial No. 09/288,344, Response to Office Action, at 18 (July 2, 2001) ("Response"); Targan Decl. accompanying Response; Pet. App. 2a. This case, therefore, is *not* one in which the promise of a patent led a company or independent inventor to come up with something new that would otherwise not have seen the light of day.

Beyond this case, moreover, as the examples discussed above should illustrate, thousands of physicians and clinical chemists are at work every day trying to discern clinically relevant levels of known substances without any purpose of seeking patent protection. What is more, even innovators who *are* driven by patent incentives to develop legitimately patentable technological advances are hindered when they are forbidden from taking advantage of fundamental knowledge.

* * * * *

The patents controlled by Prometheus typify an increasingly prevalent form of abuse. Rather than *patent an invention*, Prometheus decided to *invent a patent* on a pre-existing phenomenon – namely, the

clinical association between particular metabolite levels and particular disease states. Prometheus has used its patents to shut down further research into 6-TG and 6-MMP levels as well as to prevent the Mayo Clinic from conducting its own testing for the same substances in patients suffering from IBD. Congress never intended the patent statute to function that way. This Court's review is urgently needed to restore a reasonable balance in which patents promote rather than impede "'the Progress of Science and useful Arts.'" *LabCorp*, 548 U.S. at 126 (Breyer, J., dissenting from dismissal of writ) (quoting U.S. CONST. Art. I, § 8, Cl. 8).

CONCLUSION

For the foregoing reasons and those stated in the petition, the petition for a writ of certiorari should be granted and the case accepted for plenary review.

Respectfully submitted.

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