2008-1403

United States Court of Appeals for the Federal Circuit

Prometheus Laboratories, Inc.,
Plaintiff-Appellant,

v.

Mayo Collaborative Services (doing business as Mayo Medical Laboratories)
and Mayo Clinic Rochester,
Defendants-Appellees.

Appeal from the United States District Court
for the Southern District of California in case no. 04-CV-1200,
Judge John A. Houston.

CORRECTED BRIEF FOR AMICI CURIAE
The American College of Medical Genetics, The American Medical Association, The American Society of Human Genetics, The Association of American Medical Colleges, The Association of Professors of Human and Medical Genetics, The Association for Molecular Pathology, and The College of American Pathologists
IN SUPPORT OF DEFENDANTS-APPELLEES

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INTRODUCTION AND INTEREST OF *AMICI CURIAE*

A basic tenet of medical ethics is that discoveries and advances in medical care should be freely shared and openly disseminated. This ethical principle has served to make such discoveries readily available, at minimal cost, for use in the diagnosis and treatment of patients. It also has allowed physicians to fulfill their fundamental obligation to act in their patients' best interests.

For more than 200 years, the patent laws have, with few exceptions, existed in harmony with the professional ethical duty to publish, disseminate, and use medical advances. Misapplication of the patent laws in this case would create tension with basic principles of medical ethics. Specifically, the patents at issue in this case give Plaintiff-Appellant Prometheus exclusive private ownership—not of a new drug, or of a new diagnostic test, or even of a new method of diagnosing a particular disease—but rather of a scientific *observation*. Moreover, the patents give Prometheus exclusive rights to the 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 certain doses of thiopurine drugs, and the efficacy and toxicity of those drugs. These patents are infringed whenever a physician, having ordered that one of these drugs be

administered to a patient, reviews the levels of metabolites produced by the body and even considers adjusting the dosage. In fact, in this very case, Prometheus argues that a physician infringes the patents simply by thinking about the relationship between dosage, efficacy and toxicity. Such a reading of the patent laws puts physicians in an untenable position since they could in some instances be liable for medical malpractice if they do *not* consider those relationships.

The scope of patentable subject matter as established by Congress in the Patent Act ("the Act"),[1] although quite broad, does not extend to the recognition of a scientific fact or observation. A patient's elevated levels of the metabolites resulting from azathioprine or 6-mercaptopurine treatment may well indicate that a toxic dose of the drug has been prescribed. That a physician thinks of that relationship when reviewing laboratory test results, however, is not evidence that the physician is engaging in a "process," as that term is used in Section 101 of the Act, 35 U.S.C. § 101. Rather, it is evidence only that a physician is aware of a pre-existing scientific relationship that could affect the treatment of patients.

Once recognized, the relationship between thiopurine nucleotide levels and potential toxicity cannot be ignored or forgotten by physicians. Nor should it be.

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[1] 35 U.S.C. § 1 et seq.

Such information should be used in the diagnosis and treatment of patients and, moreover, should be publicized in order to advance medical science. Properly construed, Section 101 of the Act does not interfere with the spread and use of such information, because allowing a physician to think about the naturally occurring relationship between a metabolite level and a patient's physical condition is not a "process" within the meaning of Section 101.

Of course, if the basic fact that certain test results correlate with a given physical condition were to be incorporated into some useful application, then that application might be a patentable advance over prior art. But the fact of the correlation alone is not, under Section 101, subject matter eligible for patent protection. It therefore cannot, in itself, provide a valid basis for enjoining a physician from requesting tests—or for discouraging laboratories from providing physicians with information about the significance of test results that physicians can then use in the diagnosis and treatment of their patients.

On behalf of their hundreds of thousands of physician-members nationwide, and the patients whom they treat, amici medical associations urge this Court to enforce the limitations imposed by the Act on patentable subject matter.

* * *

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 1300 members, the 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, in and of themselves, be patentable.

The American Medical Association (AMA) is a private, voluntary non-profit organization of physicians and medical students with approximately 240,000 members, who practice in all states and in all fields of medical specialization.[2] The AMA was founded in 1847 to promote the science and betterment of public health.

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[2] The AMA submits 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 of the AMA and the medical societies of every state and of the District of Columbia, formed to represent the views of organized medicine in the courts.

From its inception, the AMA has maintained a Code of Medical Ethics, including a set of core Principles and a Code and Opinions applying those Principles, which guide the ethical practice of medicine. Several of these principles and opinions, as well as reports of the AMA's Council on Ethical and Judicial Affairs, address ethical issues raised by the issuance of patents on medically useful information.[3]

The American Society of Human Genetics (ASHG), founded in 1948, is the primary professional membership organization for human genetics specialists worldwide. It is a private, non-profit organization. The Society's nearly 8000 members include researchers, academicians, clinicians, laboratory practice professionals, genetic counselors, nurses, and others who have a special interest in the field of human genetics. ASHG serves research scientists, health professionals, and the public by providing forums to: (1) share research results at annual meetings and in *The American Journal of Human Genetics*; (2) advance genetic research by advocating for research support; (3) enhance genetics education by preparing future professionals and informing the public; and (4) promote genetic services and support responsible social and scientific policies.

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[3] *See, e.g.*, American Medical Association, *Patenting of Medical Procedures*, 53 Food & Drug L.J. 341-357 (1998).

The Association of American Medical Colleges (AAMC) is a non-profit organization representing all 129 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 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 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 Association for Molecular Pathology (AMP) is an international medical professional association representing approximately 1,600 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. The AMP is dedicated to the development and implementation of molecular diagnostic testing, which includes genetic testing in all its definitions, in a manner consistent with the highest standards established by CLIA, CAP, the ACMG, and the FDA. AMP members practice their specialty in widely diverse settings, including academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the *in vitro* diagnostic industry, and are involved in every aspect of molecular diagnostic testing. AMP provides national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing.

The College of American Pathologists (CAP) has nearly 17,000 physician members, including most of the eligible board-certified pathologists. It is the world's largest medical society composed exclusively of pathologists, who are

physicians who obtain and interpret data as the result of examination of tissues, blood, and other body fluids for diagnosis and patient care. The CAP also serves the laboratory community throughout the world. More than 6,000 laboratories are accredited by the CAP, and approximately 23,000 laboratories are enrolled in the College's proficiency testing programs.

MEDICAL CONCERNS OF AMICI

The two patents at issue in this case relate to observations of the human body's natural responses to the well-established regimen of thiopurine drug treatment for autoimmune disorders of the gastrointestinal tract (i.e., inflammatory bowel diseases) such as Crohn's disease and ulcerative colitis. The responses result from a complex biochemical pathway involving multiple gene products (enzymes) that contribute to inter-individual variation in response. The patentees observed a naturally-occurring correlation between (a) the presence of certain metabolites, known as thiopurine nucleotides, that follow from the treatment and (b) the efficacy and/or adverse side effects seen in patients receiving the treatment. The patents at issue claim this correlation—and only this correlation.

To assist this Court in understanding the patents at issue, and how their enforcement would negatively affect medical care and research, amici offer the

following medical background. It will demonstrate that the scientific observations in the patents at issue did not emerge in a vacuum. They are part of a continuum of medical research and development aimed at improving patient care. Allowing the enforcement of broad and unwarranted patent claims to the association between metabolite levels and drug toxicity and efficacy would interfere substantially with the achievement of that goal and would raise important ethical issues.

Adverse side effects from thiopurine drugs resulting from the accumulation of mercaptopurine metabolites and thiopurine nucleotides have been recognized for several decades.[4] The thiopurine derivative, azathioprine, is used in the treatment of inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis. Because thiopurines are well tolerated in many patients, they have been preferred over alternative anti-inflammatory drugs, such as steroids, which carry significant side effects.[5]

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[4] W.J. Sandborn, *Can Immunomodulatory Therapy Be Improved By Metabolite Measurement and Combination Therapy?*, in Immunoregulation in Inflammatory Bowel Diseases—Current Understanding and Innovation (A. Dignass et al. ed., 2006).

[5]Most of our understanding of thiopurine drug metabolism comes from work in acute lymphoblastic leukemia, a condition in which treatment with thiopurines is effective. Lennard, et al., *Thiopurine Pharmacogenetics in Leukemia: Correlation of Erythrocyte Thiopurine Methyltransferase Genetic Activity and 6-thioguanine Nucleotide Concentrations*. 41 Clinical Pharmacology Therapeutics 18-25 (1987).

Azathioprine is converted to mercaptopurine by naturally occurring enzymes present in the body. Mercaptopurine has three metabolic fates: conversion to 6-thiouric acid (6-TU); conversion by thiopurine methyltransferase (TPMT) to 6-methyl-mercaptopurine (6MMP); or conversion to 6-thiogunanine (6TG). Natural variation in the metabolic activity of these enzymes may lead one to one or more of the metabolites accumulating differentially in patients.[6] Although genetic testing of a patient's TPMT status may be useful in predicting appropriate dosage levels, it only explains a proportion of overall thiopurine toxicity.[7] However, it is critically important to identify the 1% of the population for whom the thiopurine drugs may have extreme toxicity and the <10% of the population with variable toxicity.[8]

Historically, the dosing of patients with thiopurine drugs has been based on the patient's weight, though there is a tendency to dose at the lower end of the range because of toxicity concerns.[9] In practice, many clinicians test for TPMT activity to guide both the choice of drug and the dose. Clinicians further test for

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[6] See Sandborn, *supra* note 4, at 102.
[7] Columbel J et al., *Genotypic Analysis of Thiopurine S-methyltransferase in Patients with Crohn's Disease and Severe Myelosuppression During Azathioprine Therapy*. 118 Gastroenterology 1025-30 (2000).
[8] W.J. Sandborn, *Is Metabolite Monitoring Essential for Rational Dosing of Azathioprine and 6-mercaptopurine?* VI International Symposium on Inflammatory Bowel Diseases (2003).
[9] *Id.*

metabolites that result from treatment with mercaptopurine or azathioprine in conditions ranging from leukemia to inflammatory bowel disease.

Clinical trials have demonstrated the effective dose for most patients, and clinical assessments of physiological responses have a long history of use.[10] It is critical that clinicians consider the measurement of metabolites such as those described above, particularly when patients: 1) may not be complying with their drug regimens; 2) are also taking other prescription drugs; 3) are known to have intermediate or low TPMT activity; or 4) fail to respond to standard doses.

When monitoring patients for toxicity, physicians consider a number of clinical and laboratory parameters, particularly in the initial treatment of the disease.[11] These parameters include gastric discomfort, flu-like symptoms, pancreatitis, hepatitis, rash, myelotoxicity, and infection. Recognition of these clinical effects may lead to treatment with laxatives, anti-diarrheals, pain relievers, iron supplements, altered nutrition and vitamins or minerals.

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[10] Many clinicians start patients at doses lower than those found to be most effective in controlled trials because of the risks of toxicity and the long period to response. *See* Sandborn, *supra* note 4, at 101.

[11] Sandborn, *supra* note 8, at 99.

In recent years, certain levels of thiopurine drug metabolites have been found to be associated with some of the adverse side effects. Thus, these levels may predict adverse side effects in some patients. Yet it is precisely the statistical observation of these levels that the patents at issue seek to claim. Indeed, as recognized by the district court, the patent claims "wholly preempt" the natural relationship between the levels of metabolites in a patient's body and the likelihood that the drug the patient received will be toxic. Dist. Ct. Op. at *10.

These measurements and observations are part of the broader clinical evaluation that physicians must undertake when treating patients. It is 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 factor those levels into other laboratory and clinical parameters to guide dosage adjustments and, thereby, to provide necessary and appropriate medical care for their patients.

SUMMARY OF THE ARGUMENT

The patent claims at issue in this case are invalid under 35 U.S.C. § 101 for at least two independent reasons. First, they impermissibly preempt the natural statistical correlation between levels of certain thiopurine drug metabolites and the likelihood of therapeutic efficacy or toxicity of those drugs. Second, they fail the "machine or transformation of matter" test recently enunciated by this Court in *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008), because they assert exclusive rights over the mere recognition by a treating physician of those correlations without limitation to any particular course of action or treatment based on that recognition. It is important that this Court affirm the district court's invalidation of these claims because overreaching claims of this sort interfere with the practice of medicine, constraining the ability of physicians to make informed treatment decisions based on the latest scientific knowledge, are likely to stifle innovation, and will serve only to increase the cost and decrease the effectiveness of treatment for serious diseases. Contrary to the allegations of Prometheus and some amici, striking down these claims will neither sound the death knell of personalized medicine nor interfere with incentives necessary for medical innovation.

ARGUMENT

A. The Claims Asserted in this Case Impermissibly Preempt Natural Phenomena

Essentially, the claims at issue here seek to patent the statistical observation that some doses of thiopurine drugs tend to be too high for some patients and some tend to be too low. The patent claims at issue in this case "have three steps: (1) administer the drug to a subject; (2) determine metabolite levels; and (3) be warned that an adjustment in dosage may be required." Dist. Ct. Op. at *9. These claims run afoul of time-honored prohibitions on patenting "laws of nature, natural phenomena, [or] abstract ideas," *Diamond v. Diehr*, 450 U.S. 175, 185 (1981) (citing *Parker v. Flook*, 437 U.S. 584, 593 (1978) and *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)), because they "wholly preempt" the natural relationship between the level of the metabolites 6-TG and 6-MMP in the human body and the likelihood of therapeutic efficacy and toxicity of thiopurine drugs. Dist. Ct. Op. at *10, citing *Benson,* 409 U.S. at 71-72. While the recognition of this correlation may be new, "a product [or process] must be more than new and useful to be patented; it must also satisfy the requirements of invention or discovery." *Funk Bros. Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127 (1948).

1. Correlations between Metabolite Levels and Therapeutic Efficacy and Toxicity are Unpatentable Natural Phenomena

As the Supreme Court has repeatedly emphasized and this Court has recently reiterated, "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Bilski*, 545 F.3d at 952, citing *Benson*, 409 U.S. at 67. Rather, "[i]f there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end." *Funk Bros.*, 333 U.S. at 130. The ban on patenting natural phenomena must apply over and above the "machine-or-transformation-of-matter" test employed in analyzing the abstract ideas issue. *Bilski*, 545 F.3d at 955. Even if a natural process, such as photosynthesis or digestion, involves the transformation of matter, it remains "the handiwork of nature" and is not patentable. *Funk Bros.*, 333 U.S. at 131.[12]

Despite this well-established prohibition, the patent here provides exclusive rights to the discovery of a statistical correlation between the levels of certain metabolites produced by the body in response to the administration of certain drugs and the efficacy and toxicity of those drugs. Just as the Supreme Court held in

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[12] In this respect we agree with amici Interested Patent Law Professors, Br. at 2-5, though we disagree with them as to whether the claims asserted here constitute natural phenomena.

Funk Brothers, which involved "inoculants for leguminous plants" that were effective because of natural interactions of bacterial strains, such a scientific discovery is not an "invention or discovery within the meaning of the patent statutes." *Id.* at 132.

The argument that the observed correlation is patentable subject matter simply because it stems from the administration of a synthetic drug is inconsistent with precedent and would lead to absurd results. In patent law, "natural" means "nature's handiwork" as generally juxtaposed with the products of human agency and ingenuity. *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980); *Flook*, 437 U.S. at 591-594. Thiopurine drugs are man-made compositions of matter, undeniably patentable under Section 101. Providing incentives to invent such drugs, which work with the body's natural processes, is a well-accepted purpose of the patent system. Prometheus does not seek to enforce patents on synthetic drugs, however. The drugs involved in the claims are well known. Instead, the patents in suit lay claim to observations about the body's natural responses to such drugs.

A natural response to a man-made invention has never been patentable. In *Funk Brothers*, for example, the patentee combined laboratory cultures of selected bacteria to form an "inoculant" that assisted nitrogen fixation in plants. *Funk*

Bros., 333 U.S. at 129. Despite the human effort required to select, culture, and combine the bacteria, the mixture was unpatentable because the mutual non-inhibition of nitrogen fixing properties was a natural response to being combined. Though the combination was artificial, the bacteria "serve[d] the ends nature originally provided and act[ed] quite independently of any effort of the patentee." *Id.* at 131.

This distinction between a man-made product and its natural behavior has long been recognized. In *O'Reilly v. Morse*, 56 U.S. 62 (1853), for example, the Supreme Court discussed the English case, *Neilson v. Harford,* 151 E.R. 1266 (1841), and 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. *O'Reilly*, 56 U.S. at 115-16. Any invention involving igniting fuel in a furnace is in some sense synthetic, yet that fact would not have rendered patentable a claim to the principle of using hot air to aid ignition. Nor did the fact that printing characters at a distance is a human endeavor save a claim to the basic scientific concept of using "the motive power of the electric or galvanic current" to make such characters. *Id.* at 119.

Similarly, the important discovery that ether (synthetically produced by distilling alcohol) could be used to produce a state of "total insensibility to pain" was not patentable because it was "only a new or more perfect effect of a well-known chemical agent, operating through one of the ordinary functions of animal life." *Morton v. New York Eye Infirmary*, 17 F.Cas. 879, 882-83 (C.C.S.D.N.Y. 1862). As explained by the court:

> A discovery may be brilliant and useful, and not patentable. No matter through what long, solitary vigils, or by what importunate efforts, the secret may have been wrung from the bosom of Nature, or to what useful purpose it may be applied. . . . The new force or principle . . . can be patented only in connection or combination with the means by which, or the medium through which, it operates.

More recently, in *Nippon Electric Glass Co. v. Sheldon*, 539 F.Supp. 542 (S.D.N.Y. 1982), the court invalidated claims to a television tube intended to reduce a viewer's exposure to X-radiation. Sheldon's claims centered on constructing the tube so that X-rays emitted through the front did not exceed a limit that he had discovered. In invalidating the patent, the court noted that "[Sheldon] claimed to have discovered a phenomenon of nature, that X-radiation in excess of 0.04 mr/hr from televisions is harmful to human health." *Sheldon*, 539 F. Supp. at 546. The health effect of radiation from television sets is a natural phenomenon, despite the fact that the television is a product of human ingenuity.

Id. The unpatentable interaction between synthetically produced X-rays and the body proceeds without human intervention.

The crabbed understanding of "natural phenomenon" advocated by Prometheus 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 sun burning would be non-natural when it occurred in tanning booths and natural when it happened on a beach, and so forth. To comport with longstanding case law, a phenomenon must be deemed natural when it proceeds without human agency even if it responds to a synthetic stimulus. Prometheus's own expert employed this interpretation of the term, 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.[13] Dist. Ct. Op. at *7 (emphasis added.)

[13] Amici Interested Patent Law Professors suggest, Br. at 13-15, that a definition of natural phenomena that encompasses the claimed correlations would also sweep in drug product claims and claims to drug methods of treatment. This is nonsense. The claims of a patent determine whether it preempts a natural phenomenon. A patent claiming a pharmaceutical chemical will not attempt to claim the natural bodily responses themselves any more than a patent on a new food product would attempt to claim the natural processes of digestion.

The district court correctly concluded that "the relevant inquiry is whether the correlations are 'man-made,' not whether a man-made drug was used to produce the correlation." Dist. Ct. Op. at *9. It is particularly clear that the correlations between drug metabolite levels and drug toxicity and efficacy claimed here are natural phenomena. Nothing in the claims purports to affect the way in which a patient's body responds to the administration of the medications: the phenomena are merely observed.

Metabolite production proceeds without human intervention once the drugs are ingested. Indeed the resulting metabolite levels are unpredictable. The unpredictability of the body's natural response to the drugs is precisely the reason there is a need to measure metabolite levels in a given patient and to use statistics about prior patients' responses to understand the implications of those measurements for the efficacy and toxicity of the drug.

Having established that the claimed statistical correlations are natural phenomena, it is easy to see that these claims are unpatentable, since they wholly preempt every substantial use of those correlations. The claims cover every instance in which anyone considers whether to adjust thiopurine drug dosage in light of the metabolite level measurements. Dist. Ct. Op. at *10.

B. The Patent Claims Asserted in this Case Fail the "Machine or Transformation of Matter" Test

Even if they were not void for attempting to patent natural phenomena, the claims at issue here would be invalid. This Court recently delineated the test for determining whether a sequence of steps is a patentable "process" or an unpatentable abstract idea. A process is patentable if "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." *Bilski*, 545 F.3d at 954. These requirements ensure that the claim is "tailored narrowly enough to encompass only a particular application of a fundamental principle rather than to pre-empt the principle itself." *Id.* To serve this purpose, the machine or transformation of matter test requires a corollary: "insignificant extra-solution activity" cannot turn an unpatentable claim to an abstract idea into a patentable process. *Id.* at 962, citing *Flook*, 437 U.S. at 590.

1. The Claims Do Not "Transform a Particular Article into a Different State or Thing" Except Perhaps as Part of a Routine Data-Gathering Step

Setting aside routine data-gathering steps, the claims here reduce to a doctor being "warned or notified that a dosage adjustment may be required" when he or she sees the results of routine and long-standing diagnostic tests. Dist. Ct. Op. at *9. The claims focus on the statistical correlations between metabolite level and

drug efficacy or toxicity. Analyzing those statistical correlations is the sum total of what the patentees contributed to the art. As the Supreme Court held in *Flook*, 437 U.S. at 590, "[t]he 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." The same reasoning applies to routine data-gathering steps. *Bilski*, 545 F.3d at 957; *see also*, *In re Grams*, 888 F.2d 835, 839-40 (Fed. Cir. 1989). Measuring metabolite levels for comparison to a particular number is precisely the type of routine data-gathering step that is insufficient to confer patentability on these highly abstract claims.

2. The Claims Do Not Require Any Action after a Physician Takes Note of Natural Correlations between Metabolite Level and Toxicity and Efficacy

The claims at issue here do not require any action whatsoever by a physician who has perused the test results and been "notified" to consider adjusting the dosage in response. Though their preambles denote them "method[s] of optimizing therapeutic efficacy" or of "reducing toxicity," the claims at issue in this case are remarkable for their complete failure to set out any specific actions to be followed after a physician is "warned" that an adjustment of dosage might be necessary. The "post-solution activity" here is not merely "insignificant"—it is non-existent. *See generally*, *Flook*, 437 U.S. at 590. This is no accident.

Interpreting diagnostic tests is not a mechanical exercise. Here, the specification makes clear that the appropriate treatment regimen cannot be dictated by metabolite measurements alone.

Table I of the asserted patents shows that in one test, for example, patients who responded positively to the medication had median metabolite levels of 295, while non-responders had median levels of 184: positive response was correlated with higher metabolite levels. Nonetheless, while 78% of responders had levels over 225 (close to the efficacy level of "about 230" called out in the claims), the other 22% responded despite lower metabolite levels. Moreover, 26% of non-responders also had metabolite levels over 225. Similarly, in the study reflected in Figure 3 of the asserted patents, 78% of patients with metabolite levels above 230 responded positively to the medication. Nonetheless, the figure shows that 42% of those with lower metabolite levels also responded.

It is not surprising, in light of this natural variation in patient response to the drugs, that the specification notes that:

> [I]f the level of a 6-MP metabolite such as 6-TG or 6-MMP is higher than a predetermined toxic level, *one skilled in the art can monitor for toxic side effects* by measuring one or more of the toxicities associated with 6-MP drug treatment, as disclosed herein. . . . *If such a patient exhibits signs of leucopenia or bone marrow suppression, the 6-MP*

> *drug dose can be reduced.* However, if it is determined that *a patient has levels of a 6-MP metabolite higher than a predetermined toxic level but does not exhibit signs of leucopenia or other 6-MP drug toxicities, one skilled in the art can determine that the current 6-MP drug dose can be maintained.* Based on measuring 6-MP metabolite levels and determining signs or symptoms of toxicities associated with 6-MP drug treatment, one skilled in the art can determine whether a 6-MP drug dose should be maintained or decreased. 6,355,623 col. 12, ll. 16-37; 6,680,302, col. 12, ll. 23-44. (emphasis added)

In other words, depending on a patient's symptoms or other test results, a physician might decide to adjust the dosage of a patient with more than the claimed toxicity level – or might not! Similarly, depending on a patient's symptoms, a physician might decide to raise the dosage of a patient with less than the claimed efficacy level – or might not! (6,355,623, col. 11, ll. 12-26; 6,680,302, col. 11, ll. 19-33).

The hedging of therapeutic recommendations in the patent specification, and the corresponding lack of a particular prescription for action in the claims, is not surprising. The statistical correlation between metabolite level and efficacy and toxicity is only one piece of data used by a physician to determine a course of treatment based on further tests, observations of the patient's symptoms, and so forth. There is no "method of optimizing treatment efficacy" reflected in these claims, but only a suggestion to consider certain test results as part of formulating a treatment plan.

3. The Claims are Directed to Unpatentable Abstract Mental Processes

Observations of statistical correlations such as those reported in the patent specification are "basic tools of scientific and technological work." *Bilski*, 545 F.3d at 952, citing *Benson*, 409 U.S. at 67. They are important inputs to the mental process of medical diagnosis, but determining whether to adjust dosages requires professional judgment that is entirely dependent on the exercise of human intelligence. *See Bilski*, 545 F.3d at 952, citing *In re Comiskey*, 499 F.3d 1365 (Fed. Cir. 2007). These claims are, as Justice Breyer remarked about the claims in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124, 135 (2006), "not at the boundary" under this Court's test for patentability of abstract ideas.

C. Public Policy is Well Served by Current Limits on Patentable Subject Matter, Which Preclude Patenting Scientific Data

Amici medical associations recognize that healthcare-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 pharmaceutical products, medical devices, diagnostic testing kits, and so forth. In this respect, the patent system has served patients and the medical profession well.

Patents on basic scientific principles underlying medical care, however, do not have these salutary effects. Such patents raise ethical concerns for physicians, threaten to stifle innovation and raise the costs of medical treatment, and erode the quality of patient care by limiting the knowledge physicians may use to diagnose and treat their patients.

1. Patents on Scientific Principles Raise Ethical Concerns for Physicians

Physicians have longstanding ethical obligations to advance and share useful medical knowledge with patients and physicians. Principle V of the AMA's Principles of Medical Ethics states that a "physician shall continue to study, apply and advance scientific knowledge," and "make relevant information available to patients, colleagues, and the public."[14] Opinion 9.08 of the Code of Medical Ethics of the AMA elaborates upon this basic principle:

> Physicians have an obligation to share their knowledge and skills and 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.[15]

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[14] Available at www.ama-assn.org/ama/pub/category/2512.html (last visited April 5, 2009).

[15] Available at http://www.ama-assn.org/ama1/pub/upload/mm/369/ceja_3i07.pdf (last visited April 5, 2009).

Discovery of a basic scientific principle that could be useful to others in devising medical applications or to physicians in reaching diagnoses and treating patients is a quintessential example of the kind of medical knowledge that physicians are obliged freely to share. To interpret the patent laws to make scientific principles eligible for patent protection threatens to undermine, rather than promote, the ethical practice of medicine.

2. Patents Solely on Scientific Facts Threaten to Stifle Innovation, Including the Development of Personalized Medicine, and to Increase Health Care Costs

Basic scientific facts "are part of the storehouse of knowledge of all men." *Funk Bros.*, 333 U.S. at 130. Ensuring wide dissemination and free access to such facts is essential to scientific progress. The discussion above of the history of research into thiopurine drugs and their relationship to metabolites such as 6-MMP and 6-TG illustrates that these patentees are neither the first nor the last to consider the implications of these metabolite levels for human health. Ready access to basic facts, such as a relationship between levels of drug metabolite and the drug's efficacy and toxicity, are essential to important, ongoing research efforts. Exclusive rights to scientific facts hinder efforts to develop or employ new and superior medical advances that would build on them.

Here, disclosure of the correlations between these metabolites and drug efficacy and toxicity creates incentives for laboratories, such as Mayo, to compete to develop fast and inexpensive ways of testing for the metabolites and for researchers such as Dr. El-Azhary to study similar correlations. Mayo Br. at 10. But a patent that covers a mere "notice" to a physician that he or she might want to adjust the dosage of the associated drug may "shut[] the door" to the development or use of such new tests, and discourage further research and development. *O'Reilly v. Morse*, 56 U.S. at 113.

Patents on scientific facts, such as the statistical correlations involved here, would stifle rather than incentivize developments in medicine, including those in personalized medicine. At its core, personalized medicine has been central to the practice of medical genetics since its inception.[16] As described by the Personalized Medicine Coalition (PMC):

> Personalized medicine . . . aims to achieve optimal medical outcomes by helping physicians and patients choose the disease management approaches likely to work best in the context of a patient's genetic and environmental profile. Such approaches may include genetic screening programs that more precisely diagnose diseases and their

[16] See Motulsky AG. *Drug reactions, enzymes, and biochemical genetics*. 165 J. Am. Med. Ass'n 835-37 (1957).

> sub-types, or help physicians select the type and dose of medication best suited to a certain group of patients. [17]

Much of the public's understanding of personalized medicine relates to pharmacogenetics—the study and clinical testing of genetic variation that gives rise to differing response to drugs, which is central to this case.

Amici agree with the PMC that:

> A strong intellectual property system is necessary to stimulate investment in innovation. It is essential that government patent systems offer protection for innovations relating to personalized medicine, as well as high quality patent examination that allows *patents of appropriate scope and quality.*[18]

The patents at issue in this case far exceed the appropriate scope for patents on diagnostic tools and methods, however. Such patents, which do not cover inventive diagnostic tests but instead seek to preempt the facts underlying proper diagnosis, threaten to slow the development of diagnostic testing. Subjecting physicians to a thicket of patent licensing obligations merely for thinking about how best to treat their patients also would increase the transaction costs of practicing medicine, and lead inevitably to higher-priced medical treatment.

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[17] http://personalizedmedicinecoalition.org/sciencepolicy/personalmed-101_overview.php (last visited April 5, 2009).

[18] http://personalizedmedicinecoalition.org/sciencepolicy/personalmed-101_overview.php. (Emphasis added.) (last visited April 5, 2009).

The unpatentability of mere observations about the body's natural responses to a drug does not threaten the development of personalized medicine. Indeed, a recent report by the Secretary's Advisory Committee on Genetics, Health, and Society found that patents "do not serve as powerful incentives for either genetics research in the diagnostic arena or the development of genetic tests."[19]

There is no need for patents to incentivize physicians to study the kinds of clinical correlations at issue in this case. On the contrary, when knowledge of such correlations is freely available there is enormous incentive for physicians to *make use of them* to provide necessary and appropriate care for their patients.

3. Patents on Scientific Facts Erode Doctors' Ability to Provide Quality Patient Care

Patent claims such as those at issue here conflict with doctors' ability to provide effective patient care. Here, the patentee argues that a doctor infringes by thinking about the correlation between dosage efficacy and toxicity after receiving results of a metabolite test even if the test was ordered for a reason other than a desire to adjust dosage in light of the limits set out in the patent claims. Mayo Br. at 10-12. There can be no design around a scientific fact. A physician who

[19] Secretary's Advisory Committee on Genetics, Health, and Society, 110 *Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Test* (March 9, 2009).

learns—from the medical literature, colleagues, continuing medical education, or elsewhere—of the statistical correlation between metabolite levels and drug efficacy and toxicity cannot put that knowledge out of mind. Thomas Jefferson aptly described this characteristic of ideas:

> If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of every one, and the receiver cannot dispossess himself of it.[20]

Such is the nature of scientific fact; once known, it must be considered. Quality patient care demands that a physician consider test results in light, among other things, of current medical knowledge.

Claims to exclusive rights to simply considering scientific facts concerning medical diagnosis and treatment distort patent law beyond recognition. By discovering a previously unknown correlation between obesity and illness, for example, a researcher could obtain a patent on the process of having a patient step on a scale, measuring a weight above a particular statistically significant value, and then thinking about whether to recommend that the patient diet to lose weight.

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[20] Letter from Thomas Jefferson to Isaac McPherson (Aug. 13, 1813) *reprinted in* The Letters of Thomas Jefferson: 1743-1826, *available at* Electronic Text Center, University of Virginia Library.

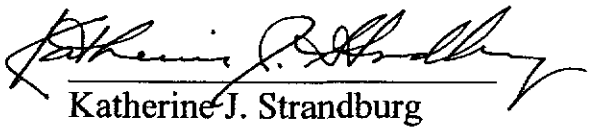
Any entity that made or sold scales, and that dared to mention that correlation in a brochure, might then be liable for intentionally inducing infringement. Such a result is unthinkable, as recognized by the district court's sound analysis in this case.

If the claims at issue here were properly patentable, a laboratory might induce infringement simply by informing a doctor of the correlation in conjunction with delivery of test results or perhaps even by publishing articles or brochures discussing the correlation. Indeed, confronting very similar facts in *Metabolite Labs. Inc. v. Lab. Corp of Am. Holdings*, 370 F.3d 1354 (Fed. Cir. 2004) (where the patentable subject matter issue was not raised) this court found that the defendant laboratory had induced infringement through the publication of medical articles. *Id.* at 1365. If patent licenses are required for physicians merely to consider newly discovered implications of well-established diagnostic tests, and if laboratories become contributory infringers merely by educating doctors about those implications, it is hard to imagine how the medical diagnostic community will continue to serve the goal of quality patient care.

CONCLUSION

For these reasons, the district court's grant of summary judgment should be affirmed.

Respectfully Submitted,



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