2008-1403

IN THE 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

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APPELLANT'S REPLY BRIEF

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Dated April 24, 2009

CERTIFICATE OF INTEREST

Counsel for Plaintiff-Appellant Prometheus Laboratories, Inc., certifies the following:

1. The full name of every party or amicus curiae represented by me is:

   Prometheus Laboratories Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

   None

3. All party corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   Apax Partners, Patricof & Co. Ventures, Inc., DLJ Banking Partners, Wachovia Capital Partners, the Sprout Group, St. Paul Venture Capital

4. The names of all law firms and the partners or associates that appeared for the party or amicus curiae now represented by me in the trial court or agency or are expected to appear in this court are:

   LATHAM & WATKINS LLP: Richard P. Bress, J. Scott Ballenger, Alexander Maltas, Gabriel K. Bell

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Dated: April 24, 2009

Respectfully submitted,

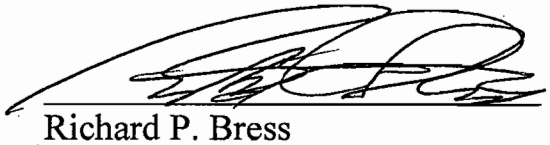

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

Page(s)

STATUTES

OTHER AUTHORITY

INTRODUCTION

For all of its rhetoric, Mayo's responsive brief either affirmatively concedes or fails to oppose the key legal and factual issues that control this appeal. First, Mayo concedes that the effects of a man-made drug in the human body are not natural phenomena. Appellees Br. 32-36 & n.5. Second, Mayo concedes that methods of treatment are patentable under § 101. Appellees Br. 22, 25-26. Third, Mayo does not contest that the steps of injecting thiopurine drugs, and extracting samples to test metabolite levels, are themselves transformative and would satisfy § 101 standing alone. Appellees Br. 32-37. Fourth, Mayo concedes that the measurement of the metabolites before calibration is done by a machine (*e.g.*, a high pressure liquid chromatograph). Appellees Br. 28-30. Finally, Mayo does not contest that injecting thiopurine drugs into patients with serious chronic diseases is a complex and risky endeavor for which proper calibration can have enormous practical benefits.

In light of those concessions, Prometheus's technique of combining knowledge derived from scientific discovery with useful physical activities to achieve a functional end plainly satisfies § 101. The patents-in-suit do not claim any purely natural phenomenon, and they do not consist of purely mental action. They inherently involve physical, transformative steps such as administering drugs, drawing blood samples, and testing blood for metabolites. Mayo does not, and

could not, contend that these steps can be performed without transformations and machines. Appellees Br. 27-38. And Mayo effectively concedes that the integral involvement of patentable compositions of matter, no less than machines, is sufficient to confer patentability on a process. These patents do not claim the correlation between metabolite levels and toxicity/efficacy in the abstract, but rather apply those relationships in concrete physical processes to generate useful treatment information for physicians. Put simply, claiming a process that facilitates diagnosis and treatment of ill patients is not the same thing as claiming a natural correlation.

Rather than confronting these truths, Mayo's responsive brief is built on three diversions, each of which is irrelevant to the question before this Court, and each of which in any event is flat wrong as a matter of law and fact. Once those errors are corrected it is quite clear that the patents-in-suit fall squarely in the heartland of patentable subject matter.

First, Mayo repeatedly imports novelty analysis into § 101 to argue that the physical, transformative steps of the patents-in-suit, such as administering thiopurine drugs to a patient and measuring metabolite levels, should be disregarded because those steps were previously "well known" in the art—and that without those steps all that remains is a mental step. Appellees Br. 5. The Supreme Court's opinions in *Gottschalk v. Benson*, 409 U.S. 63 (1972), and *Parker*

v. Flook, 437 U.S. 584 (1978), lend some support to that approach, and Mayo tellingly relies on both cases "*passim*" throughout its brief. *See* Appellees Br. iv-v. But Mayo fails to recognize that the Supreme Court completely repudiated that approach to § 101 in *Diamond v. Diehr*, 450 U.S. 175 (1981). It is now settled beyond question that a process must be evaluated under § 101 *as a whole*, that the claims should not be dissected, and that whether a patent describes patentable subject matter has nothing to do with novelty. Mayo appears to concede, for example, that the patents-in-suit would satisfy § 101 if Prometheus had invented thiopurine drugs or a novel machine for measuring metabolites in the body. But whether a process describes patentable subject matter has nothing to do with who invented what. Medical diagnostic and personalized-medicine inventions may frequently combine physical steps previously known in the art with mental steps, and no court has ever suggested that the combination is categorically excluded from patentability.

Second, Mayo argues that those same concrete and transformative steps can be disregarded because they represent merely "data gathering" for the final (warning) step. As Prometheus has explained, the administration of thiopurine drugs and the measurement of metabolites are not merely data gathering for an abstract mental step but crucial steps in the ongoing treatment of desperately ill patients which (like the preliminary steps in *Diehr*) also happen to produce

information. Mayo argues that the obvious treatment purpose of these steps should be ignored, and that Prometheus's patented methods actually have nothing to do with patient treatment, merely because the patents-in-suit do not require the doctor to adjust a patient's treatment at the end. That is incorrect. Thiopurine drugs are highly toxic and are administered only to people with serious diseases. No one performs these steps for any purpose unconnected to the treatment of a particular patient. The whole purpose of the patented processes is to improve patient treatment by delivering to doctors highly important—and previously unknown—information about patients with serious chronic diseases, which doctors can use as part of the mix of information that they employ to improve patient care. The mere fact that other factors may also be relevant to a particular treatment decision, and that a doctor may therefore ultimately decide not to alter a particular patient's dosage, does not render the invention less useful or relevant to patient treatment.

Third, Mayo argues that the patents-in-suit might randomly ensnare doctors who do nothing more than inadvertently hear about them. Such concerns ring particularly hollow coming from a company that admits that it wants to intentionally produce and sell a multimillion dollar laboratory test, the economic value of which would derive entirely from Prometheus's invention. Regardless, this concern is illusory and has nothing to do with § 101.

No one infringes Prometheus's patents merely by thinking about correlations. Infringement occurs only after potentially toxic drugs are administered to an ill patient, blood samples are extracted, metabolite levels are measured using sophisticated scientific instruments, and a warning is provided about a possible need to adjust dosage. Those steps are not taken inadvertently, and once they are completed the benefits of the patented process have been realized—even if the patient's doctor ultimately makes a medical decision not to adjust treatment. This case, moreover, is about the infringing business plans of Mayo's for-profit diagnostic laboratory, and no doctor is going to order and pay for Mayo's planned test inadvertently. Mayo spins the story of Dr. el-Azhary, and argues that Prometheus pursued an innocent doctor. But Mayo declines to explain that the allegations were directed at the conduct of the commercial Mayo diagnostic laboratory that induced Dr. el-Azhary to use Mayo's test instead of Prometheus's patented test precisely so that Mayo could calibrate its own test and train its own lab workers using Dr. el-Azhary's patients, in preparation for competition against Prometheus. This was no innocent, inadvertent infringement.

Mayo's suggestion that a physician who learns of the patents-in-suit may not be able to avoid infringing the patents in the course of patient treatment provides no basis for affirming the district court. A physician who knowingly uses the patented processes to treat her patients may be subject to Prometheus's patent

rights, just as she would be subject to the patent laws for her use of myriad other valuable diagnostic and treatment patents. If Mayo disagrees with the scope of doctor immunity, its recourse is with Congress, not the courts. But the scope of physician immunity for patent infringement does not in any event implicate § 101.

ARGUMENT

I. MAYO IS WRONG TO ARGUE THAT PATENTABILITY OF A PROCESS PATENT TURNS SOLELY ON THE NOVEL "WARNING" STEP OF THE PROCESS

A. Mayo Mischaracterizes The Patents-In-Suit By Focusing Exclusively On The Step That It Claims Is Novel

Mayo's primary error is that it repeatedly imports novelty analysis into the § 101 inquiry by dissecting the processes and then ignoring those steps that are not new in the art. *See*, *e.g.*, Appellees Br. 2, 4-5, 23-24, 30, 33-36. It protests that Prometheus did not invent thiopurine drugs or develop a new way of measuring metabolite levels. *Id.* at 4-5. According to Mayo, Prometheus's claims are not patentable because the "only asserted contribution to the field was their alleged discovery that the particular claimed metabolite levels *correlate* with therapeutic efficacy or toxicity." *Id.* at 5. *Amici* supporting Mayo fall into a similar trap. *See* Br. of *Amici Curiae* ARUP Labs., Inc. et al. 5 ("ARUP Br.") ("the patents disclose nothing new" apart from correlations); Corrected Br. for *Amici Curiae* American Coll. of Medical Genetics et al. 16 ("ACMG Br.") ("The drugs involved in the claims are well known."). These arguments echo the district court's misguided

focus on the fact that the thiopurine drugs themselves, as well as the administering and determining steps, were old in the art. *See* A13560 ("[H]ere the man-made drugs aren't new."); A13565 ("[I]t's prior art."); A13588 ("[T]hat's prior art. That's nothing new . . . ."); A00029 (administering and determining steps are "conventional method steps").

However, the processes at issue here do not consist simply of novel "correlations." The patents-in-suit improve an existing process that is both vitally important to treating sick patients with chronic diseases and fraught with serious risks of both under- and over-dosage. That existing process involves administering thiopurine drugs to ill patients, extracting blood samples, measuring metabolite levels, and attempting to calibrate dosage. Prometheus's invention improves and refines that process by identifying the levels associated with efficacy and toxicity so that patients receive effective treatment without suffering adverse effects. The fact that what is "novel" in the patents-in-suit is improved accuracy in dosage adjustments does not make the underlying process any less of a process.

One way to understand that point is that the patents-in-suit contain steps that, standing alone, are clearly processes within the meaning of § 101. For example, the steps of administering thiopurine drugs to patients, taking blood samples, and measuring metabolites are, individually or together, unquestionably "processes." Whether those steps were known in the prior art is a separate question, but a patent

claiming them would satisfy § 101 on its own. *See* Appellant Br. 21-26. Mayo does not and could not argue to the contrary. *See* Appellees Br. 22-23. Adding a step—warning the physician of a possible need to adjust dosage based on specific measurement levels—does not make that process suddenly not a process any more. An improved process is not less of a process once the improvement is added.

The clear implication of Mayo's argument is that if Prometheus had invented the thiopurine drugs, and then patented a process for calibrating dosage of its own drugs, then its process patent would be patentable. Similarly, if Prometheus had invented high pressure liquid chromatography (HPLC) and had patented a process for using an HPLC machine to improve the treatment of patients with thiopurine drugs, that too would fall within § 101. *See id.* at 24 ("[T]he patient's metabolite levels are measured by one of a number of conventional means."). But § 101 is about whether a patent claims subject matter that is a proper subject of a patent. It has nothing to do with novelty or inventorship.

B. Mayo's View That This Court Should Determine Patentability Based Solely On The Novel Components Of The Patents-In-Suit Is Squarely Foreclosed By *Diehr*

The Supreme Court has held unequivocally that novelty is not part of the § 101 analysis. *Diehr*, 450 U.S. at 193 n.15 ("The fact that one or more of the steps in respondents' process may not, in isolation, be novel or independently eligible for patent protection is irrelevant to the question of whether the claims as a

whole recite subject matter *eligible* for patent protection under § 101."); *see also State St. Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1372 n.2 (Fed. Cir. 1998) ("[T]he invention is not examined under [§ 101] for novelty . . . .") (citation omitted). The Supreme Court and this Court have repeatedly recognized that under § 101 a process must be considered *as a whole*, and that a court should not dissect a process into various constituent steps, discard those steps that are not in themselves novel, and determine patentability solely on the novel steps that remain. *Diehr*, 450 U.S. at 188; *In re Bilski*, 545 F.3d 943, 958 (Fed. Cir. 2008); *In re Alappat*, 33 F.3d 1526, 1543-44 (Fed. Cir. 1994) (en banc).

Mayo's only argument to the contrary rests on its repeated citations to *Benson* and *Flook*. There is certainly language in those cases that might support Mayo's view, but that language has been repudiated by the Supreme Court and by this Court.

In *Benson*, the applicant claimed an algorithm for converting binary-coded decimal numerals into pure binary numerals. 409 U.S. at 64. The Supreme Court rejected the patent, primarily because the applicant had not linked his invention to any particular apparatus. Stripped of any connection to an existing apparatus, the Court held that the process was "abstract and sweeping." *Id.* at 68. The Court pointed out that "[t]he mathematical procedures can be carried out in existing

computers long in use, no new machinery being necessary. And, as noted, they can also be performed without a computer." *Id.* at 67.

In *Flook*, the patent concerned a catalytic conversion process in which conditions such as temperature, pressure, and flow rates are monitored. 437 U.S. at 585. The patent claimed a method of updating "alarm limits" that indicated that conditions were abnormal. *Id.* The patent improved upon prior art by using a formula that could be useful for computerized calculations of the alarm limits. *Id.* at 586. The Court appeared to reject the patent in part because the catalytic conversion process, the monitoring of variables, and the use of alarm limits were already "well known" in the art, and the only *novel* element was a mathematical formula. *Id.* at 595. "Respondent's process is unpatentable under § 101, not because it contains a mathematical algorithm as one component, but because once that algorithm is assumed to be within the prior art, the application, considered as a whole, contains no patentable invention." *Id.* at 594.

The way that *Benson* and *Flook* incorporate novelty issues into the § 101 inquiry would lend some support to Mayo's analysis here, except that those aspects of *Benson* and *Flook* have since been repudiated by the Supreme Court—as this Court has already recognized. In *Diehr*, the Supreme Court considered an improved process for curing synthetic rubber in a mold. 450 U.S. at 177-78. To determine the optimum time for curing rubber, the improved process relied on the

Arrhenius equation. *Id.* The process of curing rubber was well-known in the prior art, and the Arrhenius equation had "long been used to calculate the cure time in rubber-molding presses." *Id.* at 177 n.2. The Court nevertheless held that the patent satisfied § 101. It made no difference to the Court that the physical transformation of the rubber flowed from a well-known process, nor that the improvement included a mathematical equation. The Court instead ruled—in a holding that is directly on point here—that "Arrhenius' equation is not patentable in isolation, but when a process for curing rubber is devised which incorporates in it a more efficient solution of the equation, that process is at the very least not barred at the threshold by § 101." *Id.* at 188. The Court squarely held that process claims "must be considered as a whole," and that "[i]t is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Id.*

That holding forecloses Mayo's arguments. This Court has previously recognized that *Diehr* abrogated *Benson* and *Flook*. *See Arrhythmia Research Tech., Inc. v. Corazonix Corp.*, 958 F.2d 1053, 1057 n.4 (Fed. Cir. 1992) ("[T]he reasoning in *Diehr* not only elaborated on, but in part superseded, that of *Benson* and *Flook*."); *see also Bilski*, 545 F.3d at 958-59 (claims are not to be dissected). It is highly telling that Mayo does not even acknowledge *Diehr* when it argues that the steps of injecting thiopurine drugs and measuring metabolites are not "new."

The patents-in-suit plainly claim improved processes that incorporates a scientific insight in "a more efficient solution" for patient treatment, and the patents are "at the very least not barred at the threshold by § 101." *Diehr*, 450 U.S. at 188.

II. MAYO'S OTHER ARGUMENTS FOR DISREGARDING THE TRANSFORMATIVE AND MACHINE-DEPENDENT STEPS IN THE PATENTS-IN-SUIT ARE CONTRARY TO LAW

In a similar vein, Mayo invokes a variety of reasons why this Court should disregard various physical, transformative aspects of the patents-in-suit. Mayo argues, for example, that the transformative and machine-dependent steps are "mere" data gathering, Appellees Br. 27, 36-41, or "natural" phenomena, *id.* at 33-36, and that the patents as a whole are not *really* about patient treatment, *id.* at 4, 20. Each of these arguments rests on incorrect understanding of the facts and law.

A. Administering Toxic Drugs, Measuring Metabolites, And Calibrating Dosage Of Sick Patients Are Not "Mere" Data Gathering Steps

Mayo does not contest that the administering and determining steps require transformations and machines, but instead discounts them as mere data-gathering. *See id.* at 29 ("incidental involvement of machines in performing the tests"); *id.* at 32-37. Those steps produce information that is utilized later in the processes, but that is not their sole purpose. The curing of the rubber in *Diehr*, and the monitoring of that process, produced data that was used in the Arrhenius equation to calculate the optimal time for opening the mold. But the Supreme Court did not

disregard those steps as mere data gathering for an equation, because the process as a whole had a concrete and tangible purpose that was not merely the solution of a mathematical equation. The same is true here. No one administers thiopurine drugs to patients *merely* so that they will produce metabolites that can then be measured and compared with reference values. Rather they perform those steps as part of patient treatment.

Mayo's reliance on *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989), is misplaced. *See* Appellees Br. 28, 37. In *Grams*, the unpatentable process claim involved diagnosing an unspecified "abnormal condition" based on the results of "unspecified clinical tests" of different unspecified parts of the body. *Bilski*, 545 F.3d at 965; *Grams*, 888 F.2d at 840 ("The specification does not bulge with disclosure on those tests."). Indeed, the *Grams* processes were so broadly targeted as to be "applicable to any complex system, whether it be electrical, mechanical, chemical, biological, or combinations thereof." *Grams*, 888 F.2d at 836. The patent was not directed at particular diagnostic methods, but basically tried to claim the very concept of diagnosis—of *any* malfunctions in *any* system. It is hardly surprising that this Court would view the unspecified tests leading up to an unspecified diagnosis as merely a general prescription for data-gathering.

But *Grams* specifically distinguished the narrower patentable claim from *In re Abele*, 684 F.2d 902 (CCPA 1982), where the "production and detection steps

were not viewed as mere antecedent steps to obtain values to solve the algorithm" because the purpose was "to improve the CAT-scan process" and the process "'encompasse[d] significantly more than the algorithm alone.'" *Grams*, 888 F.2d at 840 (quoting *Abele*, 684 F.2d at 909). The initial steps of Prometheus's processes similarly have concrete purposes beyond mere data gathering for a mental exercise, and the processes encompass significantly more than the correlations alone.

B. The Patents-In-Suit Are Inherently And Unavoidably Connected To Patient Treatment

Mayo tries to argue that the initial steps of the patents-in-suit have no purpose beyond "data gathering," because no adjustment in dosage is *required* and "nothing happens in the claimed methods after the physician makes the correlation." Appellees Br. 17; *see also id.* at 4, 20, 23-24, 26, 46; *accord* ACMG Br. 22. That argument reflects Mayo's mischaracterization of the patents-in-suit.

The entire purpose of these inventions is to improve a process of patient treatment. There are, in fact, no uses of the claimed processes other than in connection with patient treatment. The thiopurine drugs at issue are potentially toxic and administered only to seriously ill patients, and Mayo's own record citations recognize that the only use of the patents-in-suit is for patient treatment. *See* Appellees Br. 24; A12787-88 ("[P]atients . . . were administered azathioprine . . . for the treatment of autoimmune [diseases]."); A12820-21 (patients

administered azathioprine "for treating his/her autoimmune [disease]"); A12853 (patients were "treated with azathioprine"); A12854 (Mayo funded study involving patients who were "treated with azathioprine").

The fact that the patents-in-suit do not expressly require an adjustment to the patient's dosage does not change their overall purpose or negate the inventions' connection to patient treatment. As with many diagnostic patents, the information provided by these processes is only one of several data points that a doctor might use in the course of patient treatment. Few, if any, diagnostic tests compel a blind change in treatment based on no other factors. But the fact that other factors may be relevant to the physician's treatment decision does not render the inventions merely abstract or disconnected from patient treatment.

For example, Myriad Genetics developed a patented process to identify particular genes that are markers for increased risk of breast and ovarian cancer. *See* Appellant Br. 49 n.14; *see also* Br. of *Amicus Curiae* Myriad Genetics viii, 6-10 ("Myriad Br."). The patented process is a risk assessment that analyzes predisposition to cancer by identifying gene mutations associated with hereditary risk of breast and ovarian cancer. The patented tests themselves do not dictate specific subsequent treatment, but the tests are surely invaluable tools to inform the patient's treatment. No one would suggest that a process for identifying risk factors for breast cancer is "not tied to any treatment of a patient," Appellees Br. 4,

or is unpatentable because the output of the process is "merely" information or because subsequent treatment may take a variety of forms. *See Arrhythmia*, 958 F.2d at 1054 (method of "determining which heart attack victims are at high risk for ventricular tachycardia, so that these persons can be carefully monitored and appropriately treated"); *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1368 (Fed. Cir. 2008) ("The technology in this case pertains to diagnostic tools [methods] that not only detect but also classify hepatitis C virus (HCV) genotypes in a biological sample, which facilitates tailoring the treatment of patients with different genotypes.").

Mayo's contrary argument cannot be squared with this Court's holdings in *Abele*, or in *Arrhythmia*. In *Abele*, this Court's predecessor upheld a method patent on a "more useful tool for doctor's diagnosis": "an improvement in CAT scan imaging technique" that used an equation to produce clearer information than in a "conventional CAT-scan process." 684 F.2d at 904, 908 & n.9. The patentable process entailed performing calculations on X-ray data from a beam passed through a patient's body and displaying the resulting modified data. *Id.* at 908. There, as here, the method ended by providing information to the physician about the patient's body to do with as the doctor sees fit. The *Abele* court specifically held that the method could have been patentable even if it ended with a data calculation. *Id.* at 908 n.8 ("'[T]he fact that [the] equation is the final step is not

determinative of the section 101 issue.'" (citation omitted) (second alteration in original)).

Similarly, Mayo's argument would nullify the medical diagnostic patent upheld in *Arrhythmia* for "determining which heart attack victims are at high risk for ventricular tachycardia" in which the end result was a number that is "compare[ed]" to a predetermined level.[1] 958 F.2d at 1054-55. The method in *Arrhythmia* did not require that physicians do anything with the resulting data (although they will surely factor it into any treatment regime), but rather simply ended with "comparing said value with said predetermined level." *Id.* at 1055. It made no difference to this Court in *Abele* and *Arrhythmia* that "nothing necessarily happens, physical or otherwise, after the correlation is recognized." Appellees Br. 22. And there are countless similar medical diagnostic patents. *See, e.g., Griffin v. Bertina*, 285 F.3d 1029, 1031 (Fed. Cir. 2002) (addressing patent on "'method for diagnosing an increased risk for thrombosis'" consisting of taking sample from patient, assaying for certain gene mutations and correlating the mutation to risk of thrombosis) (citation omitted); A12939-3013 (collecting numerous such patents).

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[1] *Bilski* did not disturb the outcome in *Arrhythmia*. *See* Appellant Br. 28 n.7. Indeed, this Court has cited *Arrhythmia* approvingly after *Bilski*. *See In re Comiskey*, 554 F.3d 967, 979 n.14 (Fed. Cir. 2009). Mayo fails to appreciate (Appellees Br. 42 n.9) that the "inadequacy" of the *Freeman-Walter-Abele* test, which *Arrhythmia* had applied out of "convenien[ce]," 958 F.2d at 1058, is that that test was too *restrictive* and inappropriately hostile to patentability. *See*

Prometheus never suggested that practicing the patents-in-suit will always result in a change in dosage, because doctors make decisions based on many factors. Nor, in light of *Abele* and *Arrhythmia*, is such a step necessary. The point is that the inherent purpose of these patents is to improve the treatment of the patients by providing doctors with an additional tool for determining the proper dosage. That concrete context and purpose for the initial "administering" and "determining" steps means that they cannot be dismissed as merely data gathering for an abstract equation, as in *Grams*.

C. The Patents-In-Suit Do Not Fall Outside Of § 101 Merely Because They Employ The Body's "Natural" Reaction To Man-Made Drugs

Mayo appreciates that the metabolites themselves are not "naturally occurring." But Mayo and its *amici* argue that the processes here nonetheless are not transformational because the metabolites are created by the body's "natural" reaction to foreign substances. That is incorrect.

First, everything is mediated by natural forces and principles. Appellant Br. 19-20. *See Diehr*, 450 U.S. at 189 n.12 ("[A]ll inventions can be reduced to underlying principles of nature . . . ."). As Justice Frankfurter recognized, "[e]verything that happens may be deemed 'the work of nature.'" *Funk Bros. Seed*

Appellant Br. 28 n.7. Mayo's criticism of the *Freeman-Walter-Abele* precedents is also surprising, since its favorite case—*In re Grams*—was decided under that test.

Co. v. Kalo Inoculant Co., 333 U.S. 127, 135 (1948) (Frankfurter, J., concurring). But Prometheus's patents do not claim "natural phenomena" in any meaningful sense, because they consist of a specific man-made course of treatment, involving administering synthetic drugs into the body and assessing the efficacy or toxicity of the drugs by measuring the resulting levels of metabolites that would not exist but for the handiwork of man. In short, the methods are entirely *unnatural*—and in that important sense are very different from those at issue in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 584 U.S. 124 (2006).[2]

Mayo argues that "because the particular synthetic drugs at issue here have been used to treat patients since at least the 1980's, their use is certainly 'part of the storehouse of knowledge of all men.'" Appellees Br. 33 (quoting *Funk Brothers*, 333 U.S. at 130). But *Funk Brothers* was not referring to man-made inventions that just happen to be old. In *Funk Brothers*, the Court rejected an attempt to patent a combination of *natural* bacteria exhibiting nothing more than their *natural* qualities.

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[2] Of course, man-made processes may well be patentable even if employing only natural products. *See* Myriad Br. at 3-4. Contrary to Mayo's suggestion (at 33 & n.5), Prometheus does not argue that patentable processes must employ synthetic—as opposed to natural—drugs, only that doing so here removes any doubt as to patentability. Accordingly, Mayo's heavy reliance on the three-Justice dissent in *Laboratory Corp.*, which involved no synthetic drugs, is misplaced. *See* Appellant Br. 38 n.12, 45 n.13.

In contrast, here, there is nothing natural about administering synthetic drugs and deriving diagnostic information from levels of the resulting metabolites found nowhere in nature. Neither the drugs nor the patient's reaction exhibit "natural" qualities (indeed, the body's natural immune system is *suppressed* by the drugs). Accordingly, the patents-in-suit are more akin to the genetically-engineered bacteria that the Court found patentable in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). Those bacteria, which were engineered to better clean up oil spills, were patentable precisely because they did not "exist[] in nature." *Id.* at 310. Under Mayo's view, those bacteria would not have been patentable because they reacted "naturally" (that is, according to the laws of biology and chemistry) when placed in a soiled body of water just as the human body reacts "naturally" when injected with synthetic drugs.

In re Nuijten, 500 F.3d 1346 (Fed. Cir. 2007), *cert. denied*, 129 S. Ct. 70 (2008) (cited at Appellees Br. 35), is entirely irrelevant to the issues here. In that case, the court determined that a signal, although man-made, did not fall into any of the categories of patentable subject matter in § 101. Here, by contrast, the processes at issue use a man-made composition of matter.

Tellingly, in *Chakrabarty* and *Nuijten*, the associated method claims were sustained below and were not at issue on appeal. *See Chakrabarty*, 447 U.S. at 305-06; *Nuijten*, 500 F.3d at 1351. In *Chakrabarty*, for example, the Patent Office

Board of Appeals had granted the method claim associated with the synthetic bacteria even as it simultaneously (and erroneously) rejected the product claim as a "product of nature." 447 U.S. at 305-06. And in *Nuitjen*, a patent was granted on the use of the signal. 500 F.3d at 1351. Mayo's argument thus has it exactly backwards. Having effectively conceded that the drugs are patentable, and that administering drugs and determining metabolite levels are patentable processes, it necessarily follows that composite processes employing all of those elements must also satisfy § 101.

Second, any natural laws of science implicated in the patents-in-suit are incorporated in the context of processes that rely on multiple transformations and machines—which is the touchtone for patentability identified by this Court in *Bilski*. *Bilski* established that there is no concern about preempting fundamental principles where methods inherently involve transformations (of matter or data) or necessarily require machines. Appellant Br. 20. Here, Prometheus's patents require multiple transformations and machines (such those necessary to measure metabolites). *Id.* at 21-46.[3]

[3] The patents here only "preempt" use of the correlations in connection with the other specific synthetic drugs and medical treatment steps. *See* Appellant Br. 31, 37-39. They would not "preempt," for example, the use of the correlations in performing statistical analysis on historical patient data. In any case, as *Bilski*'s "machine-or-transformation test is the singular test for a process claim under § 101," *In re Ferguson*, 558 F.3d 1359, 1365 (Fed. Cir. 2009), a freestanding preemption inquiry is inappropriate.

Mayo also utterly failed to address Prometheus's separate argument that the "machine" prong of the *Bilski* test is satisfied by the involvement of synthetic drugs. Appellant Br. 30-31, 34-37. This Court has made clear that a process is always patentable if it "'is embodied in, operates on, transforms, or otherwise involves another class of statutory subject matter, i.e., a machine, manufacture, *or composition of matter*.'" *Bilski*, 545 F.3d at 961 n.24 (quoting *In re Comiskey*, 499 F.3d 1365, 1376 (Fed. Cir. 2007)) (emphasis added); *see* Appellant Br. 34-35. Indeed, *Comiskey* was recently reissued and reaffirmed that equivalence. *See In re Comiskey*, 554 F.3d 967, 979 (Fed. Cir. 2009) ("[A] claim that involves both a mental process and one of the other categories of statutory subject matter (i.e., a machine, manufacture, or composition) may be patentable under § 101."). Contrary to Mayo and its *amici*, Prometheus is not attempting to patent "basic knowledge," ARUP Br. at 14, but concrete processes employing several categories of patentable subject matter.

III. MAYO'S ARGUMENT ABOUT DOCTORS' POTENTIAL INADVERTENT INFRINGEMENT IS WRONG, AND IN ANY EVENT IS IRRELEVANT TO THE § 101 INQUIRY

The rhetorical centerpiece of Mayo's brief is its argument that Prometheus's patents have been, and will be, enforced "against wholly unintentional and unavoidable mental processes by Mayo physicians." Appellees Br. 9. Mayo's

argument is based on an misrepresentation of the record and a mischaracterization of the patents-in-suit. Its arguments, in any event, have nothing to do with § 101.

A. Prometheus's Complaint Is Directed At Mayo's Attempts To Launch A Multi-Million Dollar Competing Test Derived Entirely From Prometheus's Innovations

As an initial matter, Mayo's tale of Dr. el-Azhary, whom Mayo claims was ensnared by Prometheus's patents by simply thinking about correlations (Appellees Br. 9, 24) is a misrepresentation of the record. Prometheus accused *Mayo* of inducing Dr. el-Azhary (who works at Mayo) to use Mayo's test rather than Prometheus's patented test, so that Mayo could develop and validate its own test and train its own workers to compete against Prometheus. *See* A12758-59 (accusing Mayo entities of infringement); A12786-87 (accusing Mayo of inducing Dr. el-Azhary's use of Mayo's test "[a]s part of the development, validation and training for Mayo's Test for Mayo"); A12820-21 (same).[4] Prometheus does not sue doctors and did not sue Dr. el-Azhary. *See* A10036-41; A12595-600. Instead, Prometheus sued the Mayo entities for infringing the patents "directly, contributorily, and by inducement of others." A12596.

Mayo's invocation of Dr. el-Azhary is a blatant attempt to divert attention from the fact that this case is about Mayo's efforts to launch a multimillion dollar

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[4] The record citations on which Mayo primarily relies for its claim that Prometheus targeted Dr. el-Azhary are statements from Mayo's own lawyer. *See* Appellees Br. 24, 39 (citing A13557-58).

competing test, the value of which is entirely derived from Prometheus's inventions. There is certainly nothing innocent or inadvertent about Mayo's conduct, and no one will order and pay for that test unavoidably or inadvertently.[5]

Stripped to its essentials, Mayo's complaint is that a doctor might perform all of the pre-"warning" physical process steps in the course of patient treatment and then be unable to avoid infringement because the correlations at the heart of the "warning" step, once learned, cannot be un-learned. Of course performing all of the prior physical steps would be neither inadvertent nor unavoidable, and at that point the value of the invention has been realized (by Mayo). Mayo may be right that physicians in the course of patient care have less opportunity to avoid patent infringement than practitioners or engineers in other fields, because avoiding the patented method may be inconsistent with the physician's ethical obligations to his patient. But if there is a problem with that reality, it is not a problem that has anything to do with the language or goals of § 101.

Indeed, Congress has specifically addressed these concerns with 35 U.S.C. § 287(c), which shields doctors from patent liability for performing certain "medical activit[ies]." Congress chose to exclude from its new liability shield "the practice of a patented use of a composition of matter in violation of such patent"

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[5] Mayo asserts that Prometheus's patents are hindering the rollout of its "superior" test, *see* Appellees Br. 6-7, but that assertion is unsupported by any evidence and

and "the practice of a process in violation of a biotechnology patent." *Id.* § 287(c)(2)(A)(ii), (iii). Section 287(c) has not yet been extensively litigated, and there is no need for this Court to assess its precise implications for a hypothetical lawsuit against a doctor (which Prometheus has never brought, and would not bring) under the patents-in-suit. Two points should suffice, for present purposes.

First, the very existence of § 287(c) demonstrates why Mayo's effort to twist basic § 101 principles in order to protect doctors from infringement must be rejected. Section 287(c) immunity is Congress's response to the concerns Mayo articulates. If that statutory immunity applies in the present circumstances, then Mayo's concern for doctor liability is a red herring. If it does not, then Congress has made a deliberate choice not to immunize doctors from liability in these circumstances.

Second, Congress confirmed that even when individual doctors are protected from liability, *commercial laboratories like Mayo are not*. *Id.* § 287(c)(3). The dominant theme of Mayo's brief—that its for-profit commercial laboratory should get a pass to free-ride on Prometheus's patents because it would be unfair to hold *doctors* liable—has therefore been rejected, unambiguously, by Congress.

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is, in any case, irrelevant. Inventors frequently attempt to improve on patented inventions, but that does not mean that they are exempt from liability.

B. Mayo's Purported Concerns Are An Inevitable Feature Of Many Medical Diagnostic Process Patents

The issue that Mayo identifies also is not unique to the patents-in-suit, but rather is a feature of diagnostic patents generally. Many diagnostic patents feature physical processes that culminate in a mental step or warning. Again, the Myriad BRCA1 cancer risk assessment is a prime example—the final step of the test is that a physician is warned of the patient's potential cancer risk due to the presence of specific gene mutations. *See* Myriad Br. viii, 7-10. Any time that a medical diagnostic test culminates in a mental step, a challenger can always argue that there is no way to avoid infringing once you reach that final step. But the better question is why, having performed all of the steps up to the final one and having derived all benefit of the process, anyone should complain about paying for the value of the patent. Mayo is not arguing that a single step will cause inevitable infringement; rather it is arguing that having intentionally performed all the steps of a process except for the last one, the last step may become unavoidable.

There are very good reasons why diagnostic and treatment patents are drafted this way. The medically appropriate responses to learning that a particular patient is, for example, at greatly heightened risk for breast cancer are far too varied and individual for any draftsman to capture all of the complexities in a patent application. Mayo's suggestion that patents must always terminate in a

physical step is not only inconsistent with settled law, but would effectively destroy the field of diagnostic patents.

In any event, Mayo's professed concerns about unavoidable infringement would not actually be mitigated by adding an additional physical step of adjusting dosage. Because the only use of Prometheus's patents is in the course of patient treatment, adding a step that required an adjustment in dosage would create the same issue—in many, perhaps most, circumstances, a reading below the efficacy level or above the toxicity level will, in practice, require a change in dosage and the doctor would infringe. Again, Mayo's real complaint is that a doctor's ethical obligations may *require* the doctor to infringe these patents, if proper patient care demands it, while people working in other fields do not face such constraints. If Mayo means to suggest that it is important that doctors be given an opportunity to avoid infringement by failing to provide their patients with medically necessary adjustments in care, it should be obvious that such an opportunity would be of no value.

IV. MAYO'S ARGUMENTS WOULD HAVE SERIOUS ADVERSE CONSEQUENCES FOR MEDICAL DIAGNOSTICS AND PERSONALIZED MEDICINE PATENTS

Many patents in the field of medical diagnostics and personalized medicine involve a combination of previously-known physical steps along with mental steps or algorithms that improve the process. Many crucial innovations in the field of

medical diagnostics have involved improvements to existing processes that improve the accuracy and efficacy of those processes for patient diagnosis and treatment. *See* Appellant Br. 47-49. No court has ever suggested that the combination of an existing process plus an improved method of applying or calibrating that process somehow stops being a process once the inventive improvements are added. *See* Appellant Br. 46-52.

Mayo's *amici* argue that patentability will hinder the development of personalized medicine and scientific research, with potentially "dire" and "disastrous" consequences. *See* ARUP Br. 9-17; ACMG Br. 27-30. ARUP, for example, speculates that the lack of a patent on a particular diagnostic process for detecting overdoses "probably" saved "thousands of lives each year." ARUP Br. 17. But ARUP does not explain why such tests would be unavailable to doctors and patients if patented. Similarly, ARUP argues that "'modern life, including good health . . . , depends upon the use of artificial or manufactured substances,'" *id.* (citation omitted) (alteration in original), but does not explain why processes employing artificial substances should be any less patentable than the artificial substances themselves. Indeed, crucial medical instruments, upon which "modern life" equally "depends," are routinely patented with no detriment (indeed great benefit) to the provision and development of health care. ARUP further contends that many doctors are "trying to discern clinically relevant levels of known drugs

or metabolites even *without* any purpose of seeking patent protection." ARUP Br. 13. But Congress has chosen to provide patent protection for medical diagnostic processes. And the fundamental premise of the patent system is that in the long run patent protection will make such beneficial inventions *more* available, by incentivizing inventors.

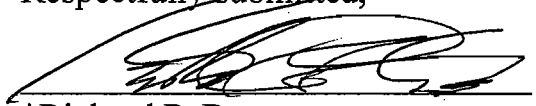
Several other *amici* recognize that "[p]atent protection is essential for continuing investment and innovation in the field of personalized medicine." Br. of *Amicus Curiae* Am. I.P. Law Ass'n 21; *see also id.* at 18-21; Br. of Novartis Corp. as *Amicus Curiae* 15; Myriad Br. 10-13, 25-30; Br. of *Amici Curiae* Interested Patent Law Professors 13-16; Corrected Br. of *Amicus Curiae* Biotechnology Industry Organization 7-12. As these *amici* understand, advances in medical diagnostics and personalized medicine require substantial investments, and an unduly restrictive interpretation of § 101 will choke these vital fields in their infancy.

CONCLUSION

Mayo's attempts at obfuscation do not undermine the basic truth that the patents-in-suit reflect an improvement on processes that employ machines and man-made compositions of matter, and inherently incorporate numerous physical, transformative steps. Those steps are not incidental but rather are central to the purpose of Prometheus's invention. The patents-in-suit therefore satisfy § 101.

This Court should reverse the judgment of invalidity and remand for further proceedings.

Respectfully submitted,



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Dated April 24, 2009

CERTIFICATE OF SERVICE

I hereby certify that on April 24, 2009, I caused twelve (12) copies of the foregoing **APPELLANT'S REPLY BRIEF** to be delivered by hand to Mr. Jan Horbaly, Clerk, United States Court of Appeals for the Federal Circuit, 717 Madison Place, NW, Room 401, Washington, DC 20439, and two (2) copies of the foregoing brief to be served via FedEx upon the following:

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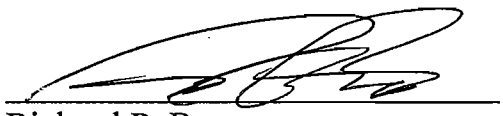

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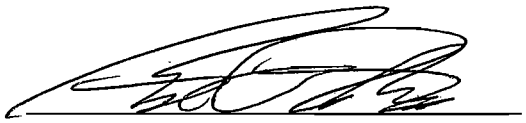

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