No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

On Writ Of Certiorari
To The United States Court Of Appeals
For The Federal Circuit

BRIEF FOR MYRIAD GENETICS, INC., AS *AMICUS CURIAE* SUPPORTING RESPONDENT

JAY Z. ZHANG
BENJAMIN G. JACKSON
MYRIAD GENETICS, INC.
320 Wakara Way
Salt Lake City, UT 84108

November 7, 2011

GREGORY A. CASTANIAS
Counsel of Record
JONES DAY
51 Louisiana Avenue, N.W.
Washington, D.C. 20001
(202) 879-3939
gcastanias@jonesday.com

Counsel for Amicus Curiae

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INTEREST OF *AMICUS CURIAE* [1]

Myriad Genetics, Inc. is a pioneer and world leader in the growing field of personalized medicine. Myriad's currently marketed personalized medicine products include innovative molecular diagnostic tests for diagnosing predisposition to disease (e.g., BRAC*Analysis*® testing assesses a woman's risk for breast and ovarian cancer); for optimizing a patient's therapy (e.g., OnDose® testing measures the levels of 5FU in a patient's blood so that dosing can be adjusted to deliver the right amount of drug for the individual patient); and for determining a patient's prognosis (e.g., PROLARIS® testing helps urologists determine a prostate cancer patient's risk of recurrence and disease-specific death). Myriad's products are now used by more than 40,000 healthcare providers in the United States in the care of their patients.

Myriad's past innovation and commercial success, as well as the patients whose lives are improved by our products, have benefited greatly from an appropriately strong U.S. patent system. In reliance on the prospect of continuing patent protection for its advances, Myriad is making substantial investment in research and development and working diligently to deliver the next generation of personalized medicine products. Myriad scientists analyze thousands of specimens, searching the human body's

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[1] All parties have consented in writing to the filing of this *amicus curiae* brief. No counsel for any party authored this brief in whole or in part, and no person or entity other than *amicus curiae*, their members, or counsel made a monetary contribution to the preparation or submission of this brief.

biochemicals (DNA, RNA, microRNA, proteins, and metabolites) to identify molecular markers that correlate with disease characters and drug response. Such correlations are key to Myriad's development of new products and methods, helping Myriad deliver the promise of personalized medicine in preventing diseases, optimizing disease treatment, improving lives, and reducing healthcare costs.

The massive investment in researching and developing these new products and methods would not be feasible for Myriad, or for any company, without the promise of patent protection for the resulting inventions. The cost of discovering, validating, and commercializing such personalized medicine products is significant. In the context of BRACAnalysis® testing alone, Myriad—

- has invested hundreds of millions of dollars in creating the innovative isolated BRCA1 and BRCA2 molecules, developing methods of using such molecules to detect predisposition to breast and ovarian cancer, and in establishing and refining its laboratory and data analysis processes to where they are now the gold standard;
- has invested well over $200 million in raising doctor and patient awareness of hereditary breast and ovarian cancer;
- employs a sales force of over 350 throughout the country to educate doctors on the power of genetic testing; and
- employs hundreds of skilled customer service, billing, and medical services personnel who help guide doctors and

patients through the testing and insurance reimbursement process.

This level of investment cannot possibly be made, and the resulting level of testing quality and patient access cannot possibly be maintained, absent strong patent protection, which allows a company a fair return on its investment in the inventive process.

Myriad thus has an interest in ensuring that patent claims to specific and practical diagnostic uses of correlations such as those in this case are affirmed as directed to patent-eligible subject matter. Absent such claims, there would not be adequate patent protection for future personalized medicine products, long-settled expectations would be upset, and the significant investment by Myriad and others in research and development would not be adequately incentivized. The important and developing industry of personalized medicine would be seriously jeopardized if such substantial and innovative contributions to science and medicine were denied patent protection at the doorway to the Patent Act, 35 U.S.C. § 101.

SUMMARY OF ARGUMENT

Personalized medicine uses molecular diagnostic tests to obtain information on a patient's genetic and molecular markers which are correlated to clinically useful disease characters. It holds enormous promise for significantly improving people's lives and reducing healthcare cost at each stage of patient care, including preventing disease by predicting which patients are at increased risk and improving disease outcomes by determining the best course of treatment (*e.g.*, the claims at issue in this case).

The significant investment and substantial risk involved in the innovation, development and delivery of personalized medicine products mandate strong patent protection. As with the pharmaceutical industry, personalized medicine relies on expensive and risky clinical studies to investigate, analyze, decipher, and confirm useful correlations between molecular markers and specific disease characters. Differences between pharmaceuticals and diagnostics, however, including a very different regulatory environment for molecular diagnostics, make broad patent coverage for the innovation underlying a diagnostic test critical.

In the post-Human Genome Project era, claims to diagnostic applications of such correlations may be the only meaningful claims available to adequately protect and incentivize the large investment needed to bring new and useful personalized medicine products to patients. Composition-of-matter claims, *e.g.*, isolated nucleic acids or proteins, may now be largely unavailable for patenting in light of the Human Genome Project. Claims like those at issue in this case, therefore, are particularly important

because they will be the only vehicle for introducing (and incentivizing) new and pathbreaking personalized medicine products for the public good.

Allowing such method patent claims to pass through the initial gateway to patentability will stimulate innovation. Numerous molecular markers can be correlated with each particular disease character. Patent claims to one diagnostic use of the correlation between a particular molecular marker and a specific disease character do not hinder, and actually drive, the innovations of other diagnostically useful correlations between other markers and that disease character for use in alternative diagnostic tests. Therefore, by allowing patent claims to practical diagnostic uses of specific correlations, the Constitutional purpose of the patent law is served and society reaps the benefits.

The Federal Circuit correctly found these claims patent-eligible under this Court's § 101 decisions, *e.g.*, *Diamond v. Diehr*, 450 U.S. 175 (1981), because they are directed to a specific and practical application of a personalized medicine correlation and not to the correlation *in the abstract*. Though it is no longer the exclusive test, the Federal Circuit also found an important clue to patent-eligibility in the fact that Prometheus's claims "necessarily involve" transformative steps.

Moreover, these claims do not pre-empt the basic tools of science. Indeed, these claims involve a technical aspect (*i.e.*, determining the level of a biomarker) *interacting* with the correlating step, which comports with the European approach to medical diagnosis process claims. In the words of *Diehr*, which harmonize well with the European

approach, such claims are patent-eligible because "they do not seek to pre-empt the use of [a correlation]. Rather, they seek only to foreclose from others the use of that [correlation] *in conjunction with* all of the other steps in their claimed process." *Diehr*, 450 U.S. at 187 (emphasis added).

The Prometheus claims *as a whole* are drawn to a specific and practical application of a personalized medicine correlation, rather than the correlation in the abstract, because they necessarily involve a transformation interacting *in conjunction with* the correlation. Personalized medicine method claims still have significant hurdles to clear under the other substantive sections of Title 35 (especially §§ 102, 103, and 112), and requirements of other areas of the law. But these methods are new and useful additions to the body of public knowledge that should, at minimum, be considered eligible for patent protection. They are certainly not so manifestly abstract that they should be barred at the gate by the coarse filter of § 101.

Amicus urges this Court to sustain a strong patent incentive to continue to protect important American investment in personalized medicine by affirming the patent-eligibility of molecular diagnostic method patent.

ARGUMENT

I. PERSONALIZED MEDICINE IMPROVES AND EXTENDS LIFE WHILE LOWERING HEALTHCARE COSTS BY CORRELATING MOLECULAR MARKERS TO CLINICALLY USEFUL DISEASE CHARACTERS

Personalized medicine uses diagnostic tests to obtain information on a patient's molecular markers (gene sequence variations, gene or protein expression levels, metabolites, etc.) that are associated with particular disease characters (*e.g.*, specific disease risk, presence or absence of disease, prognosis, response to particular drug therapies, etc.). Based on this information, preventive measures or tailored treatment regimens can be applied to the right patient at the right time and in the right amount.

The Human Genome Project ("HGP") heralded the dawn of the age of personalized medicine. With the completion of the HGP (and related projects), human genes have all been identified, and most genetic variations between individuals revealed. Such information has enabled further innovations utilizing the correlations between molecular markers and specific disease characters. These correlations are essential in developing molecular diagnostic products for use in personalized medicine.

Already, a number of personalized medicine products are widely used, exemplifying the current value and future promise of personalized medicine in improving quality of life and reducing costs.

One example is *Prometheus*'s product at issue in this case, which involves testing thiopurine levels in an autoimmune disease patient's blood to determine whether they are receiving an efficacious and

minimally toxic dose of a thiopurine-producing drug. The test is based on the correlation between a certain upper metabolite level and toxicity, on the one hand, and a certain lower metabolite level and lack of efficacy on the other. This enables doctors to optimize drug doses for individual patients.

An example of a widely available molecular diagnostic is HER_2 testing, which predicts a patient's response to the breast cancer drug Herceptin®. The test utilizes the correlation between HER_2 expression in a tumor and the tumor's predicated response to Herceptin®. Patients whose tumors overexpress (*i.e.*, overproduce) HER_2 show dramatic response to treatment with Herceptin® while patients whose tumors do not overexpress HER_2 show little or no benefit. Herceptin® costs over $50,000 a year and can cause severe side effects. *See* Bruce E. Hillner & Thomas J. Smith, *Do the Large Benefits Justify the Large Costs of Adjuvant Breast Cancer Trastuzumab?*, 25 J. Clinical Oncology 611, 612 (2007); Herceptin® Package Insert, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/trasgen020900LB.htm. Thus, a simple diagnostic test for HER_2 overexpression can spare a woman enormous cost and suffering if her tumor's biology indicates the drug will not work. *See generally*, Nandini Dendukuri et al., *Testing for HER_2-positive Breast Cancer: A Systematic Review and Cost-effectiveness Analysis*, 176 CAN. MED. ASS'N J. 1429 (2007).

More importantly, because treatment with an ineffective drug can erode part of a patient's window of opportunity for effective treatment, drug response tests such as the HER_2 test can help physicians and

patients make the right treatment decision at the right time. *See id.* Indeed, given the commonly low rate of drug efficacy in many medical fields,[2] there is a clear need for additional molecular diagnostic tests predicting a patient's response to many other drugs.

In prostate cancer, standard treatment in the U.S. is surgical resection of the prostate (prostatectomy) or radiation therapy. These aggressive treatments are expensive and the costs to the patient's quality of life can be severe (including incontinence and impotence). The unique characteristics of prostate cancer present newly diagnosed men with a challenging dilemma: treat, with all of the potential serious side effects, or roll the dice and engage in active surveillance. Prostate cancer is often slow growing, with a large percentage of diagnosed men never dying of the disease. Thus, unlike most other cancers, it is not a given that the benefits of treatment outweigh the risks for a man with prostate cancer. However, it is still cancer, and without the ability to determine indolent from aggressive cancer, most men choose to treat aggressively because it is potentially lethal.

Molecular diagnostic, pathological and histological tools, such as PSA measurements and Gleason scoring, are available to gauge prostate cancer aggressiveness. However, these techniques, especially measuring PSA, are notoriously inaccurate and subjective, and there is a serious unmet clinical

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[2] Selected major drugs are effective in 50% of rheumatoid arthritis, 30% of Alzheimer's, and 25% of cancer patients. Brian B. Spear *et al.*, *Clinical Application of Pharmacogenetics*, 7 TRENDS MOLECULAR MED. 201, 202 (2001).

need for more accurate, objective tools in prostate cancer prognosis.

After over four years of research and millions of dollars and counting in investment, *Amicus*'s researchers and academic collaborators recently demonstrated that the expression of genes associated with cell-cycle progression correlates with both prostate cancer recurrence and death. Jane Cuzik *et al.*, *Prognostic Value of An RNA Expression Signature Derived From Cell Cycle Proliferation Genes in Patients With Prostate Cancer: A Retrospective Study*, 12 LANCET ONCOL. 245, 255 (2011). The Prolaris® test is a patented molecular diagnostic assay that measures gene expression levels within a prostate tumor sample, derives a quantitative cell-cycle progression score ("CCP Score") from this information, and uses the CCP Score either independently or together with clinical parameters to predict the patient's risk of death. This knowledge can help men and their doctors decide whether to opt for aggressive treatment or active surveillance. In this way, Prolaris® promises to significantly improve prostate cancer treatment and help reduce unnecessary cost and suffering.

The BRAC*Analysis*® test commercialized by *Amicus* is a widely utilized personalized medicine product that predicts predisposition to hereditary breast and/or ovarian cancer. The test is based on the isolation and characterization of the *BRCA1* and *BRCA2* DNA molecules, done by *Amicus* and its collaborators in the mid-1990s. Women testing positive for a BRCA mutation can have up to a 92 percent risk of developing breast or ovarian cancer, or both, by age 70. *See* D. Ford *et al.*, *Genetic*

Heterogeneity and Penetrance Analysis of the BRCA1 and BRCA2 Genes in Breast Cancer Families, 62 AM. J. HUM. GENETICS 676, 682, Table 5 (1998). Additionally, mutation carriers previously diagnosed with cancer have a significantly increased risk of developing a second cancer.

For the BRAC*Analysis*® test, patients who meet certain criteria (*e.g.*, family history of cancer) are identified and the patients' *BRCA1* and *BRCA2* genes are analyzed for mutations in a clinical laboratory. If a cancer-predisposing mutation is found, preventive measures such as chemoprevention therapy and prophylactic surgery can be taken to avoid the suffering and treatment costs associated with cancer. Alternatively, increased surveillance can be adopted to detect cancer at an early, more treatable stage. BRAC*Analysis*® is proven to improve quality and duration of life and reduces lifetime healthcare costs. *See* Kristin Anderson *et al.*, *Cost-effectiveness of Preventive Strategies for Women with a BRCA1 or a BRCA2 Mutation*, 144 ANNALS INTERNAL MED. 397, 397 (2006) ("[C]ost-effective policies on [BRAC*Analysis*®] testing and preventive treatment options may save up to $800 million of the more than $8 billion or more spent each year on breast cancer diagnosis, prevention, and treatment."). Due to the efforts and investment of *Amicus* in test development and physician and patient education, over 400,000 women have been tested and have received critical information that can be used to make life-saving decisions.

These are just a handful of products that illustrate personalized medicine's potential. Indeed, personalized medicine is often touted as one of the

promising solutions to the current crisis in our healthcare system. *See* Personalized Medicine Coalition, *The Case for Personalized Medicine* at 4-6, *available at* http://www.personalizedmedicinecoalition.org/sites/default/files/TheCaseforPersonalizedMedicine_5_5_09.pdf (last visited Nov. 4, 2011).

II. THE PERSONALIZED MEDICINE INDUSTRY IS BUILT ON THE SETTLED EXPECTATIONS OF THE INCENTIVE PROVIDED BY STRONG PATENT PROTECTION FOR CLAIMS TO DIAGNOSTIC USE OF CORRELATIONS

A basic understanding of challenges in the personalized medicine industry shows that patents in general, and patents claiming diagnostic use of correlations in particular, are vital to its full emergence and continued viability.

A. As in the Pharmaceutical Industry, Strong Patent Rights Are Needed to Ensure Recovery of the Substantial Investment Required to Fund Research, Development, and Product Delivery in Personalized Medicine

Much like in the pharmaceutical industry, personalized medicine research and development are extremely costly and offer a very low rate of success. *See generally*, Jim Kling, *Diagnosis or Drug? Will Pharmaceutical Companies or Diagnostics Manufacturers Earn More from Personalized Medicine?*, 8 EMBO REP. 903 (2007). Primary among these barriers to entry are the cost and difficulty of innovation and validation. *See, e.g.*, Christopher B. Granger *et al.*, *National Heart, Lung, and Blood Institute Clinical Proteomics Working Group Report*,

109 CIRCULATION 1697, 1700 (2004). A typical discovery study requires hundreds or thousands of carefully selected patient samples, each having expertly collected clinical information. After generating data on thousands or tens of thousands of molecular markers from these samples, scientists must then sift through millions of data points in hopes of discovering a statistically significant correlation between one or more of these markers and a particular disease character.

The amount of time and effort required is enormous. Additional clinical trials are required to demonstrate the clinical utility of the discovered correlation. Many trials are essentially equivalent to pharmaceutical trials in both design and scope, sometimes involving following patients for years to determine long-term survival. Costs for research tools such as reagents and laboratory equipment (especially high-throughput platform equipment such as microarray chips) can also be substantial, especially since many of these reagents and platforms are themselves patented products. For example, researchers at Genomic Health reportedly spent well over 100 million dollars and 7 years, including numerous clinical studies involving hundreds of patients, in bringing Onco*Type* DX® to market.[3]

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[3] Department of Health & Human Services, *Personalized Health Care: Pioneers, Partnerships, Progress*, 84 (2008), *available at* http://www.hhs.gov/myhealthcare/news/phc_2008_report.pdf. Onco*Type* DX® determines a breast cancer patient's risk of recurrence after surgery based on the correlation between the expression levels of selected genes in tumor and the likelihood of cancer recurrence.

Even after such significant time and capital outlays, success is not guaranteed; failures far outnumber successes. Again there are clear parallels to the drug industry, where many drugs that were successful in a phase II clinical trial inexplicably fail in a larger phase III trial. Similarly, many personalized medicine products with promising results in a small discovery study will fail to show any predictive value in a larger validation study.

While personalized medicine shares many of the challenges of the pharmaceutical industry, it is also adversely affected by the differences. Despite the similar costs and barriers to success between pharmaceuticals and molecular diagnostics, personalized medicine ironically promises investors an inherently smaller potential payoff compared to pharmaceuticals for the very same reason it reduces aggregate healthcare costs. Personalized medicine testing is often a one-time event—*i.e.*, the test determines once and for all whether a patient will respond to a particular treatment. Pharmaceutical products, on the other hand, often have "repeat" customers taking a daily dose for a very long time.

Another key challenge in personalized medicine (as compared to pharmaceuticals), which calls for broader patent protection in personalized medicine, is the regulatory environment. Laboratory-developed personalized medicine products presently are not FDA-regulated and are instead subject to CLIA certification for the technical aspects of the clinical laboratory where the test is performed. This is a significant difference. For pharmaceuticals, narrow patent coverage of the specific compound marketed by the innovator company is typically sufficient. This

is because any company hoping to market a competitive drug must either market the identical compound (and thus infringe even a very narrow patent claim covering only the innovator's specific compound) or undertake its own expensive clinical trials. This choice provides a significant barrier to entry in pharmaceuticals. For molecular diagnostics, however, broader patent coverage is required because there is no regulatory framework that puts would-be generic diagnostic providers to the difficult choice required of would-be generic drug marketers. Someone looking to offer a competing diagnostic test may make trivial changes to the innovator's diagnostic process, piggyback on the innovator's clinical studies, and merely validate the technical aspects of the laboratory to satisfy CLIA requirements. Unlike in pharmaceuticals, broad claims are needed to prevent easy circumvention of the patents protecting the significant investment in a new and useful personalized medicine product.

Even greater than the cost of innovation and validation of such personalized medicine products is the cost of actually delivering them to patients. *Amicus*'s BRAC*Analysis*® testing is an excellent example. *Amicus* has invested hundreds of millions of dollars in raising doctor and patient awareness of hereditary breast and ovarian cancer and in building the technical and personnel infrastructure to deliver genetic testing of the highest quality to over 700,000 patients.

The reason investors, both private and public, have been willing to pour such huge sums of capital into such risky ventures is the settled expectation that limited exclusivity will provide for a reasonable

return. *Amicus* urges this Court to tread very carefully when asked, as by the petitioner in this case, to upset those expectations. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 799 (2002) ("[C]ourts must be cautious before adopting changes that disrupt the settled expectations of the inventing community." (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997))).

B. Claims to Diagnostic Use of Correlations Such as Those in Prometheus's Patents Are Usually the Only Patent Claims Available That Can Provide Meaningful Protection for Personalized Medicine Products

> The § 101 patent-eligibility inquiry is only a threshold test. Even if an invention qualifies as a process, machine, manufacture, or composition of matter, in order to receive the Patent Act's protection the claimed invention must also satisfy 'the conditions and requirements of this title.' § 101. Those requirements include that the invention be novel, *see* § 102, nonobvious, *see* § 103, and fully and particularly described, *see* § 112.

Bilski v. Kappos, 130 S. Ct. 3218, 3225 (2010). Personalized medicine patents face significant challenges under the "conditions and requirements" of Title 35 beyond the initial one of § 101.[4] These

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[4] One challenge facing personalized medicine claims, which is made worse by a restrictive reading of § 101, is so-called "divided infringement." Narrowing application of § 101 in personalized medicine is forcing many applicants to settle for patent claims that are exceedingly easy to circumvent by splitting up the laboratory process and data analysis portions of

other provisions give ample, and better-calibrated opportunities to sift out undeserving patent claims. While the Human Genome Project ("HGP") has provided a boon to personalized medicine by greatly facilitating the discovery of important correlations, it has simultaneously made patenting in personalized medicine much more challenging, because human genes (including most genetic variations) have been elucidated and virtually all proteins encoded by these genes are now known to the public.

Claims to new techniques for analyzing molecular markers may still be available, but this does not solve the problem of incentivizing personalized medicine products. The development and manufacture of diagnostic tools is a wholly distinct industry that services the molecular diagnostic industry.

(continued…)

the typical personalized medicine process. William L. Warren & Lei Fang, Biotechnology Patent Validity in Jeopardy, GENETIC ENGINEERING NEWS: LEGAL AFFAIRS, Oct. 1, 2010 *available at* http://www.genengnews.com/gen-articles/biotechnology-patent-validity-in-jeopardy/3421/ (last accessed Nov. 4, 2011) ("To the extent that diagnostic method claims involve only mental correlative steps, they are at risk for being characterized as merely an unpatentable 'abstract idea.' On the other hand, for claims that involve multiple steps of the medical continuum, in order to capture a more clearly patentable transformation step along with the diagnostic mental correlation step, it is more likely that a single entity will not infringe the claim, precluding any remedy."); *see also Akamai Techs., Inc. v. Limelight Networks, Inc.*, 629 F.3d 1311 (Fed. Cir. 2010), *rehearing en banc granted*, 419 F. App'x 989 (Fed. Cir. 2011); *McKesson Techs. Inc. v. Epic Sys. Corp.*, 98 U.S.P.Q.2d 1281 (Fed. Cir. 2011), *rehearing en banc granted*, 2011 WL 2173401 (Fed. Cir. May 26, 2011).

Patenting of new tools or techniques does nothing to incentivize the discovery of new correlations and the development of the use of such correlations into commercial personalized medicine products. Invalidation of a claimed method for the diagnostic use of correlations—particularly at the threshold of the Patent Act—threatens to destroy the personalized medicine industry in its infancy.

III. THE FEDERAL CIRCUIT CORRECTLY RULED THAT THE PROMETHEUS CLAIMS ARE PATENT-ELIGIBLE UNDER 35 U.S.C. § 101 BECAUSE THEY ARE NOT DRAWN TO AN ABSTRACT IDEA OR LAW OF NATURE *PER SE*

Section 101 of the Patent Act broadly mandates that a patent may be obtained for "*any* new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. § 101 (2006) (emphasis added). The use of the expansive "any" as well as the legislative history of the Patent Act have led the Court to interpret the scope of patent-eligible subject matter broadly. *Diehr*, 450 U.S. at 182. Of course, there are limits to § 101. *See id.* at 185 ("Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas."); *see also Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584 (1978). Nevertheless, such judicially created exclusions must be narrowly applied, for "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diehr*, 450 U.S. at 182 (citing S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., Sec. 2d Sess., 6 (1952)).

A. The Prometheus Claims Do Not Claim a Fundamental Principle in the Abstract but Instead Claim a Specific and Practical Application of a Personalized Medicine Correlation

If a claimed process is an *application* of a law of nature, natural phenomenon or abstract idea, the process is patent-eligible. *Diehr*, 450 U.S. at 187. For example, while this Court has repeatedly explained that "Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity," *id.* at 185 (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)), the Court has explicitly upheld a patent claiming a specific and practical application of the law of gravity. *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45, 64-65 (1923). However, "[a]n idea *of itself* is not patentable." *Diehr*, 450 U.S. at 185 (citing *Rubber-Tip Pencil Co. v. Howard*, 87 U.S. (20 Wall.) 498, 507 (1874) (emphasis added). Thus, "when a claim recites a mathematical formula (or scientific principle or phenomenon of nature), an inquiry must be made into whether the claim is seeking patent protection *for that formula in the abstract*."[5] *Id.* at 450 U.S. at 191 (citing *Benson*, 409 U.S. 63 (1972)) (emphasis added).

All inventions originate as an "abstract idea" and all processes employ some "physical phenomenon"

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[5] The American Heritage® Dictionary of the English Language, defines "abstract" as withdrawn or considered apart from concrete existence; not applied or practical; theoretical. "Abstract." THE AMERICAN HERITAGE® DICTIONARY OF THE ENGLISH LANGUAGE 8 (3d ed. 1992).

and embody some "law of nature." *Diehr*, 450 U.S. at 189 n.12 ("To accept the analysis proffered by the petitioner would, if carried to its extreme, make all inventions unpatentable because all inventions can be reduced to underlying principles of nature which, once known, make their implementation obvious."); *Funk Bros. Seed Co. v. Kalo Co.*, 333 U.S. 127, 135 (1948) (Frankfurter, J., concurring) ("Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent."). The real question is whether the patent *claim* is directed to an idea or law of nature *in the abstract* or whether the claim recites *a practical application* of that idea or law. *Diehr*, 450 U.S. at 187; *id.* at 191; *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 868 (Fed. Cir. 2010) ("[T]he Supreme Court in *Bilski* refocused this court's inquiry into processes on the question of whether the subject matter of the invention is abstract"). This is hardly a binary question. Instead courts are tasked with deciding where a claimed invention falls along the continuum between a purely abstract idea or law and a clearly practical process.

Judge Learned Hand's "levels of abstraction" analysis in copyright may provide a helpful framework, by analogy, for deciding whether a patent claim is directed to an abstract idea or law of nature.[6] *Nichols v. Universal Pictures Corp.*, 45 F.2d 119 (2d

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[6] This Court has often used patent principles in analyzing copyright cases, and *vice versa*. *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2067 (2011) (citing *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913 (2005)); *eBay Inc. v. MercExchange LLC*, 547 U.S. 388 (2006).

Cir. 1930). In *Nichols*, Judge Hand was faced with a claim that one play infringed a copyright held on another play. Judge Hand reached his decision of no infringement by breaking the two works down into a "series of abstractions," with the highest levels of abstraction being unprotectable as representing "ideas." *Id.* at 121 ("otherwise the playwright could prevent the use of his 'ideas,' to which, apart from their expression, his property is never extended"). He noted that themes shared between the two plays were shared with innumerable other creative works and "no more susceptible of copyright than the outline of Romeo and Juliet." *Id.* at 122. In language strikingly similar to that used by this Court in giving examples of laws of nature that cannot be patented, Judge Hand explained that "[t]hese would be […] as little capable of monopoly as *Einstein's Doctrine of Relativity*, or Darwin's theory of the Origin of Species." *Id.* at 121 (emphasis added); *accord Chakrabarty*, 447 U.S. at 309.

Here, no one has rigorously identified the "abstract idea" or "law of nature" supposedly being preempted, *per se*. At the highest level of abstraction, the abstract idea at issue could be stated as follows: "Efficacy and toxicity of most drugs are dose-dependent, such that exposure to a drug below a certain level will lead to lower than desired efficacy and exposure above a certain other level will result in greater than desired toxicity." No one alleges, and with good reason, that Prometheus's claims are directed to this idea (or law) *per se*. However, it is helpful to take a step back and, following Judge Hand's analysis in *Nichols*, consider what lies at the clearly "abstract" end of the spectrum, since only the highest levels of abstractness should be barred from

patenting by § 101. *Research Corp.*, 627 F.3d at 868 ("[T]his court also will not presume to define 'abstract' beyond the recognition that this disqualifying characteristic should exhibit itself so manifestly as to override the broad statutory categories of eligible subject matter and the statutory context that directs primary attention on the patentability criteria of the rest of the Patent Act.").

Personalized medicine claims such as Prometheus's are often summarized as being directed to "(1) obtain[ing] test results and (2) think[ing] about them." *Lab. Corp. of Am. Holdings v. Metabolite Labs.*, 548 U.S. 124, 136 (2006) (Breyer, J., dissenting); Pet. Br. i (Prometheus's claim "covers observed correlations between blood test results and patient health"). This is slightly more concrete than the abstract idea stated above and, if Prometheus had claimed at this level of abstraction (*e.g.*, a process for determining response comprising measuring *any* metabolite levels in a patient and thinking about the results), such a claim would still likely be patent-ineligible.

This shortcut—of boiling a claim down to its "gist"—is not only improper under this Court's precedent, but it also seriously mischaracterizes the actual process claimed here. *Compare* Pet. Br. i ("a patent claim that covers observed correlations between blood test results and patient health") *with Diehr*, 450 U.S. at 188-89 ("It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis."). One need merely glance at *the claims themselves* to see that they are not so broad and abstract as to cover *any* act of testing for *any*

metabolite and then thinking about it. "[T]he claims recite *specific* treatment steps, not just the correlations themselves. And the steps involve a *particular* application of the natural correlations: the treatment of a *specific* disease by administering *specific* drugs and measuring *specific* metabolites." *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1355 (Fed. Cir. 2010) ("*Prometheus II*") (emphasis added).

The familiar pair of cases of *Flook* and *Diehr* help to further illustrate the continuum from abstractness to patent-eligibility. Flook's patent failed because it attempted to claim a mathematical formula for updating alarm limits *in the abstract*. *Diehr*, 450 U.S. at 191. "An 'alarm limit' is *simply a number*, and the Court concluded that the application sought to *protect a formula* for computing this number." *Diehr*, 450 U.S. at 186 (emphasis added). The patentee in *Flook* included post-solution steps (*e.g.*, replacing the old number with the number newly produced) as well as a field-of-use limitation (in processes "comprising the catalytic chemical conversion of hydrocarbons") in the claims. *Flook*, 437 U.S. at 589-90.

The Court, however, saw such post-solution steps and field-of-use limitations as illusory since neither the claims nor the specification gave any teaching on how the formula was especially suited to the process or even on how the formula might be used in such a process. *Diehr*, 450 U.S. at 186. The patent application did not explain how the variables used in the formula were to be selected, nor did the application "contain any disclosure relating to the chemical processes at work, the monitoring of process

variables, or the means of setting off an alarm or adjusting an alarm system. *All that it provides is a formula* for computing an updated alarm limit." *Diehr*, 450 U.S. at 186-87 (citing *Flook*, 437 U.S. at 586) (footnote omitted) (emphasis added). In other words, the claims were patent-ineligible because they were an example of "[a] competent draftsman […] attach[ing] some form of post-solution activity to [a] mathematical formula." *Flook*, 437 U.S. at 590.

In contrast, the claims in *Diehr* were directed to a process for curing rubber that made use of a mathematical formula. The patents and claims recited detailed information on the process for curing rubber, how the formula was applied in the process, and how the process variables were measured and calculated. *Diehr*, 450 U.S. at 178-79. Rather than a thinly veiled attempt to claim a mathematical formula *per se*, the claims in *Diehr* were clearly directed to an industrial process that used a formula in a beneficial way. *Id.*

The Prometheus claims are unlike the *Flook* claims and similar to the *Diehr* claims on every relevant point identified by the Court. Claim 46 is representative. Unlike *Flook*, Claim 46 does not seek to claim any natural law or phenomenon or idea *in the abstract* because: (1) the preamble and "wherein" clauses of Claim 46 impose meaningful limits by restricting it to a *specific* and practical application of the correlation (low level of abstraction); and (2) the specification includes detailed teachings on how the underlying correlation is specifically suited to use in the fields specified in the claims (more *Diehr* than *Flook*). *Prometheus II*, 628 F.3d at 1355.

B. The Prometheus Claims Are Patent-Eligible Because They "Necessarily Involve" a Machine or Transformation "In Conjunction With" a Correlation Step

Moving beyond *Flook* and *Diehr*, the Prometheus claims are patent-eligible because they necessarily involve a machine or transformation. *Prometheus II*, 628 F.3d at 1357. While this Court recently held that the "machine-or-transformation test" is not the exclusive test for patent-eligibility, the Court acknowledged that it is a "useful clue." *Bilski*, 130 S. Ct. at 3227.

The Federal Circuit found that the step of "determining the level of 6-thioguanine" in Claim 46 of the '623 patent "necessarily involves" the use of devices ("machines"), chemical reagents ("compositions of matter") and the transformation of patient samples. *Prometheus II*, 628 F.3d at 1357. These physical transformations recite defined test subjects (a subject having an "immune-mediated gastrointestinal disorder") and specific factors that are tested ("level of 6-thioguanine"). Finally, the test data generated by the claimed process "clearly represent physical and tangible objects," i.e., the concentrations of analytes, and are in fact transformed when applied to the correlation. *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008) (en banc) (discussing *In re Abele*, 684 F.2d 902 (C.C.P.A. 1982)). The application of such test data to the correlations recited in the claims for diagnostic purposes is a specific, practical application of these correlations. The claims *as a whole* recite a specific, practical and tangible application of the correlation.

Petitioner urges this Court to follow Justice Breyer's dissenting opinion in *LabCorp* by dissecting Prometheus's claims into two steps: "(1) obtain test results and (2) think about them," and then disregarding the first (transformative) step for § 101 purposes simply because that test step is in the prior art. *LabCorp*, 548 U.S. at 137 (Breyer, J., dissenting); Pet. Br. 37. However, this analysis clearly violates *Diehr*'s firm admonition that, for § 101 purposes, the claim "must be considered *as a whole*. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Diehr*, 450 U.S. at 188, 189 n.12, 193 n.15.

Petitioner's and the *LabCorp* dissent's dissection of the claims is doubly questionable because the transformations in the claims are necessary and "central to the purpose of the claimed process." *Prometheus II*, 628 F.3d at 1355 (quoting *Bilski*, 545 F.3d at 962). There can be no therapeutic optimization without the "determining" step. *Id.* at 1357. The determining and correlating steps work "in conjunction" to accomplish the diagnosis. *See Diehr*, 450 U.S. at 187 (finding patent-eligible a process that "admittedly employs a well-known mathematical equation" because the patentee did not "seek to pre-empt the use of that equation" but rather "only to foreclose from others the use of that equation *in conjunction with* all of the other steps in their claimed process.") (emphasis added).

C. This Court Has Repeatedly Stated That a Claim to a Process Need Not Explicitly Recite a Transformative Step to Be Patent-Eligible

While the Prometheus claims appear to explicitly recite a "transformation," *Amicus* urges this Court to reaffirm that they need not. As a plurality of this Court recognized in *Bilski*, much modern scientific and technological advancement involves the assembly and transmission of newly generated knowledge, including "advanced diagnostic medicine techniques." *Bilski*, 130 S. Ct. at 3227. Thus, it should not matter for purposes of patent-eligibility under § 101 whether the Federal Circuit in *Prometheus* construed the patent claims to require the physical process of measuring metabolite levels in a sample, or to necessarily involve such a physical measurement (*i.e.*, as a preceding step not explicitly recited but still necessary before any "determining" can be done). Certainly, the word "determining" does not *per se* imply any physical act of measuring, as this term is often used to refer to mental activities.[7] This ambiguity has unfortunately led some to interpret both *Prometheus* decisions as holding that *explicit* recitation of a physical transformation is *required* for patent-eligibility, when this Court in *Bilski* held that

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[7] *Compare Prometheus II*, 628 F.3d at 1357 ("Prometheus's asserted claims recite transformative […] 'determining' steps") *with In re Bilski*, 545 F.3d at 962-63 (discussing the CAT scan of *In re Abele*, with no clearly recited physical transformation, as meeting the machine-or-transformation test). The Federal Circuit in *Bilski* and *Abele* held that transforming data was sufficient to be a "transformation" and for patent-eligibility, so long as the data had some clear nexus to and represented something tangible. *In re Abele*, 684 F.2d at 908.

even the machine-or-transformation test was not the exclusive inquiry for § 101 patent-eligibility.

In so holding, this Court in *Bilski* repeated what it said in *Flook:* "[A] valid process patent may issue even if it does not meet [the machine-or-transformation test]." 130 S. Ct. at 3227 (quoting *Flook*, 437 U.S., at 588, n. 9); *accord Benson*, 409 U.S. at 71;*In re Abele*, 684 F.2d at 908. Even if they are not explicitly recited as required physical steps in the claimed process, the fact that these physically transformative activities must inherently take place before the claimed method can be practiced is sufficient to remove the claimed subject matter from the "abstract" realm and place it squarely in the real world of patent eligibility.

D. Looking for a Transformation, Explicitly Recited or Not, Interacting with a Correlation Accords with the European Approach and Will Incentivize Critical Domestic Investment

Under the European Patent Convention, discoveries, scientific theories and mathematical methods are excluded from the scope of patentable subject matter. *Eur. Pat. Conv.*, Art. 52(2)(a) (2000). In EPO G1/04, the European Patent Office Enlarged Board of Appeal considered whether a diagnostic method claim that includes a step of "purely intellectual exercise" falls within the scope of patent-eligible subject matter under the European Patent Convention. *See EPO* G1/04, p.19-20.[8] The Board

[8] The Enlarged Board characterized a typical medical diagnosis method to "include (i) the examination phase involving the collection of data, (ii) the comparison of these data with

held that "[t]he subject-matter of a claim including technical and non-technical features may satisfy the requirements of Article 52(1) EPC [predecessor to EPC 2000 Article 52(2)(a)] if the non-technical features interact with the technical features in order to bring about a technical effect." *EPO* G1/04, p.19 (citation omitted). This "interaction" rule resonates well with the notion of "in conjunction with" in *Diehr* and is easily workable. *Diehr*, 450 U.S. at 187. Under this rule, European patents have been routinely granted on medical diagnosis method claims like those at issue in this case. *See, e.g.*, *EPO* T310/99.

Failure to protect medical diagnosis claims similarly in the United States threatens to put the U.S. at a competitive disadvantage. *Bilski*, 130 S. Ct. at 3227 (expressing concern over "uncertainty as to the patentability of [...] advanced diagnostic medicine techniques" and other "inventions in the Information Age"). This disadvantage "is not theory but history." *Classen Immunotherapies, Inc. v. Biogen Idec*, Nos. 2006-1634 & 2006-1649, 2011 U.S. App. LEXIS 18126, at *49 (Fed. Cir. Aug. 31, 2011) (Rader, J., additional views). In "Additional views" reminiscent of Justice Frankfurter's prediction that "[a]rguments drawn from such terms [as 'laws of nature' …] could fairly

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(continued…)

standard values, (iii) the finding of any significant deviation, *i.e.* a symptom, during the comparison, and (iv) the attribution of the deviation to a particular clinical picture, *i.e.* the deductive medical or veterinary decision phase." *EPO* G1/04, p.18. The last step, *i.e.* the deductive medical decision phase, is often an intellectual exercise, and is of a non-technical nature. *Id.* at 19.

be employed to challenge almost every patent," *Funk Bros.*, 333 U.S. at 135 (Frankfurter, J., concurring), Judge Rader bemoaned "a rising number of challenges under 35 U.S.C. § 101." 2011 U.S. App. LEXIS 18126, at *45. However, the problem goes far beyond wasting judicial resources:

> In the past, this cause-effect relationship of eligibility restrictions and stifling innovation favored our country in, for example, biotechnology[,where,. . .] with some considerable blame on its eligibility doctrines, Europe lost innovation investment to the United States [and o]ur country became the world leader in biotechnology innovation.

Id. at 49, 50. Judge Rader's ominous warning has the very real potential of coming true for personalized medicine depending on the outcome of this case: "Nevertheless, the tide can turn against us, too." *Id.*

E. A Time-Limited Patent Monopoly On a Particular Diagnostic Use of a Particular Correlation Does Not Wholly Pre-empt that Correlation

One oft-cited concern over claims directed to fundamental principles in the abstract is that such claims "pre-empt" all uses of that principle. *Diehr*, 450 U.S. at 187; Pet. Br. i ("the patent effectively preempts use of the naturally occurring correlations"). Some worry that such claims would block all use of the basic tools of invention and innovation, which should be made freely accessible to promote technological advances. *See Benson*, 409 U.S. at 67; *see also LabCorp*, 548 U.S. at 128 (Breyer, J., dissenting). Though this may be a valid concern in

some cases, it simply does not apply to personalized medicine claims such as Prometheus's.

Properly limited personalized-medicine method claims such as these do not preclude the public from using the recited correlations for other purposes or from finding analogous correlations using the same analytes. *Prometheus II*, 628 F.3d at 1355 ("The Supreme Court's decision in *Bilski* did not undermine our preemption analysis of Prometheus's claims[, which] do not […] preempt natural correlations"). Prometheus did not attempt to claim the abstract idea of correlating drug metabolite levels to efficacy or toxicity. Instead these claims are directed to using a very specific correlation for "optimizing […] treatment of an immune mediated gastrointestinal disorder" and do not preclude the public from any other uses of the correlation, such as for optimizing therapeutic efficacy of 6-thioguanine-providing drugs (*e.g.*, 6-mercaptopurine and azathioprine) for treatment of leukemia [9] or kidney transplantation rejection.

Nor do they pre-empt the use of the correlation (1) for studying the correlation itself, *e.g.*, the mechanisms underlying the drug toxicity or efficacy; (2) for determining the types and degree of toxicity; or (3) for developing alternative genetic tests for predicting a patient's response to 6-thioguanine-

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[9] 6-Mercaptopurine is approved by the FDA as Purinethol® for treating acute lymphatic leukemia. *See* FDA, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, *available at* http://www.fda.gov/medwatch/SAFETY/2004/jul_PI/Purinethol_PI.pdf.

providing drugs. Through these diagnostic process claims, patentees are granted—in exchange for bringing these discoveries to the public as a whole—a time-limited, exclusive right to the concrete use of a particular correlation for the diagnosis of a particular medical condition. Nothing more.

Unlike Einstein's $E=mc^2$ and Newton's law of gravity, the correlations in medical diagnosis process claims such as the Prometheus claims have a qualitatively narrower spectrum of applicability, and thus exert much less impact on upstream scientific and technological research. Far from granting a monopoly on "basic tools" of a fundamental or upstream nature, such claims grant relatively narrow exclusivity over a downstream research endpoint that has matured into a process that is ready to be marketed for the benefit of the public.

F. Because There Are Numerous Possible Correlations for a Particular Disease Character, a Patent on a Particular Diagnostic Use of a Particular Correlation Incentivizes Scientists to Discover New Correlations and Develop Better Personalized Medicine Products

These patent claims do not "interfere with, or discourage, development and the further spread of useful knowledge," *LabCorp*, 548 U.S. at 128 (Breyer, J., dissenting). Rather, they stimulate innovation, create competition and spur the further spread of useful knowledge. *See State Indus., Inc. v. A.O. Smith Corp.*, 751 F.2d 1226, 1236 (Fed. Cir. 1985) ("One of the benefits of a patent system is its so-called 'negative incentive' to 'design around' a competitor's products, even when they are patented,

thus bringing a steady flow of innovations to the marketplace."); Peter Lee, *Patents, Paradigm Shifts, and Progress in Biomedical Science*, 114 YALE L.J. 659, 686-88 (2004). A basic understanding of molecular biology shows that personalized medicine is no exception to, and in fact exemplifies, this principle.

In the human body, all biological components—from individual genes to small molecules, proteins, cells, tissues and entire organs—work together through an array of interconnected biological pathways that facilitate communication among genes, molecules, and cells, to accomplish biological functions and properties of life (*i.e.*, response to stimuli, reproduction, growth and development, and maintenance of homeostasis). *See* National Institutes of Health, *Building Blocks, Biological Pathways, and Networks*, *available at* http://nihroadmap.nih. gov/buildingblocks/ (last visited Nov. 4, 2011). Each pathway may be comprised of thousands of macromolecules interacting with and influencing each other as well as members of other pathways. When functioning properly, these pathways maintain the human body as a dynamic but stable unit.

Disturbance of any one member of a pathway may lead to changes in not only other members of the same pathway but also members of other pathways, resulting in a disease or disorder. Likewise, a single disease or disorder can be associated with numerous changes in many pathways. *See generally*, Ali Torkamani *et al.*, *Pathway Analysis of Seven Common Diseases Assessed by Genome-Wide Association,* 92 GENOMICS 265 (2008). Therefore,

there can be numerous biomarkers correlating with a particular disease. Indeed, the primary goals of research and development in the field of personalized medicine are to discover such correlations and biomarkers and to use these to develop molecular diagnostic tests.

With so many possible correlations to the same disease, a patent monopoly on a particular diagnostic use of a particular correlation between one biomarker and a particular disease would not preclude scientists from discovering other, potentially better correlations between other biomarkers and the same disease. Just as in pharmaceuticals there are seemingly endless variations on a chemical compound that will still target the same enzyme (sometimes even better than the original compound), there are nearly infinite possible correlation combinations between biomarkers and diseases. As an illustration, more than four patented diagnostic tests, beside Onco*type* DX®, are currently commercially available for the same diagnostic purpose: Predicting a breast cancer patient's benefit from chemotherapy as well as her risk of recurrence. *See* Jeffrey S. Ross *et al.*, *Commericalized Multigene Predictors of Clinical Outcome for Breast Cancer*, 13 ONCOLOGIST 477 (2008). Other tests for the same diagnostic purposes are still being developed. *Id.*

When claims drawn to the use of a particular correlation for diagnosing a particular medical condition are made patent-eligible, the roadblock of such patent claims, together with the roadmap of the disclosure required to get a patent, will actually stimulate scientists to discover new correlations that can be used to design better diagnostic tests for the

same medical condition. As such, the Constitutional purpose of the patent law is served and society reaps the benefits. *See* Lee, 114 YALE L. J. at 686-88.

CONCLUSION

The decision of the Federal Circuit should be affirmed.

Respectfully submitted.

JAY Z. ZHANG
BENJAMIN G. JACKSON
MYRIAD GENETICS, INC.
320 Wakara Way
Salt Lake City, UT 84108

November 7, 2011

GREGORY A. CASTANIAS
Counsel of Record
JONES DAY
51 Louisiana Avenue, N.W.
Washington, D.C. 20001
(202) 879-3939
gcastanias@jonesday.com

Counsel for Amicus Curiae