No. 2010-1406

United States Court of Appeals
For the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, MD, ARUPA GANGULY, PHD, WENDY CHUNG, MD, PHD, HARRY OSTRER, MD, DAVID LEDBETTER, PHD, STEPHEN WARREN, PHD, ELLEN MATLOFF, M.S., ELSA REICH, M.S., BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, and KATHLEEN RAKER,

Plaintiffs-Appellees,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant, and

MYRIAD GENETICS, INC.,

Defendant-Appellant, and
(continued on inside cover)

Appeal from the United States District Court for the Southern District of New York, in case no.09-CV-4515, Senior Judge Robert W. Sweet

BRIEF FOR AMERICAN MEDICAL ASSOCIATION, AMERICAN SOCIETY OF HUMAN GENETICS, AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, AMERICAN COLLEGE OF EMBRYOLOGY, AND THE MEDICAL SOCIETY OF THE STATE OF NEW YORK AS *AMICI CURIAE* IN SUPPORT OF PLAINTIFFS-APPELLEES AND ARGUING FOR AFFIRMANCE

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December 6, 2010
(continued on inside cover)

(caption, continued)

LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, and MICHAEL K. YOUNG, in their official capacity as Directors of the University of Utah Research Foundation,

Defendants-Appellants.

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CERTIFICATE OF INTEREST

Counsel for *Amici* Medical Organizations certifies the following:

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

The American Medical Association, the American Society of Human Genetics, the American College of Obstetricians and Gynecologists, the American College of Embryology, and the Medical Society of the State of New York.

2. The name of the real party in interest represented by me is:

The American Medical Association, the American Society of Human Genetics, the American College of Obstetricians and Gynecologists, the American College of Embryology, and the Medical Society of the State of New York.

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

None.

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

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

As physicians, we encounter people at the happiest moments of their lives and at the most traumatic. Increasingly, each of those encounters—from conception to terminal disease—requires physicians to have access to genetic information about the patient to make correct diagnostic and treatment decisions. Genetic information is relevant to determining which disease a patient might be suffering from and which medication might benefit or harm that patient. The patent system should not interfere with such decisions, and if properly implemented it would not do so.

Amici medical organizations seek to provide this Court with insight into the adverse effects on medical care and innovation caused by gene patents. These adverse effects could and should have been avoided because genetic sequences and comparisons between sequences—including those covered by the Myriad patents at issue—have never been patent eligible inventions.

Amici are not criticizing the patent system as a whole. We routinely use patented inventions in our practices, such as pharmaceuticals and operating room

[1] The Parties have consented to the filing of this brief. No part of this brief was authored or funded by counsel for any Party, person, or organization besides *Amici* and their counsel. *Amici* believe they have no direct personal stake in the outcome of this case, but that *Amici's* members, along with the general public, may benefit from affirmance by avoiding the numerous harms and costs described herein.

tools. But gene patents are profoundly different from other patents. They limit access to products of nature, laws of nature, and information about those natural phenomena. They also interfere with physicians' use of abstract ideas and mental steps. This conflicts with long-standing principles of scientific and medical ethics that the sharing of natural scientific and medical information is a basic necessity for further advances in science, technology, and medical care.

Patents on gene sequences and on comparisons between a patient's gene sequence and a patented gene sequence affect physicians' practices differently than patents on pharmaceuticals or operating room devices. When a physician prescribes a medicine to a patient or uses a patented scalpel, he or she does not have to worry about patent infringement. The authorization and royalty are already built into the cost of the item the physician is recommending or using. But when a physician seeks to find out information about a patient's genetic makeup or compare a patient's gene sequence to a reference sample—even if these are merely conscious thoughts—the physician has to worry about whether he or she is infringing a patent. The physician cannot readily determine before potentially incurring liability whether the comparison will infringe and the physician cannot ethically refuse to perform the comparison. It could only harm patient care for a physician to stop, mid-examination or mid-operation, and be compelled to access a

patent database or call a patent lawyer to determine if his or her assessment of the patient's status infringes upon a gene patent.

Consequently, *Amici* medical organizations urge the Court to uphold the lower court's decision and to find the claims at issue in this case invalid. Although the U.S. Government also urges affirmance for claims applying to isolated and purified genetic sequences, its rationales for reversal for claims to cDNA would allow these harms to medical care and innovation to continue. Similarly, affirming solely on either the composition claims or the method claims will not adequately protect medical care and innovation. Accordingly, *Amici* urge the Court to establish clearly that not only isolated and purified genes but also cDNA, synthetic genetic materials lacking markedly different functions from naturally occurring gene sequences, and methods of comparing and analyzing genetic sequences are ineligible subject matter.

***Amicus Curiae* American Medical Association (AMA)** founded in 1847, is the largest professional association of physicians, residents and medical students in the United States. Additionally, through state and specialty medical societies and other physician groups seated in its House of Delegates, substantially all U.S. physicians, residents and medical students are represented in the AMA's policy making process. The objectives of the AMA are to promote the science and art of medicine and the betterment of public health. The AMA's Code of Ethics forbids

physicians from patenting medical procedures because these patents compromise patient care.

The AMA joins this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies. The Litigation Center is a coalition of the AMA and the medical societies of every state and the District of Columbia.

***Amicus Curiae* American Society of Human Genetics (ASHG)** is a non-profit, tax-exempt organization that consists of over 8,000 professionals in the field of human genetics including researchers, clinicians, academicians, ethicists, genetic counselors, and nurses whose work involves genetic testing. ASHG has studied the gene patent issue and found that patents on sequences and correlations interfere with research and medical care.

***Amicus Curiae* American College of Obstetricians and Gynecologists** is a private, non-profit, voluntary membership organization that consists of over 51,000 health care professionals dedicated to providing quality health care to women. More than ninety percent of Board-certified obstetricians and gynecologists in the U.S. are affiliated with the College. The patents at issue in this case interfere with the ability of the College's members to provide appropriate health care and undertake research.

***Amicus Curiae* American College of Embryology (ACE)** develops and maintains professional standards for embryologists. Its members offer a number of clinical services, including pre-implantation diagnosis—a technique used to test an embryo for genetic diseases before the embryo is transferred into the uterus of a woman. Its members are also involved in research on innovative treatments, such as embryonic stem cell research. Patents on gene sequences and correlations have impeded embryologists' ability to study complex cellular and genetic interactions, such as those related to organ development.

***Amicus Curiae* Medical Society of the State of New York (MSSNY)** is a voluntary association of approximately 24,000 licensed physicians, medical residents, and medical students in all specialties in New York. The patents at issue in this case interfere with the mission of MSSNY to provide high quality medical care to all people in the most economical manner.

SUMMARY OF ARGUMENT

Patents on gene sequences, DNA molecules, cDNA, and comparisons of gene sequences harm the practice of medicine and the pursuit of science. They interfere with diagnosis and treatment, quality assurance, access to health care, and scientific and medical innovation.

Non-patent incentives are fully adequate to encourage scientific and medical innovation, as demonstrated by the most comprehensive analysis and past practices regarding genetic test development. The examples supplied by Appellants' *Amici* only confirm the harms that the patent system causes when extended to genetics.

The U.S. Government has now admitted that it erred in issuing thousands of isolated and purified sequence claims without possessing authority to do so. This error has imposed untold costs on the health care system. It is time for it to end.

The patent claims on isolated gene sequences and cDNA should be invalidated, because they are products of nature that not only occur in nature but also lack markedly different functions when synthetically created through human intervention.

The patent claims on "comparing" and "analyzing" gene sequences improperly claim mental processes and thus ineligible abstract ideas, and even if data gathering steps were added to the claims those steps would constitute only trivial pre-solution activity and would not make the process claims patent-eligible.

ARGUMENT

I. Patents on Gene Sequences, DNA Molecules, cDNA, and the Comparison of Such Sequences Harm Medical Practice and Scientific Innovation.

Gene patents are being asserted against physicians across the country. Debra G.B. Leonard, *Medical Practice and Gene Patents: A Personal Perspective*, 77 Academic Medicine 1388 (2002). Physicians and researchers receive cease-and-desist letters to "stop conducting tests … developed for a neurodegenerative condition of the cerebellum, for hereditary hemochromatosis, for cystic fibrosis delta F508, and for Canavan's disease." Gina Shaw, *Does the Gene Patenting Stampede Threaten Science?*, 9 AAMC Reporter (2000). Like other gene patent holders, Myriad has manifested a clear intent to enforce its patent rights. Erik Stokstad, *Genetic Screen Misses Mutations in Women at High Risk of Breast Cancer*, 311 Science 1847 (2006).

Myriad's assertions about standing suggest that physicians and scientists have no reason to fear a patent infringement suit and thus have no standing to challenge the patents at issue. Appellants' Br. 20-28. In Australia, this is the case because Myriad returned its *BRCA1* patent to the public domain, where it belongs. IP Australia, 24 Australian Official Journal of Patents 91, 92 (Sep. 2, 2010). However, in the United States where Myriad continues to assert its *BRCA1* and *BRCA2* patents, physicians and scientists have reason to fear an infringement suit

from these and similar patents on isolated or purified gene sequences, cDNA, and medical and research uses of discovered genetic information.

A. Gene Patents Interfere with Diagnosis and Treatment.

Patents on gene sequences interfere with diagnosis and treatment. For example, a company has filed for patent protection on a genetic sequence that indicates whether patients will benefit from its asthma drug. The company, however, has said that, for the 20-year term of the patent, it will not allow anyone to use the sequence to determine whether its drug will help or harm patients. Geeta Anand, *Big Drug Makers Try to Postpone Custom Regimens*, Wall Street Journal, June 18, 2001, at B1. While such information is crucial to physicians and patients, the use of the sequence to identify people who would not benefit from the drug would diminish the market for the drug.

Patents on gene sequences have contributed to patients' deaths. Long QT syndrome is a disorder of the heart's electrical system that is characterized by irregular heart rhythms and a risk of sudden death. A gene associated with Long QT was patented and assigned to the University of Utah Research Foundation. U.S. Patent No. 6,207,383. The company with the exclusive license to the Long QT sequence went through corporate upheavals. For a two year period, the licensee did not offer diagnostic testing for Long QT syndrome. Other laboratories

had the capability and willingness to offer the test, but were forbidden to do so by the patent licensee. During this period at least one patient, age 10, died from her undiagnosed Long QT syndrome; her death could have been prevented had testing been available. *Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing: Hearing Before the Subcomm. on Cts., the Internet and Intell. Prop. of the H. Judicary Comm.*, 110th Cong. 40 (2007) (statement of Dr. Marc Grodman) [hereinafter "Grodman"].

B. Gene Patents Interfere with Quality Assurance.

Myriad's exclusive control over the use of the *BRCA1* and *BRCA2* sequences has led to the misdiagnosis of patients and has precluded the deployment of improved genetic tests. Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 JAMA 1379, 1386 (2006) (12% of the 300 people examined from high risk families had mutations that the Myriad tests missed). Women thus have made decisions about whether to forego surgery or other treatment based on tests that missed mutations. Further, no woman can get an independent second opinion about her condition before deciding to have her healthy breasts or ovaries removed in order to avoid cancer, because Myriad has exclusive use of the breast cancer gene sequences. As a result, women may have their breasts or ovaries removed

unnecessarily when they receive a false positive on a *BRCA1* or *BRCA2* test because they do not have access to an independent confirmatory test. *See, e.g.*, Judy Peres, *Genetic Testing Can Save Lives – but Errors Leave Scars,* Chicago Tribune, Sep. 26, 1999 (patient underwent unnecessary removal of ovaries based on erroneous *BRCA* genetic test result).

C. Gene Patents Interfere with Access to Health Care.

Patents on gene sequences and patents on the comparisons of gene sequences increase the costs of health care unnecessarily, making genetic tests inaccessible for many people and imposing the costs of unnecessary medical procedures due to false positive results on others. Because of the ability to charge royalties under patents on the *BRCA*1 and *BRCA*2 breast cancer genes, Myriad's test costs $3,000 (A3396), despite the existence of other labs willing to offer testing for one third of that cost. CBC News, *Ontario to Offer New Genetic Test for Breast, Ovarian Cancer* (Jan. 8, 2003), *available at* http://www.cbc.ca/health/story/2003/01/06/test_genetic030106.html. Patents on the Long QT genes drove the cost of the test to $5,400, when the test could have easily been undertaken for 75% less. Grodman, *supra*, at 39.

Technology will soon allow the sequencing of a person's entire genome of approximately 30,000 genes for $1,000 or less. Francis S. Collins et al., *A Vision*

for the Future of Genomics Research, 422 Nature 835, 846 (2003); Nicholas Wade, *Cost of Decoding a Genome Is Lowered*, The New York Times, Aug. 11, 2009, at D3. The patient can then take preventive measures to minimize his or her risk for disease. But testing all 30,000 genes at Myriad's royalty rate would cost over $45 million. Applying even a seemingly modest royalty of $100 per gene would total an unaffordable $3 million per test. Even with much lower royalty rates on many fewer genes, personalized gene analyses would be infeasible.

D. Gene Patents Interfere with Scientific and Medical Innovation.

Appellants and their *Amici* willfully ignore the volume of literature that has found that patents on genes actually harm research and innovation. Forty-nine percent of the members of the American Society of Human Genetics have had to limit their research due to gene patents. Isaac Rabino, *How Human Geneticists in U.S. View Commercialization of the Human Genome Project*, 29 Nat. Genetics 15 (2001). A survey of directors of laboratories that perform DNA-based genetic tests indicated that over half (53%) of the respondents had not developed a test for fear of infringing patents, and that one in four laboratories had stopped performing certain genetic tests because of patent restrictions or excessive royalty costs. Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. Molecular Diagnostics 3 (2003). SARS research was

impeded because of concerns about the patents on the genetic sequence of the SARS virus. James H.M. Simon et al., *Managing Severe Acute Respiratory Syndrome (SARS) Intellectual Property Rights*, 83 Bull. World Health Org. 707, 709 (2005).

Notably, *Amicus* BIO erroneously claims that "[a]rguments about stifling research also ignore the ... research exception." BIO Br. 32. However, under current Federal Circuit doctrine, the very narrow research exception that exists "for all practical purposes [is] a nullity." Janice M. Mueller, *The Evanescent Experimental Use Exemption from United States Patent Infringement Liability: Implications for University and Nonprofit Research and Development*, 56 Baylor L. Rev. 917, 980 (2004); *Madey v. Duke Univ.*, 307 F.3d 1351, 1362 (Fed. Cir. 2002).

II. Existing Non-Patent Incentives are Sufficient to Encourage Innovation in Genetics.

The possibility of patents serves to encourage innovation in many fields. But, simply put, patents are not necessary with respect to gene sequences and comparisons between sequences. Secretary [of Health and Human Services]'s Advisory Committee on Genetics, Health, and Society, *Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*, 30 (April 2010), *available at* http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf. Once gene sequence information is made public, moreover, existing incentives to provide medical care are already more than sufficient to encourage the development of tests and to perform comparisons to those genes.

Despite assertions by Myriad and its *Amici* that patents on gene sequences are necessary for the discovery and development of genetic diagnostic tests, genetic diagnostic tests have been routinely developed by clinical laboratories without the incentive of patents on gene sequences or correlations. *Id.* at 30-31. "[P]atents were not needed to develop genetic tests for hearing loss, SCA [spinocerebellar atrophy], breast cancer, LQTS [long-QT syndrome], Canavan disease, and HH [hereditary hemochromatosis]. Indeed, all of these tests were on the market before the test offered by the relevant patent-rights holder." *Id*. at 31.

Scientists were searching for and finding genes long before patents were available for them, and there is no evidence that the grant of gene patents (as opposed to the patent on the gene sequencing machine) facilitated this process. Scientists and doctors try to discover genes for a number of reasons—to help mankind, to aspire to Nobel Prizes, and to achieve academic advancement. When the Human Genome Project was undertaken to identify the sequence of the human genome at the cost of billions of taxpayer dollars, key researchers in the field at the time warned about the risks of granting intellectual property rights over genes. Leslie Roberts, *Who Owns the Human Genome?*, 237 Science 358 (1987). If scientists were allowed to "own" genes and reap financial rewards by having exclusive rights to any diagnostic or treatment technologies developed with the gene they discovered, they would be less likely to share copies of those genes or even to share information about them. Those harms have come to pass.

Moreover, many geneticists are eager to discover and sequence genes and to develop diagnostic tests without patenting either the genes or methods of comparing gene sequences. In a study of American Society of Human Genetics members, 61% of its members in industry, 78% of those in government, and 77% of those in academic science stated that they disapproved of patenting DNA. Rabino, *supra*, at 15.

Amici supporting Myriad assert that patents are needed to promote genetic innovations. BIO Br. 4; PhRMA Br. 17. However, none of these *Amici* actually provide evidence that the possibility of obtaining gene patents was necessary for the discovery of gene sequences and their correlation to breast cancer or other diseases, or for the discovery of new diagnostics or treatments for those diseases. Rather, the examples cited by these *Amici* actually prove the harm that such patents have caused. For example, *Amicus* BIO argues that the patenting of the hepatitis C genome was a success story. *See* BIO Br. 20. But it actually has been a disaster for public health, as the patent holder blocked the deployment of an inexpensive effective test developed by a small biotechnology company and, as a result, many patients have not been tested or timely treated. Letter from Martin Munzer to Xavier Becerra, U.S. Congressman (May 25, 2007).

Similarly, Myriad argues that the Taxol patent proves that patents on isolated products of nature are necessary for beneficial therapeutics to reach the market. Appellants' Br. 46. But Myriad is clearly mistaken, since patents were never granted on the compound isolated from the yew tree, but only on a means of administering it. Ken Garber, *Battle Over Generic Taxol Concludes, But Controversy Continues*, 94 J. Natl. Cancer Inst. 324 (2002); Patent 5,641,803; Patent 5,670,537. And even if there had been a patent on the isolated compound, it would not prove that the research to isolate Taxol required the patent incentive.

Even the genetic sequences at issue in this case would have been discovered without the patent incentive. The international Breast Cancer Linkage Consortium was fully engaged in sequencing the *BRCA1* gene in a cooperative effort and planned to make the sequence publicly available and not to patent it. Jordan Paradise, *European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for U.S. Patent Law and Public Policy: A Case Study of the Myriad Genetics' BRCA Patent Controversy*, 59 Food & Drug Law J. 133, 143-144 (2004); Phyllida Brown & Kurt Kleiner, *Patent Row Splits Breast Cancer Researchers*, New Scientist, Sept. 24, 1994, at 44. The consortium had already located the *BRCA1* gene on chromosome 17 (of the 23 human chromosomes), but as it was completing its work, Mark Skolnick, a member of the consortium, founded Myriad Genetics and sought a patent on the *BRCA1* gene. Paradise at 143.

The publicly-funded consortium did most of the work to identify the *BRCA1* gene. Moreover, Skolnick utilized over $5 million of taxpayer money in the form of a direct grant from the National Institute of Health to sequence the *BRCA1* gene. Bryn Williams-Jones, *History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing*, 10 Health Law J. 123, 131 (2002). A federal researcher for the National Institute of Environmental Health Sciences (NIEHS) in North Carolina also aided Myriad in its work. Rachel Nowak, *NIH in*

Danger of Losing Out on BRCA1 Patent, 266 Science 209 (1994). The public thus has paid for the work underlying Myriad's patents, yet is paying nearly two hundred million dollars more in royalties each year because of the patents at issue here.[2] And if Skolnick had not sought the patent, the gene sequence would have been put in the public domain.

III. The Government's Admitted Error of Granting Patents on Gene Sequences Has Needlessly Imposed Untold Costs on the Health Care System.

The United States now properly admits that the US Patent and Trademark Office (USPTO) never possessed authority to grant and thus has improperly granted numerous patents on isolated and purified genetic sequences. U.S. Br. 18. To justify its grant of genetic sequence patents, the USPTO relied on the 1873 grant of a patent to Louis Pasteur for a purified yeast and on a lower court decision upholding a patent for isolated and purified adrenaline. *Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001); *Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F. 95 (S.D.N.Y. 1911), *aff'd*, 196 F. 496 (2d Cir. 1912). But Pasteur never enforced his patent, so there was no judicial assessment of whether the patent was valid. Maurice Cassier, *Louis Pasteur's Patents: Agri-Food*

[2] In 2008, Myriad spent $32,340,000 to perform molecular diagnostic tests, and had revenue for their tests totaling $222,855,000. Form 10-K, submitted by Myriad Genetics, Inc., Commission file number: 0-26642, at 27 (Aug. 28, 2008).

Biotechnologies, Industry and Public Good, *in* Living Properties, 39 (2009) (Jean-Paul Gaudillere et al., eds.). Moreover, the Pasteur patent and *Parke-Davis* preceded the U.S. Supreme Court decision in *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931). As noted shortly thereafter by Pasquale J. Federico (later Commissioner of Patents and principal drafter of the 1952 Patent Act), the Supreme Court's decision in *American Fruit Growers* undermined the earlier Patent Office holding that isolated and purified natural materials might be patent eligible subject matter. Pasquale J. Federico, *Louis Pasteur's Patents,* 86 Science 327 (October 8, 1937) (citing *American Fruit Growers*). "A claim of this type would now probably be refused by the examiner, since it may now be doubted that the subject-matter is capable of being patented." *Id*.

The costs and harms resulting from these erroneous and unauthorized patent grants cannot be overstated. Billions of dollars have likely been spent by patients and the health care system due to this mistake. Gene sequence patents have prevented medical treatment and interfered with innovation. None of this should ever have occurred given the Supreme Court precedents. It is long past time to put an end to the grant of such patents, by following those precedents and clearly declaring gene sequence, cDNA, and comparison claims to be ineligible subject matter.

IV. Isolated Gene Sequences and cDNA Are Not Patentable Inventions under 35 U.S.C. § 101.

Patent eligibility is a "threshold test" to be applied before other requirements of the patent law are applied to the purported invention. *Bilski v. Kappos*, 130 S. Ct. 3218, 3221 (2010). A categorical threshold for eligibility preserves the public domain of "laws of nature, physical phenomena, and abstract ideas" that may not be privately owned. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). It also reduces burdens on the patent system and directs investment and innovation efforts towards the kinds of inventions that are the goal of the patent system.

Patents are not needed to incentivize the discovery of human genes or other physical phenomena, and patent law does not exist to reward the discovery of products of nature and laws of nature with exclusive rights to such discoveries. As the medical and scientific communities have long held, and as the patent law continues to reflect, to do so would be unethical. *See, e.g.*, American Medical Association, *Opinion 9.095—The Use of Patents and Other Means to Limit Availability of Medical Procedures* (adopted June 1995), *available at* http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion9095.shtml; 1 William C. Robinson, The Law of Patents for Useful Inventions 39 (Little, Brown 1890). Rather, such discoveries must remain "'free to all men and reserved exclusively to none,'" both to meet shared ethical commitments and to foster further scientific discovery and more rapid sequential

innovation. *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) (products of nature and laws of nature are the "basic tools of scientific and technological work").

For over 150 years, the products and processes of nature have not *legally* been patent eligible subject matter. *Bilski*, 130 S. Ct. at 3221 (citing *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 174 (1853)); *Chakrabarty*, 447 U.S. at 313 (stating that the relevant distinction for Section 101 patent eligibility is "between products of nature, whether living or not, and human-made inventions"). Myriad seeks to deny the very existence of this longstanding products of nature doctrine (Appellants' Br. 34), although the history is clear and indisputable, as the United States recognizes (U.S. Br. 13-14).

A. Isolated Gene Sequences Are Unpatentable Products of Nature.

"A new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter." *Chakrabarty*, 447 U.S. at 309. Just as removing a mineral from the surrounding rock and earth, or removing a plant from the surrounding flora and soil does not transform the mineral or plant (a product of nature) into patentable subject matter, "isolating" a genetic sequence does not make it patentable. Thus, the Supreme Court in *American Wood-Paper Co. v.*

Fibre Disintegrating Co. held that a patent claim directed to isolated cellulose (vegetable pulp) derived from straw, wood, and fibrous sources was not patent eligible subject matter. 90 U.S. (23 Wall.) 566, 594 (1874).

> There are many things well known and valuable in medicine or in the arts which may be extracted from divers[e] substances. But the extract is the same, no matter from what it has been taken. A process to obtain it from a subject from which it has never been taken may be the creature of invention, but the thing itself when obtained cannot be called a new manufacture.

Id. at 593-94.

As Myriad's own brief and Myriad's experts admit, an "'isolated' DNA" gene sequence is one that "has been removed from its naturally occurring environment," for example, from the cell and chromosome where it is found. Appellants' Br. 7; A4291; A4322.[3] The isolated gene sequence is the same string of nucleotides that exist as the gene sequence in the cell and chromosome. Extracting the gene sequence from the chromosome (or elsewhere in the cell) does not make the gene sequence any more patentable than isolating cellulose from wood. Myriad's claims covering gene sequences—claims 1, 2, 5, 6, 7 of patent

[3] Myriad thus contradicts its own efforts to suggest a narrow claim construction that "isolated DNA" sequences should be understood as "structurally distinct from native DNA." Appellants' Br. 7. Because genetic sequences with the non-coding regions removed naturally exist within cells, *see infra,* all of Myriad's claims to "isolated DNA" apply to sequences merely "removed" from their natural environment.

5,747,282; claims 1, 6, and 7 of patent 5,837,492; claim 1 of patent 5,693,473—are thus invalid, as they apply to such isolated sequences.

B. cDNA Are Unpatentable Products of Nature.

cDNA (complementary DNA) is DNA with the non-coding regions removed. The cDNA has the same nucleotide sequence as the coding regions (exons) of the naturally occurring DNA and can perform the same functions as a full nucleotide sequence or DNA molecule. It can produce the same protein that the full chromosomal gene produces. cDNA is single-stranded DNA that is complementary to naturally occurring mRNA. Stedman's Medical Dictionary 28th ed., 513 (2005). In fact, cDNA molecules *can be found existing naturally in the human body* and make up about seventeen percent of the human genome. *See* International Human Genome Sequencing Consortium, *Initial Sequencing and Analysis of the Human Genome*, 409 Nature 860, 880 (2001). Contrary to Myriad's assertion that DNA components of genes are not found to "float freely" in the body (Appellants' Br. 6), cDNA *does* exist in cells outside of the chromosomes. *See* Nicolas Gilbert et al., *Multiple Fates of L1 Retrotransposition Intermediates in Cultured Human Cells*, 25 Molecular and Cellular Biology 7780 (2005).

Even if Myriad had claimed only isolated DNA gene sequences having some of the non-coding DNA nucleotides removed, that would not have made Myriad's claimed "inventions" any less products of nature. And this would still be true even if cDNA did not occur without human intervention. As the Supreme Court held in *Funk Brothers*, isolating certain naturally occurring species of root nodule bacteria and recombining them in a different mixture did not convert the bacteria from ineligible "phenomena of nature" to eligible inventions. 333 U.S. at 130. To permit the patent for such isolated and recombined materials performing their natural functions would have required "allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Id.* at 132. Rather, combining naturally occurring exons to generate a cDNA would serve as mere "packaging." *Id*. at 131. Each exon, like each bacterial species in *Funk Brothers*, "has the same effect it always had.... [and] perform[s] in [its] natural way." *Id.* "They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Id.* Myriad's claims applicable to cDNA of the *BRCA1* and *BRCA2* genes—claims 1, 2, 5, 6 and 7 of patent 5,747,282; claims 1, 6, and 7 of patent 5,837,492; claim 1 of patent 5,693,473—should thus be invalidated.

C. Synthetically Created Versions of Genetic Materials that Lack Markedly Different Functions from Natural Products Are Not Patent Eligible Inventions.

Even though none of its claims use the term "synthesized," Myriad is apparently trying to avoid application of the products of nature doctrine by asserting that it is entitled to patents on the *BRCA1* and *BRCA2* genes because the claimed isolated DNA and cDNA were "synthesized." Appellants' Br. 7. The process of synthesis, routinely done today by biology students, was not invented by Myriad, but is merely a way to make a copy of a gene. The "synthesis" of DNA is the process of stringing together naturally existing nucleotides in the same order to function in the same way as the naturally occurring DNA. Michael J. Czar et al., *Gene Synthesis Demystified*, 27 Trends in Biotechnology 63 (2009).

Synthetic substances are not patentable unless they are "markedly different" from the products of nature from which they derive. *Chakrabarty*, 447 U.S. at 310. In *Cochrane v. Badische Anilin & Soda Fabrik*, the Supreme Court held that a patentee that had made and claimed a synthetic version of a naturally occurring dye (alizarine)—but having a brighter hue—did not claim a patent eligible invention but only an ineligible product of nature. 111 U.S. 293, 311 (1884). "Calling it artificial alizarine *did not make it a new composition of matter, and patentable as such, by reason of its having been prepared artificially*." *Id.* (emphasis added).

Even synthesizing a new material from a natural product by adding a new

and non-naturally occurring function is not sufficient to convert a product of nature into a patent eligible invention, unless the resulting product is markedly different from the natural product. *See American Fruit Growers*, 283 U.S. at 11 (addressing fruit preservation by coating with borax and rejecting as "not tenable" the Court of Appeals' holding that because "'the complete article is not found in nature'" it was patent eligible as an "'article of manufacture'") (citation omitted).

> Addition of borax to the rind of natural fruit does not produce from the raw material an article for use which possesses a *new or distinctive form, quality, or property*.... There is no change in the name, appearance, or general character of the fruit. It remains a fresh orange, fit only for *the same beneficial uses* as theretofore.

Id. at 11-12 (emphasis added). This was true even though the borax-treated fruit did not exist in nature, was the result of synthetic human action, and achieved a useful new function by preserving the fruit.

The isolated DNA and cDNA claimed in the Myriad patents do not possess a markedly different form, quality, or property than naturally occurring DNA. The traits that Myriad points to as being markedly different are the ability to detect natural "complementary sequence[s]" and to "'hybridize[]' to a DNA target." Appellants' Br. 7, 51. Even more than for preserved fruit, these uses rely entirely on the natural function of genetic DNA, *i.e.* its sequence.

The District Court below did not, as Myriad asserts, "erroneously divine[] from *Chakrabarty*" the "markedly different" standard. Appellants' Br. 41. This

requirement has been part of the Patent Act essentially since its inception. The Patent Act of 1793 stated that "simply changing the form or the proportions of any machine, or composition of matter, in any degree, shall not be deemed a discovery." Patent Act of 1793, Ch. 11, § 2, 1 Stat. 318-23 (Feb. 21, 1793). As the District Court held, even synthetically produced cDNA performs the same function as naturally occurring DNA coding for a particular protein and thus is not "markedly different" from its naturally occurring counterpart. A214-A228.

The U.S. Government errs when it suggests that any of the cDNA claims at issue might be valid. U.S. Br. 14-15. As noted above, cDNA is a product of nature and excluded as such. Further, products of nature, abstract ideas, and laws of nature, must be "'*assumed to be within the prior art,*'" even when their discovery by a patent applicant was the result of substantial investments and difficult scientific research efforts. *Bilski,* 130 S.Ct. at 3230 (emphasis added) (quoting *Parker v. Flook,* 437 U.S. 584, 594 (1978)); *O'Reilly v. Morse,* 56 U.S. (15 How.) 62, 115 (1853) (citing *Neilson v. Harford,* Web. Pat. Cases 295, 371 (1844)). Accordingly, even "synthetic" cDNA would reflect at most "token post-solution components" to the "prior art" natural DNA molecules and sequences. *Bilski*, 130 U.S. at 3231.

Since the DNA molecules, as well as the exon sequences used in cDNA, are products of nature and as they must be treated as prior art, any "synthetic" cDNA

would *necessarily* be obvious as well as being ineligible under Section 101. *See Dann v. Johnston*, 425 U.S. 219, 228 (1976) (reiterating the need to evaluate whether the difference between the prior art and the claim is "sufficient to render the claimed subject matter unobvious"). Accordingly, holding synthetic cDNA claims categorically ineligible under Section 101 will not cause *any* hardship to the biotechnology industry, because they should be found obvious in any case.

D. Section 103(b) Does Not Address the Patent Eligibility of Nucleotide Sequences.

Myriad seeks to rely on Section 103(b) to argue that Congress "thought DNA molecules were patent eligible," analogizing to the Supreme Court's focus on Section 273(a)(3) in its *Bilski* opinion. Appellants' Br. 32; 130 U.S. at 3228. However, Myriad omits from its discussion the relevant language and purpose of Section 103(b), which demonstrate that Congress had no intent regarding what, if any, nucleotide sequences were patent eligible. Rather, Section 103(b) addresses only the *obviousness* of "biotechnological process[es] using or resulting in a composition of matter that is novel under Section 102 and nonobvious under subection (a)." 35 U.S.C. § 103(b)(1). The section further defines "biotechnological process" to include *methods* of altering cells to alter their expression of an "exogenous" or "endogenous" "nucleotide sequence." *Id.* § 103(b)(3)(A). Nothing in this language expresses anything more than that

Congress recognized that cells could contain native or introduced genetic material and that patents could issue for non-obvious *methods* of affecting their expression. Further, Congress made clear that the compositions used in or resulting from the process must themselves be patented or patentable, as they must either be contained in the same patent or set to expire at the same time. *Id.* § 103(b)(2). This recognition by Congress that *patentable* compositions may be used in or produced by an otherwise obvious process says absolutely nothing about *what* compositions *are* patentable.

V. Methods of Comparing and Analyzing Genetic Sequences Are Ineligible Subject Matter.

Myriad's method claims are extremely broad, and on their face are not limited to any steps other than "comparing" or "analyzing" genetic sequence information—however that information is obtained. Isabelle Huys et al., *Legal Uncertainty in the Area of Genetic Diagnostic Testing*, 27 Nature Biotechnology 903, 907 (2009) (describing Myriad Patent 6,033,857 as a "blocking patent" and claims 1-8 as "almost impossible to circumvent"). Myriad has not invented a new machine to determine the presence of a mutation in a gene, nor has Myriad invented a new method of determining the existence of a mutation in a gene. Yet, Myriad's method claims on "comparing" or "analyzing" genetic sequences cover the use of any and all techniques (none of which Myriad invented) to determine the

presence of a mutation from the "normal" *BRCA1* and *BRCA2* genes, including by visually inspecting the sequence data (however obtained). In doing so, the method claims prohibit the use of the very information that the "inventors" disclosed to the public as the "quid pro quo" for obtaining patent rights. *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 161 (1989). The "analyzing" claims, moreover, may be infringed merely by reading and thinking about the sequence data disclosed in the patent. The patent system was never designed to allow such claims.

If a technique is developed to enable scientists to sequence and read DNA in its completely natural state while it exists in the body, that technique would be covered by these method claims. In fact, although Myriad argues that someone cannot perform their method by merely analyzing or comparing the sequence data (Appellants' Br. 58), a software program already has done just that. Steven Salzberg and Mihaela Pertea have created and made available to the public free of charge a software program that will allow users to search the *BRCA1* and *BRCA2* genes for 68 known cancer-causing mutations. Steven Salzberg and Mihaela Pertea, *Do-it-yourself Genetic Testing*, 11 Genome Biology 404 (2010). This software is performing the "comparing" and "analyzing" of sequences that are claimed in Myriad's method claims. This example highlights how broad Myriad's claims really are: using software to compare raw sequence data generated by a

sequencer infringes the claims. In fact, Salzberg and Pertea managed to practice the method claims without actually collecting the tissue from an individual, or "isolating" the gene, or sequencing the gene.

Myriad's method claims are invalid because no limitations are included on how the information that the patent discloses is to be obtained or used. Myriad's claims thus encompass physicians' and researchers' thoughts, speech, and written expression, interfering with diagnosis, research, and education.[4] The District Court correctly found these claims to be directed to ineligible subject matter.

Mental processes are not patentable. *Flook*, 437 U.S. at 589; *Benson*, 409 U.S. at 67. Myriad's method claims recite only an ineligible mental process. "'Analyzing' or 'comparing' would be understood by one of ordinary skill in the art to mean looking at the sequence to determine its characteristics, or looking at two or more things to determine if there is a difference." A2480. Comparing two things to determine a difference is a process that has been performed by man for millennia and takes place entirely in the mind.

Further, these claims are ineligible as laws of nature. The claims add nothing of significance to the medical fact that a mutation in the *BRCA1* or *BRCA2* genes increases the likelihood that a person will develop breast or ovarian cancer.

[4] *Amici* agree with the Plaintiffs' argument in the District Court and on appeal that the patents at issue violate the First Amendment.

Claiming the medical fact as a process of mentally recognizing it does not change its character. *See Flook*, 437 U.S. at 590 (skill of the draftsman cannot "transform an unpatentable principal into a patentable process"). While this medical fact may have been previously unknown, it has always existed; Myriad may have discovered it, but did it not invent it (and, as noted above, it must be treated as if it were in the prior art). Myriad can no more prevent people from using the fact by thinking than Bilski could prevent people from employing the abstract idea of hedging risk. *Bilski*, 130 S.Ct. at 3231.

Even if Myriad's claims were to be construed to require data gathering to perform the patented comparison, the Supreme Court just reiterated that, "*Flook* rejected '[t]he notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process.'" *Bilski*, 130 S.Ct. at 3230 (quoting *Flook*, 437 U.S. at 590). Similarly, this Court held in *In re Grams* that trivial pre-solution activity of performing a clinical test and using data from the test to determine whether an abnormality exists is not patentable subject matter. 888 F.2d 835, 837-41 (Fed. Cir. 1989). Such data gathering steps would constitute only "token post-solution components," just like the "use of well-known random analysis techniques to help establish some of the inputs into [Bilski's] equation." *Bilski*, 130 S.Ct. at 3231. Myriad's method claims—claim 1 of patent 5,709,999; claim 1 of patent 5,710,001; claim 1 of patent

5,753,441; claims 1 and 2 of patent 6,033,857; and claim 20 of patent 5,747,282—are thus invalid.

CONCLUSION

One cannot patent "laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). For the foregoing reasons, the Court should affirm the District Court's holding that all of the claims at issue are ineligible under Section 101. It is crucial to patient care and to medical research that the natural biological materials and basic scientific information that Myriad has sought to propertize be freely shared, used, and analyzed.

Dated: December 6, 2010

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I certify that:

1. This brief complies with the type-volume limitation of the Federal Rules of Appellate Procedure 29(d) and 32(a)(7)(B) and Federal Circuit Rule 32(b), in that the body of this brief – not including the cover page, table of contents, table of authorities, Appendix, and certificates –contains 6892 words as determined by Microsoft Word 2007, including the statement of interest, summary of argument, headings, footnotes, quotations, signature lines, and date.
2. This brief complies with the type face requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared using Microsoft Office Word 2007 in a proportionally spaced typeface: Times New Roman, font size 14.

Dated: December 6, 2010

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CERTIFICATE OF SERVICE

I certify that on this 6th day of December, 2010, I caused two copies of the foregoing Brief for Amici Curiae American Medical Association et al. to be sent by U.S. mail, postage pre-paid to each of the following counsel of record for the following parties and amici:

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