No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

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

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BRIEF OF *AMICI CURIAE* AMERICAN MEDICAL ASSOCIATION, AMERICAN SOCIETY OF HUMAN GENETICS, AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, AMERICAN OSTEOPATHIC ASSOCIATION, AMERICAN COLLEGE OF LEGAL MEDICINE, AND THE MEDICAL SOCIETY OF THE STATE OF NEW YORK IN SUPPORT OF PETITIONERS

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Amici are organizations of health care professionals. Their members number in the hundreds of thousands and they provide health care across the country.

Genetic information is integral to health care professionals' determination of which diseases a patient might be suffering from and which treatments might benefit or harm that patient. Patents on human genes interfere with health care professionals' ability to provide appropriate care to their patients. These patents inhibit, rather than encourage, scientific research and technological innovation. These adverse effects could and should have been avoided because human genes are not patentable subject matter.

Amicus Curiae **American Medical Association (AMA)**, a non-profit organization, is the largest professional association of physicians, residents, and medical students in the United States. The AMA joins this brief on its own behalf and as a

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[1] No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No party or entity other than *amici*, their members, or their counsel, made a monetary contribution to this brief's preparation or submission. Counsel of record received timely notice of the intent to file this brief under Supreme Court Rule 37. Petitioners have filed a letter with the Clerk of the Court granting consent to the filing of any and all *amicus curiae* briefs. Respondents' consent has been filed with the Clerk of the Court.

representative of the Litigation Center of the American Medical Association and the State Medical Societies.

***Amicus Curiae* American Society of Human Genetics (ASHG)** is a non-profit organization of over 8,000 professionals in the field of human genetics including researchers, clinicians, academicians, and counselors.

***Amicus Curiae* American College of Obstetricians and Gynecologists (ACOG)** is a non-profit organization of over 55,000 health care professionals dedicated to providing quality health care to women. Over 90% of Board-certified obstetricians and gynecologists in the U.S. are affiliated with ACOG.

***Amicus Curiae* American Osteopathic Association (AOA)**, with over 44,000 members, is the largest professional association of osteopathic physicians. The AOA promotes osteopathic medicine, a holistic approach to prevent, diagnose, and treat illness, disease, and injury.

***Amicus Curiae* American College of Legal Medicine (ACLM)** is a non-profit professional society comprised primarily of members holding degrees in both medicine and law. The ACLM serves medical and legal professionals and advises health policymakers.

***Amicus Curiae* Medical Society of the State of New York (MSSNY)** is a voluntary association of approximately 21,000 licensed

physicians, residents, and medical students in all specialties in New York.

SUMMARY OF THE ARGUMENT

Patents on human genes impede the provision of health care, thwart public health objectives, shackle innovation, and violate ethical tenets. Patents are not needed to create an incentive for the discovery of human genes, and patent law does not exist to reward such scientific and medical discoveries.

Human gene patents—in this case, Myriad's claims over isolated DNA and cDNA—conflict with this Court's jurisprudence on subject matter patent eligibility, which holds that "laws of nature, natural phenomena, and abstract ideas" are not patentable subject matter. *Mayo Collaborative Services v. Prometheus Labs,* 132 S. Ct. 1289, 1293 (2012).

Myriad did not invent the DNA sequences covered by its patents; it has only removed them from people's bodies and taken them out of the cellular environment using common, long-standing techniques. Nor has Myriad invented any chemical or mechanical methods of determining whether there is a mutation in a breast cancer gene. Rather, what the patentee claims to have discovered are pre-existing, naturally-occurring genetic sequences and a natural relationship between certain mutations and breast cancer.

Myriad now suggests that even if its claims do not meet the requirements of patent law, the claims should be held valid due to reliance on long-standing patent practice. This argument is both factually and legally flawed. At the time Myriad sought its patent,

the scientific and legal communities were in agreement that patents on genetic sequences were legally inappropriate and morally indefensible.

Are human genes patentable? Human genes are products of nature. Neither the breaking of the chemical bonds that incorporate specific sequences into the full genome nor the removal of non-coding regions from the naturally occurring gene create a new, markedly different composition of matter that merits the protection of patent law.

ARGUMENT

I. PHYSICIANS' AND RESEARCHERS' ACCESS TO HUMAN GENE SEQUENCES IS VITAL TO HEALTH CARE AND RESEARCH.

A person's genetic sequences hold a vast array of information relevant to his or her health. They can indicate a predisposition to disease, as well as pinpoint a diagnosis and provide guidance regarding what treatments might be beneficial (or risky) for that person. Genetic sequence information can mean the difference between life and death in the diagnosis and treatment of patients.

The benefits of genetic testing are not limited to people with rare diseases. Genetic factors contribute to the leading causes of death: cancers of all types, heart disease, hypertension, Alzheimer's, diabetes, susceptibility to infectious diseases (e.g. the flu), kidney disease, and asthma. Richard A. King, Jerome I. Rotter, and Arno G. Motulsky, The Genetic Basis of Common Diseases (2d ed. 2002). Even with respect to the narrow range of diseases that do not have a known genetic component, genetic testing has a role in determining how well patients will metabolize and respond to proposed medications.

Francis Collins, now director of the National Institutes of Health, said:

> By 2020, the impact of genetics on medicine will be even more widespread. The pharmacogenomics approach for

> predicting drug responsiveness will be standard practice for quite a number of disorders and drugs. . . . By 2020, it is likely that every tumor will have a precise molecular fingerprint determined, cataloging the genes that have gone awry, and therapy will be individually targeted to that fingerprint.

Francis S. Collins and Victor A. McKusick, *Implications of the Human Genome Project for Medical Science*, 285 Journal of the American Medical Association 540, 544 (2001). The benefits of access to genetic sequences are extensive, but patents on human genes thwart the realization of these benefits.

A. Patents on Human Genes Interfere with Diagnosis and Treatment of Patients.

A patent on the genetic sequence of a human gene grants the patent holder complete control over the use of that sequence for the life of the patent. The patent holder can forbid health care providers from using even unpatented methods to learn the sequence of a patient's gene. The patent holder can demand whatever royalty it sets from the person who seeks to learn his or her genetic sequence or it can completely prohibit a person from learning his or her own sequence.

Gene patent holders have prevented physicians and laboratories from offering genetic

testing for medical conditions such as breast cancer, hearing loss, Alzheimer's, Long QT syndrome, Canavan disease, leukemia, hemochromatosis, and neurodegenerative disorders. 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*, 40-42 (2010) [hereinafter "SACGHS"]; Debra G.B. Leonard, *Medical Practice and Gene Patents: A Personal Perspective*, 77 Academic Medicine 1388 (Dec. 2002).

Myriad's patents on the BRCA1 and BRCA2 gene sequences give it exclusive control over all previously and subsequently discovered means of testing for inheritable BRCA1 and BRCA2 breast cancer mutations. Myriad's exclusive control 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 Journal of the American Medical Association 1379, 1386 (2006) (12% of the 300 people examined from high risk families had mutations that the Myriad tests missed).

The patenting of the BRCA1 and BRCA2 genes in the United States means that Americans must undergo tests that are inferior to and more costly than those available in other countries. In France, for example, a physician found a breast cancer gene mutation in an American family that the Myriad test had missed. Sophie Gad et al., *Identification of a Large Rearrangement of the BRCA1 Gene Using Colour Bar Code on Combed DNA in an American*

Breast/Ovarian Cancer Family Previously Studied by Direct Sequencing, 38 Journal of Medical Genetics 388, 389 (2001). Similarly, in countries where the Alzheimer APOE gene sequence and the hemochromatosis gene sequence were *not* patented, researchers found previously unknown mutations. *Gene Patents and Other Genomic Inventions: Hearings Before the Subcommittee on Courts and Intellectual Property of the House Committee of the Judiciary*, 106th Congress, 121-127 (2000) (statement of Dr. Jon F. Merz). If Myriad's patent claims over the BRCA1 and BRCA2 genes are invalidated, competition from other laboratories would allow the development of better tests. Swisher Decl. ¶¶ 24-26.

In this case, because Myriad has exclusive use of the BRCA1 and BRCA2 gene sequences, no woman in America can get an independent second opinion about her condition before deciding to have her healthy breasts or ovaries removed in order to avoid cancer. As a result, women may have their breasts or ovaries removed unnecessarily when they receive a false positive result 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, September 26, 1999, at 1. Even when surgery is not performed, a false positive result could lead to a lifetime of medical testing and prophylactic treatment and fear that other family members may also be at risk for cancer. Myriad's exclusive control of the BRCA1 and BRCA2 gene sequences also restricts men's access to diagnostic testing. Although breast cancer is rarer in men,

mutations in the BRCA genes of men do increase the risk of male breast cancer as well as prostate and pancreatic cancer.

Patents on genetic sequences have even led to the death of patients, as in the case of Long QT syndrome, a disorder of the heart's electrical system that is characterized by irregular heart rhythms and a risk of sudden death. The disease can be treated with an implanted defibrillator. A genetic sequence associated with Long QT was patented and assigned to the University of Utah Research Foundation. U.S. Patent No. 6,207,383. For a two-year period, the exclusive licensee did not offer diagnostic testing for Long QT syndrome. Other laboratories had the capability and willingness to assess whether patients had a potentially fatal mutation of the Long QT gene, but were prevented from doing so due to the patent on the genetic sequence. During this period at least one patient, a 10-year-old girl, died from undiagnosed Long QT syndrome. Her death could have been prevented if the isolated genetic sequence had not been patented. *Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing: Hearing Before the Subcommittee on Courts, the Internet and Intellectual Property of the House Judicary Committee*, 110th Congress 40 (2007) (statement of Dr. Marc Grodman).

The promise of pharmacogenomics—the ability to test a patient's genetic sequence to determine whether a treatment might be helpful or deadly—has also been undermined by the patenting of genetic sequences. A company filed for patent protection on a genetic sequence that indicates whether patients

will benefit from its asthma drug. For the 20-year term of the patent, the company will not allow anyone to analyze any patient's version of that gene sequence to determine whether its asthma drug will help or harm patients. Geeta Anand, *Big Drug Makers Try to Postpone Custom Regimens*, The Wall Street Journal, June 18, 2001, at B1. Even though such information is crucial to physicians and patients, the use of the sequence to identify people who would not benefit from a drug would diminish the market for the drug.

Patents on genetic sequences also interfere with multiplex testing, where the sequences of several genes (or even a person's entire genome) are tested at once. SACGHS at 49. For example, as many as 80 genes can indicate a predisposition to asthma. G. Malerba and P.F. Pignatti, *A Review of Asthma Genetics: Gene Expression Studies and Recent Candidates*, 46 Journal of Applied Genetics 93 (2005). For a complete diagnosis, all the relevant genetic sequences could be analyzed in one test. But genetic sequence patents preclude a single test from being used. Because some genetic sequence patents are exclusively licensed, a patient's tissue sample must be sent to multiple laboratories, increasing costs and introducing additional chances of error.

B. Patents on Human Genes Increase the Cost of Genetic Testing.

Patents on gene sequences unnecessarily increase the costs of health care, making genetic tests inaccessible for many people and imposing costs on others of unnecessary medical procedures due to

false positive results. Because of the ability to charge royalties under patents on the BRCA1 and BRCA2 breast cancer genes, Myriad's test costs $3,000 (Answer to Complaint at 12 (S.D.N.Y. Nov. 20, 2009)), despite the existence of other laboratories willing to offer testing for one third of that cost. *Ontario to Offer New Genetic Test for Breast*, *Ovarian Cancer*, CBC News, Jan. 8, 2003, 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.

The technology exists to allow the sequencing of a person's entire genome of approximately 20,000 genes at an affordable rate, so that the person could take steps to prevent the disease. "The goal of completely sequencing a human genome for $1,000 is in sight." W. Gregory Feero, Alan E. Guttmacher, and Francis S. Collins, *Genomic Medicine – An Updated Primer*, 362 New England Journal of Medicine 2001, 2008 (2010). However, patents on genetic sequences impede the deployment of a whole genome analysis for patients. Sulston Decl. ¶ 38; Ledbetter Decl. ¶ 24. Technologies suitable for whole genome analysis require the use of isolated gene sequences. *See, e.g.,* Pauline C. Ng and Ewen F. Kirkness, *Whole Genome Sequencing,* 628 Methods Molecular Biology 215, 216 (2010). Even under the conservative estimate that 3% of existing gene sequence claims would block genetic diagnostic testing, "a full-genome sequence analysis would still infringe several hundred patents." Robert Cook-Deegan and Christopher Heaney, *Patents in*

Genomics and Human Genetics, 11 Annual Review of Genomics and Human Genetics 383, 414 (2010).

Testing all 20,000 of a person's genes at the Myriad BRCA rate would convert a test that could be done for $1000 to one that cost over $37 million. Applying even a seemingly modest royalty of $100 per gene would result in an unaffordable $2 million royalty per test. If the decision of the Court of Appeals for the Federal Circuit is upheld, physicians will be unable to provide meaningful analysis and comprehensive genetic information to patients.

C. Patents on Human Genes Impede Innovation.

Patents on "isolated" DNA impede innovation. Any research or diagnosis done on a gene from a patient's body is controlled by the patent holder because research and diagnosis cannot be undertaken without "isolating" the DNA from the body. Myriad has stopped research involving BRCA1 and BRCA2 at major universities such as Yale. Kimberly Blanton, *Corporate Takeover Exploiting the US Patent System,* Boston Globe Magazine, Feb. 24, 2002, at 10.

Myriad has misrepresented the ability to invent around its patent claims by arguing that there are alternative technologies for determining a patient's predisposition to developing breast and ovarian cancer that do not involve the use of isolated DNA. Myriad Br. at 26 (S. Ct. Oct. 31, 2012). Myriad claims that random ("shotgun") sequencing, single-molecule sequencing, nanopore sequencing,

protein truncation testing, and gene expression profiling can be performed without infringing Myriad's patent claims. Myriad Br. at 5-7 (S. Ct. Oct. 31, 2012). However, each of these technologies requires the use of isolated DNA controlled by Myriad's patents.

The term "isolated" is defined broadly in Myriad's patents: "the term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems." U.S. Patent No. 5,747,282. The technologies cited by Myriad require that a DNA sequence is removed from its naturally occurring environment during sequencing, that a DNA sequence separate from its naturally occurring environment is assembled during sequencing, or that cDNA is used while testing for an expression profile. Pauline C. Ng and Ewen F. Kirkness, *Whole Genome Sequencing*, 628 Methods Molecular Biology 215, 216 (2010); John Eid et al., *Real-Time DNA Sequencing from Single Polymerase Molecules,* 323 Science 133 (2008); Johan T. Den Dunnen and Gert-Jan B. Van Ommen, *The Protein Truncation Test: A Review*, 14 Human Mutation 95, 96 (1999); Asher Y. Salmon et al., *Determination of Molecular Markers for BRCA1 and BRCA2 Heterozygosity Using Gene Expression Profiling*, 6 Cancer Prevention Research 1, 2 (2013). All those approaches are covered by the Myriad patent claims.

Patents on human genes in general, and Myriad's patents in particular, thwart rather than

promote innovation. Over half (53%) of laboratory directors say they have been impeded from developing tests due to gene patents. Cho Decl. ¶ 10; Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 Journal of Molecular Diagnostics 3 (2003). Moreover, in the face of threats and the potential costs of a suit for patent infringement, researchers may elect to use limited resources elsewhere rather than build on already useful research. This sort of over-deterrence hinders the normal process of scientific advances.

Patent law is supposed to be a bargain in which the patent holder gets a time-limited exclusive right to make, use, or sell a claimed invention of proportional scope to the inventive contribution to the field, in exchange for publishing in the patent the description of the invention that all can use to further develop the frontiers of science and technology. *See generally* Suzanne Scotchmer, *Standing on the Shoulders of Giants: Cumulative Research and the Patent Law,* 5 Journal of Economic Perspectives 29 (1991). However, the system breaks down when a patent is granted for information itself—such as the sequence of a gene. That patent gives the holder a right to prevent others from using the disclosed information entirely.

D. Existing Non-Patent Incentives Are Sufficient to Encourage Innovation in Genetics.

Myriad argues that patents are necessary to encourage innovation (such as the discovery and

isolation of genetic sequences). Myriad Supp. Br. at 16-18 (Fed. Cir. June 15, 2012). But the majority of geneticists are willing to undertake the research to discover genes and develop genetic tests without the possibility of a patent. In fact, in a study of ASHG members, 61% of those in industry, 78% of those in government, and 77% of academic scientists stated that they disapproved of patenting DNA. Isaac Rabino, *How Human Geneticists in U.S. View Commercialization of the Human Genome Project*, 29 Nature Genetics 15 (2001).

"[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." SACGHS at 31.

Amici supporting Myriad also assert that patents are needed to promote genetic innovations. Amici Curiae Br. for Biotechnology Industry Organization and Association of University Technology Managers at 4 (Fed. Cir. Oct. 29, 2010) ("BIO Br."); Amicus Curiae Br. for Pharmaceutical Research and Manufacturers of America at 17 (Fed. Cir. Oct. 24, 2010). However, none of these *Amici* provide any actual 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. In fact, the examples cited by these *Amici* 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. at 20. But it actually has been a disaster for public health because 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 received timely treatment. 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. at 46 (Fed. Cir. Oct. 22, 2010). But Myriad is clearly mistaken, since patents were never granted on the compound isolated from the yew tree (Taxol), but only on a means of administering it. Ken Garber, *Battle Over Generic Taxol Concludes, But Controversy Continues*, 94 Journal of the National Cancer Institute 324 (2002); U.S. Patent No. 5,641,803; U.S. Patent No. 5,670,537. Furthermore, 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 identifying 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, 59 Food & Drug Law Journal 133, 143-144 (2004); Phyllida Brown & Kurt Kleiner, *Patent Row Splits Breast Cancer Researchers*, New Scientist, Sept. 24, 1994, at 44. The publicly-funded consortium did most of the work to identify the BRCA1 gene, but shortly before it completed its work, Mark Skolnick, a member of the consortium, founded Myriad Genetics, and sought a patent on the BRCA1 gene, in violation of the goals of the Consortium. Paradise at 143.

Skolnick utilized over $5 million of taxpayer money (a grant from the National Institutes of Health) and relied on the aid of federal researchers 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 Journal 123, 131 (2002). Rachel Nowak, *NIH in Danger of Losing Out on BRCA1 Patent*, 266 Science 209 (1994). The public thus paid for the work underlying Myriad's patents, yet is paying over $400 million more in royalties each year because of the patents at issue here.[2] If Skolnick had not sought the patent, the gene sequence would have been placed in the public domain.

A similar situation occurred with BRCA2. Myriad collaborated with Dr. Michael Stratton of the Institute for Cancer Research, London, and other researchers. Stratton ended the collaboration upon learning of Myriad's plans to patent the gene. The

[2] In 2012, Myriad spent $51,500,000 to perform molecular diagnostic tests, and gained revenue for their tests totaling $472,390,000. Form 10-K, submitted by Myriad Genetics, Inc., Commission file number: 0-26642, at 44 and F-3.

day after Myriad filed its patent for the BRCA2 gene, the Stratton group published its identification of the BRCA2 gene in the journal Nature. Richard Wooster, et al., *Identification of the Breast Cancer Susceptibility Gene BRCA2,* 378 Nature 789 (1995). As the district court pointed out, "the consensus among the scientific community is that the Stratton group, rather than Myriad, was the first to sequence the *BRCA2* gene." *Association for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F. Supp. 2d 181, 202 (S.D.N.Y. 2010). *See also* Robert Dalpé et al., *Watching the Race to Find the Breast Cancer Genes*, 28 Science, Technology, and Human Values 187 (Apr. 2003). Thus, the Myriad patents were not necessary for the discovery of these genes.

II. MYRIAD'S CLAIMS ARE INVALID UNDER SECTION 101 JURISPRUDENCE AND UNDER ARTICLE I, SECTION 8, CLAUSE 8 OF THE U.S. CONSTITUTION.

Nature's handiwork is excluded from patentability. *Mayo Collaborative Services v. Prometheus Labs,* 132 S. Ct. 1289, 1293 (2012); *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010). "'Laws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293 (citations omitted). "[A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter." *Id.*; *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (citing *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). Rather, a newly discovered natural phenomenon must be "treated as though it were a familiar part of the prior

art" and free for all to use. *Parker v. Flook*, 437 U.S. 584, 591-92 (1978). *See also Bilski v. Kappos*, 130 S. Ct. 3218, 3230 (2010).

Even when a newly-discovered law of nature or product of nature is novel, nonobvious, and useful, it is still not patentable under Section 101. *Mayo*, 132 S. Ct. at 1304. Nor can a patent be granted on a synthetic product that is not markedly different from what is found in nature. *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884).

To be valid, a claimed invention involving a product of nature must have an inventive concept that involves significantly more than describing the product of nature. The claimed invention must be "markedly different" from what occurs in nature.[3] *Chakrabarty*, 447 U.S. at 310. *See also Funk Bros.*, 333 U.S. at 130; *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11-12 (1931); *Cochrane*, 111 U.S. at 311.

Section 101 of the Patent Act, 35 U.S.C. § 101, ensures that innovators in our society—including physicians and scientists—have access to the raw materials for innovation. Laws of nature and products of nature are the "basic tools of scientific

[3] This test is no more difficult to apply than any other analysis of patentability. If an inventor patents one type of mousetrap and another inventor files for a patent on another type of mousetrap, a judgment must be made about whether the second mousetrap involved an inventive concept and was markedly different from the prior art (the first mousetrap). In the application of Section 101, a similar analysis is made. But in that case the prior art is the product of nature itself.

and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). Innovation is enhanced when all researchers have access to these basic tools.

The patent claims at issue in this case, covering isolated DNA and cDNA which are described by their genetic sequences, are invalid because they are patents on products of nature without an inventive concept and because isolated DNA and cDNA are not markedly different from what occurs in nature in every human being

Allowing Myriad's claims to stand would be inconsistent with the goals of the patent clause of the U.S. Constitution and the policies that have been part of the Patent Act since its inception. The drafters of the Constitution sought to give Congress the power to promote the widespread distribution of knowledge in the most effective way possible. The U.S. Constitution, Article I, Section 8, Clause 8, grants Congress the power to provide inventors time-limited exclusive rights over their inventions in order "to promote the progress of Science and the useful Arts." However, patents for human genetic material directly threaten that idea, essentially blocking future research and development and stopping science in its tracks.

Since the inception of the patent system, products of nature and laws of nature have been excluded from patentability. Writing in 1889, a patent law scholar noted that someone "may invent a machine, and may discover an island or law of nature. For doing the first of these things, the patent laws may reward him, because he is an inventor in

doing it; but those laws cannot reward him for doing either of the others, because he is not an inventor in doing either." Albert A. Walker, *Text-Book of the Patent Laws of the United States of America* 2-3 (L. K. Strouse & Co., 2d ed. 1889). Myriad is not an inventor under patent law and should not have been allowed to claim patents on isolated DNA and cDNA.

A. Isolated DNA Is an Unpatentable Product of Nature.

Myriad has not invented the genes that exist naturally in people's bodies; it has only removed them from those bodies and taken them out of the cellular environment, using common, long-standing techniques. Beginning in 1869, scientists learned to isolate DNA from the body by removing it from the rest of the cellular material. Ralf Dahm, *Discovering DNA: Friedrich Miescher and the Early Years of Nucleic Acid Research*, 122 Human Genetics 565-581, 567-8 (2008) (documenting the activities of Dr. Miescher). A century later, in the 1970s, scientists could not only isolate DNA from the cell but could also synthesize DNA. Jeffrey Ross et al., *In Vitro Synthesis of DNA Complementary to Purified Rabbit Globin mRNA*, 69 Proceedings of the National Academy of Sciences 264 (1972).

Myriad claims that its inventive step was isolation of the BRCA1 and BRCA2 genes. Yet, as the Federal Circuit stated in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, "isolation of interesting compounds is a mainstay of the chemist's art," and "[i]f it is known how to perform such an isolation doing so 'is likely the product not of

innovation but of ordinary skill and common sense.'" 499 F.3d 1293, 1302 (Fed. Cir. 2007) (quoting *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

Nor does the breaking of covalent bonds make isolated DNA patentable. The breaking of covalent bonds (itself a natural process that occurs in the body) is not an "inventive concept" and does not make the gene sequence "markedly different" and therefore patentable subject matter. The change in chemical bonds is insignificant because the isolated gene sequence is the same string of nucleotides that exists in the cell. In fact, the sequences patented by Myriad would be of no use in diagnosis or treatment if they were different from the sequences that occur naturally in the human body. Additionally, because the claims are written in terms of the genetic sequences, patentability should be determined by an analysis of the genetic sequence, not by the chemical structure and its relation to covalent bonds. Moreover, it makes no sense to have patentability turn on the issue of whether covalent bonds are broken, since DNA that is not covalently bonded exists in the body and since the other bonds (such as hydrogen bonds) are actually more important than covalent bonds in terms of DNA functioning. Amici Curiae Br. for Academics in Law, Medicine, Health Policy and Clinical Genetics (S. Ct. Oct. 26, 2012).

Finding a gene is like finding a new plant in the wild, even if isolated from surrounding flora. To allow a patent on a gene "isolated" from the body is akin to allowing the first surgeon who removed a

kidney to patent any and all "isolated" kidneys.[4] The holder of the patent on an isolated kidney could prevent other surgeons from removing ("isolating") diseased kidneys. The patent holder could also use its exclusive rights to charge a royalty of $3,000 or more each time a person donated a kidney to a relative.

B. cDNA Is an Unpatentable Product of Nature.

Every gene contains exons (sequences which direct the production of proteins) and introns (sequences which do not code for the creation of proteins). cDNA (complementary DNA) is the DNA sequence of a gene with the non-coding regions removed. cDNA is useful because it has the same nucleotide sequence and contains the same information as the coding regions of naturally occurring genes and can perform the same functions as a full genetic sequence or DNA molecule. Bruce Alberts et al., Molecular Biology of the Cell 469-546 (4th ed. 2002).

cDNA is not "markedly different" from the sequences that occur naturally within the

[4] When Myriad's counsel was pressed to identify its inventive concept at oral argument on remand, Myriad's main argument was that the decision of the scientist about where to "cut" the gene sequence to remove it from the chromosome was the inventive concept. Fed. Cir. Oral Arg. on Remand Trans. at 42:48 (July 20, 2012). Under such logic, the first surgeon who successfully removed a kidney for transplant, because he decided where to cut, could obtain a composition of matter patent covering all kidneys later removed by anyone else.

chromosome. Myriad's use of routine techniques to isolate the coding regions of the BRCA1 and BRCA2 sequences lacks the inventive concept necessary for patentable subject matter.

In *Funk Brothers,* the patent applicant isolated certain naturally-occurring bacteria and combined them in a novel and useful way, yet this did not convert the bacteria from ineligible "phenomena of nature" to eligible inventions. 333 U.S. at 130. To permit the patent would have required "allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Id.* at 132. With respect to cDNA, in combining naturally-occurring exons, each exon, like each bacteria in *Funk Brothers*, "has the same effect it always had. . . . [and] perform[s] in [its] natural way." *Id.* at 131. "They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Id.* Moreover, once the gene's naturally occurring DNA sequence—an unpatentable product of nature—is known, creation of cDNA is a routine mainstay of the art of biologists and chemists. Allowing a patent on cDNA would be a disproportionate reward in relation to what the alleged inventor contributed.

C. Synthetically Created Versions of Genetic Sequences Are Not Patent Eligible Inventions.

Even though none of its claims uses 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. at 7 (Fed. Cir. Oct. 22, 2010); Myriad's Br. at 1 (S. Ct. Oct. 31, 2012). 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 whole gene or, in the case of cDNA, a copy of the sequences of the coding regions. 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). Synthesis occurs through the use of the naturally-occurring functions of DNA (such as annealing to its complementary strand), not because of some patent-worthy innovation of the scientist.

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*, 111 U.S. at 311, 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. "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).

Allowing patents on synthesized DNA would be inconsistent with policies that have been part of the Patent Act since its inception. The Patent Act of 1793, drafted by Thomas Jefferson, 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).

Moreover, 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 (quoting *Parker v. Flook,* 437 U.S. 584, 594 (1978) (emphasis added)); *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 postsolution components" to the "prior art" natural DNA molecules and sequences. *Bilski,* 130 S. Ct. at 3231.

D. Myriad's Contributions Do Not Justify the Threat to Innovation.

In a Section 101 analysis, courts need to weigh "how much future innovation is foreclosed relative to the contribution of the inventor." *Mayo*, 132 S. Ct. at 1303. Indeed, "[t]he reason for the exclusion is that sometimes *too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts.'" *Laboratory Corp. of America Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126 (2006) (Breyer, J., dissenting). In *O'Reilly v. Morse*, this Court held that by patenting all uses of electromagnetism to produce characters at a distance, "while he shuts the door against inventions of other persons, the patentee would be able to avail

himself of new discoveries in the properties and powers of electro-magnetism which scientific men might bring to light." 56 U.S. (15 How.) at 113. In this case, Myriad can improperly avail itself of all later discoveries related to human breast cancer genetic diagnosis and treatments, disproportionate to its efforts.

Myriad's contribution to the sequencing and identification of the BRCA1 and BRCA2 genes was minor in comparison to what its patents foreclose. Myriad used common techniques to isolate, sequence, and clone the BRCA1 and BRCA2 genes. The purported invention was not markedly different from the gene sequence in the body.

The core of the patents at issue is the discovery of a natural phenomenon—the sequence of a gene. But that discovery is not patentable since it was created by nature and occurs in every person's body. Once it is conceded that the gene sequence in the body cannot be patented, Myriad's action in isolating that sequence is minimal and not inventive.

Myriad not only patented the entire genetic sequence of BRCA1 and of BRCA2, but also every sequence of 15 nucleotides that appears in the BRCA1 genetic sequence. *See* claims 5 and 6 of U.S. Patent No. 5,747,282. These sequences appear hundreds of thousands of times in the 3 billion base pairs of the human genome. Myriad now can demand a royalty for the use of numerous genetic tests that have nothing to do with breast cancer because those sequences of 15 nucleotides occur in so many places in the genome. There are 340,000

infringing sequences on Chromosome 1 alone. Thomas Kepler, Colin Crossman, Robert Cook-Deegan, *Metastasizing Patent Claims on BRCA1*, 95 Genomics 312 (2010). Since those 15 nucleotide sequences occur an average of 14 times per gene, Myriad could ask for a royalty on every test done on any gene. Myriad could hold hostage the deployment of whole genome sequence testing by threatening to pursue an infringement action for every instance one of those 15 nucleotide segments is sequenced.

III. MYRIAD'S RELIANCE ARGUMENT IS INCONSISTENT WITH PATENT LAW AND IS NOT SUPPORTED IN FACT.

In 1995, when Myriad filed its first patents on the BRCA genetic sequences at issue in this case, the understanding in the medical, scientific and legal community was that a human gene sequence could not be and should not be the subject of intellectual property claims.

George Cahill, the Vice President of Scientific Training and Development at the Howard Hughes Medical Institute, pointed out that intellectual property claims on gene sequences would create an incentive to delay publication in contravention of scientific tradition. Leslie Roberts, *Who Owns the Human Genome?*, 237 Science 358 (1987). University of Washington professor Maynard Olson said, "it's like patenting the periodic table. To put patent value on cream skimming sends the wrong signal." Norton D. Zinder, *Patenting cDNA 1993: Efforts and Happenings*, 135 Gene 295 (1993).

Scientific and medical organizations across the world wrote that human genes did not—and should not—qualify for patentability. The Human Genome Organization, the international organization of genomic scientists, wrote in 1992 that "the human genome is our common heritage and collective property; genetic information is . . . in the public domain. . . . [H]uman DNA is not patentable, but belongs to humankind." Barbara Looney, *Should Genes Be Patented? The Gene Patenting Controversy: Legal, Ethical, and Policy Foundations of an International Agreement*, 26 Law & Pol'y Int'l Bus. 231, 239 (1994) (quoting Human Genome Organization, Ethical Implications of the Human Genome Project: International Issues 10 (1992)).

The World Medical Association declared that genetic information "should be general property and should not be used for business aims. Therefore no patents should be given for the human genome or parts of it." World Medical Association Declaration on the Human Genome Project Adopted by the 44th World Medical Assembly, Marbella, Spain, September 1992, reprinted in 87 Bulletin of Medical Ethics 9 (1993).

Science ministers in Europe took a stance against patenting genes. G. Kenneth Smith and Denise M. Kettelberger, *Patents and the Human Genome Project*, 22 American Intellectual Property Law Association Q.J. 27, 47-48 (1994). The French science minister, writing in the prestigious American research publication, Science, said:

It would be prejudicial for scientists to

> adopt a generalized system of patenting knowledge about the human genome. This would increase costs and penalize low-budget research teams and countries with fragile economies. In addition, such a development would be ethically unacceptable. A patent should not be granted for something that is part of our universal heritage.

Hubert Curien, Letter*, The Human Genome Project and Patents*, 254 Science 1710 (1991).

The scientific, legal and medical literature prior to 1995 also indicated that gene sequences would likely fail to meet requirements for patentability. *See, e.g.* Joseph H. Nadeau, *Who Owns Our Genes?*, 27 Hospital Practice 12 (1992); N. Byrne, *Patents for Human Genes, Ownership of Biological Materials and Other Issues in Patent Law*, 199 World Patent Information 15 (1993); Barbara Looney, *Should Genes Be Patented? The Gene Patenting Controversy: Legal, Ethical, and Policy Foundations of an International Agreement*, 26 Law & Pol'y Int'l Bus. 231, 234 (1994).

A 1995 article in Medical Law International pointed out that patent law protection for Human Genome Project work was "neither desireable nor defensible." Philippa Gannon, Tom Guthrie and Graeme Laurie, *Patents, Morality and DNA: Should There Be Intellectual Property Protection of the Human Genome*, 1 Medical Law International 321, 337 (1995).

At the time the applications for the patents at issue in this case were filed, what Myriad had done was already quite ordinary. It was widely felt that, cDNA did not meet the requirements of patent law because "it is difficult to see any inventive activity" since "cDNA sequences . . . can now [in 1995] be generated relatively quickly by automatic sequencers." Philippa Gannon, Tom Guthrie and Graeme Laurie, *Patents, Morality and DNA: Should There Be Intellectual Property Protection of the Human Genome*, 1 Medical Law International 321, 337 (1995).

In 1992, James Watson, co-discoverer of the double-helix and the first director of the Human Genome Project, voiced his opposition to human gene patents. In his brief in this case, Watson explained, "A scientist does not—and should not—expect to obtain a legal monopoly controlling the information encoded by human genes. And the average scientist should not expect a windfall simply for revealing the sequence of DNA bases that encode various genes." Amicus Brief for James D. Watson in Support of Neither Party at 12-13 (Fed. Cir. June 15, 2012).

The genetics and legal community at the time of Myriad's patent applications acknowledged that intellectual property rights could be sought on therapeutics developed based on genetic knowledge, but that gene sequences themselves were not patentable subject matter. Hubert Curien, Letter, *The Human Genome Project and Patents*, 254 Science 1710 (1991).

Myriad claims it "relied on the certainty of patent protection" for isolated molecules at the time of filing its patents. Myriad's Br. at 2 (S. Ct. Oct 31, 2012). But there was no "certainty" at the time of filing its patents nor is there any now. Myriad was on shaky legal and moral ground when patenting genes, so its reliance argument is not meritorious. The United States Patent and Trademark Office had not even adopted guidelines about gene patents when Myriad sought the patents at issue in the case. Rather than being harmed by a detrimental reliance, Myriad for years has been unjustly enriched by the money it has made based on its patents on BRCA1 and BRCA2—patents that should never have been granted. *See generally Greenberg v. Miami Children's Hospital Research Institute, Inc.*, 264 F.Supp.2d 1064 (S.D. Fla. 2003).

IV. THE UNITED STATES PATENT AND TRADEMARK OFFICE ERRED IN GRANTING HUMAN GENE PATENTS AND ITS ERRONEOUS DECISION SHOULD NOT BE GIVEN DEFERENCE.

The United States Patent and Trademark Office (USPTO) ignored this Court's precedents and applied flawed reasoning to permit patents on genetic sequences. Consequently, that reasoning should not be accorded deference. In 2001, the USPTO relied on the 1873 grant of a patent to Louis Pasteur for a purified yeast and on a 1911 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),

affirmed, 196 F. 496 (2d Cir. 1912). However, the Pasteur patent and *Parke-Davis* preceded this Court's decision in *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931). That decision elaborated on the products of nature doctrine in a way that calls into question the grant of the yeast patent and adrenaline patent. Indeed, no less an authority than Pasquale J. Federico (later Commissioner of Patents and principal drafter of the 1952 Patent Act, which includes Section 101) stated that in light of *American Fruit Growers*, a claim like Pasteur's "would now probably be refused by the examiner, since it may be doubted that the subject-matter is capable of being patented." Pasquale J. Federico, *Louis Pasteur's Patents*, 86 Science 327 (1937).[5] Thus, the USPTO erred when it began granting patents on genetic sequences.

The Federal Circuit compounded this error by looking to *Parke-Davis* in assessing the genetic sequence claims. *Association for Molecular Pathology*, 689 F.3d at 1329; *see also id.* at 1339 (Moore, J., concurring-in-part). Judge Moore additionally cited the discredited Pasteur patent as precedent. *Id.* at 1333 (Moore, J., concurring-in-part).

The Federal Circuit also held that the

[5] The Pasteur patent might not even have been valid according to the law at the time it was issued. Since Pasteur never enforced his patent, there was no judicial assessment of whether the patent was valid. Maurice Cassier, *Louis Pasteur's Patents: Agri-Food Biotechnologies, Industry and Public Good*, *in* Living Properties, 39 (Jean-Paul Gaudillière, *et al.*, eds., 2009).

USPTO's actions created "settled expectations" that prohibited the Federal Circuit from holding genetic sequence claims invalid. *Id.* at 1332-1333; *see also id.* at 1366-1367 (Moore, J., concurring-in-part). However, allowing settled expectations to dictate the validity of a patent would lead to absurd results. The examiners at the USPTO are not infallible. Sometimes whole categories of claims have been erroneously included or excluded from patentability. In fact, in a study of challenges to patent validity, 46% of challenged patents were found to be invalid. John R. Allison and Mark A. Lemley, *Empirical Evidence on the Validity of Litigated Patents*, 26 American Intellectual Property Law Association Q.J. 185 (Summer 1998).

If the USPTO were owed the level of deference that the Federal Circuit proposes, there would be no recourse to challenge invalid patents. Anytime a court reviews a patent there inevitably is a chance to change settled expectations. In *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, 149 F.3d 1368 (Fed. Cir. 1998), the Federal Circuit changed the settled expectation of business owners who had previously felt free to use business methods without concern for patent infringement. As is clear in *Mayo*, settled expectations do not provide an adequate reason for courts to uphold otherwise invalid patents. 132 S. Ct. at 1304-1305.

Furthermore, the U.S. Government asked the Federal Circuit not to give deference to the USPTO's practice of granting patents on isolated DNA. The Department of Justice submitted an *amicus* brief to the Federal Circuit arguing that isolated DNA is a

product of nature and not patentable subject matter. Amicus Brief for the United States in Support of Neither Party at 11 (Fed. Cir. Oct. 29, 2010).

> The chemical structure of native human genes is a product of nature, and it is no less a product of nature when that structure is "isolated" from its natural environment than are cotton fibers that have been separated from cotton seeds or coal that has been extracted from the earth.

V. INVALIDATION OF HUMAN GENE PATENTS IS NOT ONLY REQUIRED BY SECTION 101 AND ARTICLE I, SECTION 8, CLAUSE 8 OF THE U.S. CONSTITUTION, IT IS CONSISTENT WITH SCIENTIFIC AND MEDICAL ETHICS CODES.

Scientists have long-standing, historically recognized duties to freely disseminate their discoveries of products of nature and laws of nature and not to subject those discoveries to private property rights. *See, e.g.*, Robert K. Merton, On the Shoulders of Giants: A Shandean Postscript (1985). Medical professionals, too, recognize the ethical duty to share scientific knowledge rather than to patent it.

Amicus AMA's Ethics Opinion 2.105, entitled "Patenting Human Genes," states, "One of the goals of genetic research is to achieve better medical treatments and technologies. Granting patent protection should not hinder this goal." Similarly,

Amicus ACOG's ethics opinion finds medical and surgical patents to be unethical and urges that genetic sequence patents not be granted. The American College of Obstetricians and Gynecologists, *ACOG Committee Opinion Number 364: Patents, Medicine, and the Interests of Patients*, 109 Obstetrics & Gynecology 1249, 1252 (2007, reaffirmed 2009).

Just as patent law recognizes that discoveries of nature must be widely shared to promote innovation, physicians' and scientists' ethical duties recognize that laws of nature and products of nature must be treated as prior art and shared to benefit the public and to encourage innovation.

CONCLUSION

Under the U.S. Constitution Art. I, § 8, cl. 8, and 35 U.S.C. § 101, isolated genetic sequences are not patentable subject matter. The mere fact of isolation is not enough of a change from what exists in nature to find patentability, as the products *do not have any functions that they did not have already.* Similarly, "synthetic" genetic sequences that are not materially different from their naturally occurring counterparts are not patentable inventions.

Patents on gene sequences, including patents on isolated DNA and cDNA, harm patient care and the progress of science. They interfere with diagnosis and treatment, quality assurance, access to health care, and scientific and medical innovation. They prevent people from receiving appropriate individual health care and thwart public health initiatives.

Non-patent incentives are fully adequate to encourage scientific and medical innovation with respect to human genes. The examples supplied by petitioner's *Amici* only confirm the harms that the patent system causes when extended to genetic sequences.

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 to put an end to human gene patents.

Myriad's patent claims over isolated DNA and cDNA should be invalidated. If gene discoverers want to expand the scope of patentable subject matter under Section 101, their remedy lies with Congress, not the courts.

Respectfully submitted,

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