UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

ASSOCIATION FOR MOLECULAR PATHOLOGY; AMERICAN COLLEGE OF MEDICAL GENETICS; AMERICAN SOCIETY FOR CLINICAL PATHOLOGY; 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; KATHLEEN RAKER,	:	09-CV-4515 (RWS)
Plaintiffs,	:	ECF Case
vs.	:	
UNITED STATES PATENT AND TRADEMARK OFFICE; MYRIAD GENETICS; 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.	:	

BRIEF FOR AMICI CURIAE

March of Dimes Foundation, Canavan Foundation, Claire Altman Heine Foundation, Massachusetts Breast Cancer Coalition, National Organization for Rare Disorders, National Tay-Sachs & Allied Diseases Association

IN SUPPORT OF PLAINTIFFS

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INTERESTS OF *AMICI CURIAE*

***Amicus Curiae* March of Dimes Foundation** is a non-profit organization dedicated to improving the health of babies by preventing birth defects, premature births, and infant mortality. For over 70 years, March of Dimes has carried out its mission through research, community services, education, and advocacy, originally to fight polio and, for the past 50 years, more generally to save babies' lives. It was March of Dimes that funded Jonas Salk's revolutionary research into polio vaccine. On the day the field tests were pronounced a success, Edward R. Murrow interviewed Salk live on his television show See It Now. "Who owns the patent on this vaccine?" Murrow asked. "Well, the people, I would say," Salk replied, "There is no patent. Could you patent the sun?"

Today, the Foundation funds research into genetic diseases and therapies, among many other fields. For example, two funded researchers have used gene therapy successfully in treating hemophilia and retinitis pigmentosa in the laboratory. March of Dimes' mission and research are directly affected by patents on gene sequences and correlations with disease, like the patents-in-suit in this case.

***Amicus Curiae* Canavan Foundation** is a non-profit organization founded by the parents and friends of children affected by the Canavan disease. Canavan disease is a relatively rare, but always fatal, inherited degenerative brain disorder that primarily affects children of eastern and central European Jewish (Ashkenazi) descent. The disease causes loss of body control and death, generally before the children reach their teens. The Canavan Foundation's mission is to provide funding for research efforts to find an effective therapy, raise awareness of the disease, and to help avoid Canavan disease through carrier screening and prenatal testing. Although it is believed that research advances may eventually lead to treatments or even a cure,

there is currently no cure for the disease. Genetic testing is an important part of prevention and early detection.

However, low-cost carrier screening and prenatal testing programs for families at risk for Canavan disease were stopped by the holder of the patent on the Canavan gene based on patent claims very similar to those at issue in this case.

***Amicus Curiae* Claire Altman Heine Foundation (CAHF)** is a non-profit organization and a publicly supported charity. The Foundation is dedicated to establishing population-based pan-ethnic carrier screening for Spinal Muscular Atrophy (SMA), which is the number one genetic killer of children under two. The Foundation aims to raise awareness by educating the public and medical communities, and it works closely with medical associations, genetic counselors, leading SMA researchers, clinicians, laboratories, the NIH, Congress, industry and federal agencies such as the National Human Genome Research Institute (NHGRI), and others in the field of genetics research, prevention, treatment, and counseling.

In CAHF's direct experience, the enforcement and use of patent rights relating to the gene responsible for SMA, similar to the patent claims at issue in this case, adversely affects clinical access to SMA carrier screening.

***Amicus Curiae* Massachusetts Breast Cancer Coalition (MBCC)** is an organization dedicated to eradication of breast cancer, particularly through understanding the interaction of genes and environmental toxins. The incidence of breast cancer has dramatically risen over the past several decades. MBCC supports research into a wider variety of genetic interactions for diagnosis and treatment of breast cancer. The organization's goals include creating public and political will to eradicate breast cancer, and equal access to treatment and testing for breast cancer, currently impeded by enforcement and licensing of patent rights such as those at issue in

this case. The organization is a part of the Alliance for a Healthy Tomorrow (AHT), which is a coalition of citizens, scientists, health professionals, workers, and educators seeking preventive action on toxic hazards. The MBCC and the AHT participate in legislative advocacy to reduce harm to health and to the environment.

***Amicus Curiae* National Organization for Rare Disorders (NORD)**, established by patients and families in 1983, is a non-profit federation of voluntary health organizations dedicated to helping people with rare or "orphan" diseases. A rare or "orphan" disease is one that affects fewer than 200,000 people in the United States. There are more than 6,000 rare disorders that, taken together, affect approximately 25 million Americans. NORD assists health organizations, and is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service. NORD provides information about diseases, referrals to patient organizations and support groups, research grants and fellowships, and advocacy for the rare-disease community. For almost twenty years, NORD has served as the primary non-governmental clearinghouse for information on rare disorders.

Many rare disorders are genetic in nature and, in NORD's experience, patents on gene sequences and correlations have a significant impact on NORD's mission.

***Amicus Curiae* National Tay-Sachs & Allied Diseases Association (NTSAD)** is a non-profit organization founded in 1957 by the parents of children afflicted with Tay-Sachs, Canavan and related genetic diseases, as well as other lysosomal storage diseases and leukodystrophies. In general, these are progressive, degenerative disorders that cause loss of body control and death. There are currently no cures for these diseases, but it is believed that research advances may lead to treatments and eventually cures.

NTSAD's mission is (1) to support research aimed at treating and curing these diseases, (2) to provide support for the individuals and families afflicted with these diseases, and (3) to educate the public about these diseases and genetic screening for carriers through community outreach efforts. NTSAD has funded research initiatives aimed at producing gene therapies for Tay-Sachs and other related genetic diseases. NTSAD is particularly concerned with the currently limited availability of prenatal testing for disorders such as Tay-Sachs and Canavan. NTSAD strives to ensure that carrier screening for Tay-Sachs, Canavan, and other related diseases is readily available. Patent rights, like those of Myriad in this case, directly affect clinical access to carrier screening for this family of diseases and the ability to conduct research for new treatments and cures.

Patient Group *Amici Curiae* Members Are Adversely Affected by Myriad's Patents

Amici Curiae patient groups and their members cannot achieve their goals and objectives for widespread and easy access to genetic screening and research and development of treatments and cures for their target diseases if Myriad's patent claims to gene sequences and bare correlations, and similar claims in other patents related to other diseases, are held to be valid.

Already, Myriad's gene sequence and correlation patents have caused problems for *Amici Curiae*. For example, Myriad's BRCA sequence patents and BRCA correlation patents interfere with the goals of MBCC in preventing and eliminating breast cancer, diagnosing women predisposed to breast cancer, or testing pregnant women interested in prenatal genetic testing, by restricting access to affordable genetic diagnostic testing. Furthermore, women are not able to use diagnostic tests from another provider for a second opinion before undertaking radical surgery, such as the removal of their breasts and ovaries. Myriad's patent claims also prevent

access to new technologies and better testing methods, limit research and innovation, and thus prevent the development of new screening procedures and preventions, treatments, and cures.

As with the BRCA genes, the genes responsible for other diseases such as Tay-Sachs disease, Canavan disease and Spinal Muscular Atrophy, are also subject to similar patent claims to the gene sequences themselves and bare correlations. Such claims interfere with *Amici Curiae's* missions to identify, screen for, treat, and cure genetic-related diseases. Genetic tests are an important way to identify such diseases. If a gene patent or a bare correlation patent for a genetic-related disease is held valid, it would cause the harmful result of limiting innovation and preventing development of genetic tests and treatments for those diseases. Such patents will prevent the public from accessing better genetic testing and new treatment methods. *Amici Curiae* understand the need to encourage innovation and investment, but patents on gene sequences themselves and bare correlations to a disease hinder rather than promote vital progress. The exclusivity such patent rights provide is wholly out of proportion to the innovation they foster. *Amici Curiae* therefore urge the Court to deny Defendants' motions to dismiss and grant Plaintiffs' motion for summary judgment that the disputed claims are invalid.

SUMMARY OF ARGUMENT

The central issue in this case concerns the scope of patentable subject matter under the Patent Act of 1952. The Act provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. Although the scope of patentable subject matter is thus broad, it is settled precedent that "[e]xcluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

The patents-in-suit, U.S. Patent numbers 5,693,473, 5,709,999, 5,747,282, 5,710,001, 5,735,441, 5,837,492, and 6,033,857 (the "Myriad patents," or the '473, '999, '282, '001, '441, '492, and '857 patents respectively) claim the DNA sequences of two normal ("wild-type") genes, BRCA 1 and BRCA 2, mutations of those DNA sequences that contribute to susceptibility to breast cancer or ovarian cancer, and any method of detecting these mutations, even if that method was not invented by Myriad.

The patent claims in dispute (the "Myriad patent claims") can be divided into two groups: (1) claims directed to isolated DNA sequences that the alleged inventors observed in the genomes of specific individuals; and (2) claims to methods of using these isolated DNA sequences by making bare correlations of the sequences to the likelihood of disease. The sequence claims are claims 1, 2, 5, 6 and 7 of the '282 patent, claims 1, 6 and 7 of the '492 patent, claim 1 of the '473 patent. Representative sequence claims are claims 1 and 2 of the '282 patent:

> 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
>
> 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.

where the nomenclature "SEQ ID NO:1," for example, refers to the DNA sequence, made up of a four-letter code of nucleotide bases, set out in the '282 patent at columns 68 to 80. These claimed DNA sequences are natural phenomena merely uncovered by the "inventors," which do not change upon "isolation" (that is, extraction from cells of the human body).

The method claims are claim 20 of the '282 patent, claim 1 of the '999 patent, claim 1 of the '001 patent, claim 1 of the '441, and claims 1 and 2 of the '857 patent. A representative method claim is claim 2 of the '857 patent:

> 2. A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer.

This involves simply the step of comparing a person's BRCA2 gene sequence with the normal or "wild-type" gene sequence – a bare correlation, nothing more. As explained below, the disputed claims in all these patents are to unpatentable products of nature and laws of nature.

Myriad has exercised its exclusivity by prohibiting others from using the claimed sequences and from carrying out the claimed methods using tests for the BRCA genes,[1] making it impossible for a patient to obtain a second opinion on Myriad's results,[2] and preventing other laboratories from effectively building a database of other mutations affecting breast cancer. This exclusivity is harmful and worrying:

> [T]he exclusive practice of any medical procedure or clinical diagnostic test is an important issue for the medical profession and raises important questions of public health and science policy. For example, the performance of a gene-based clinical test in an academic setting often generates rich databases of newly detected genetic variations that can be correlated with an array of clinical phenotypes. Such admixed medical practice and research provides important new information about the mutational repertory of specific disease-linked genes, as well as the phenotypic correlations that provide new insights into disease mechanisms and identify potential new targets for therapeutic intervention. [3]

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[1] National Research Council Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH 147-49 (2006) (*available at* http://www.nap.edu/openbook.php?isbn=0309100674/).

[2] *Id*. at 131.

[3] *Id*. at 147. In this case, Myriad's BRCA patents already appear to have harmed medicine and patient care. There are reports that the exclusive supplier of the tests has missed relevant mutations. *See* Jordan Paradise, *European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for US. Patent Law and Public Policy: a Case Study of the Myriad Genetics' BRCA Patent Controversy*, 59 Food & Drug L.J. 133, 147-49 (2004).

Thus, there are special dangers in allowing only one laboratory, in this case Myriad, exclusive rights to conduct research on a particular genetic phenomenon. If laboratories can both compete with and collaborate with one another through common access to natural phenomena and laws of nature, test quality will improve, second opinions will be available, the tests will become more affordable and allow for collaborative research, all of which will allow science to advance more rapidly and benefit patients.

In crossing over the line between patents on human invention and patents on nature itself, the Myriad patents upset the "careful balance" inherent in the patent laws that is "the very lifeblood of a competitive economy." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989). A United States patent confers upon its owner the powerful right to exclude others from practicing whatever invention is claimed in the patent for a defined period of time. *See* 35 U.S.C. § 271 (defining infringement) and § 154 (twenty-year term). Such powerful rights should not be conferred upon claims to natural phenomena and laws of nature so as to preempt the future progress of scientific research and advances in medical technology.

Allowing Myriad's patent claims to stand will damage such future research and scientific progress. These patents and others just like them allow no room to design around, imitate, or improve upon the so-called "invention" of a law of nature or natural phenomena. DNA technology has opened up a vast array of tests based on naturally occurring biochemical mechanisms. But if claims like these are sustained, such tests will be blocked by patents on the products of nature and laws of nature on which they are based. Myriad's claims are monopolies to existing "facts" or information, not man-made products or processes. If a discovered gene sequence causes a disease, or is associated with an increased susceptibility to a disease, *that*

sequence is the critical sequence which must be used and detected in genetic testing, not any other sequence. Consequently, it is impossible to invent around gene patents.

Patent claims like Myriad's are especially harmful given the nature of modern genomic research, which focuses not on one gene or gene function at a time, but rather on complex interconnections among genes and gene functions. Such interconnections cannot be studied if portions of the larger genomic map are blocked out. By contrast, invalidating these patent claims and reaffirming the principles set forth in Supreme Court precedent will not disrupt or impede scientific research, but rather improve the progress of science thereby benefiting those affected by genetic diseases and conditions.

ARGUMENT

I. THE MYRIAD PATENTS IMPROPERLY REMOVE NATURAL PHENOMENA AND LAWS OF NATURE FROM THE PUBLIC DOMAIN

A. Patentable Subject Matter Does Not Include Laws Of Nature, Natural Phenomena, Or Abstract Ideas

Congress intended the scope of patentable subject matter to be broad and inclusive, even for technologies that had yet to be imagined. But this broad scope has limits, as both Congress and the Supreme Court have made clear. In particular, natural phenomena and laws of nature, among other things, are not patentable.

The Committee Reports accompanying the 1952 Patent Act state that "[a] person may have 'invented' a machine or manufacture, which may include anything under the sun that is made by man, but it is not necessarily patentable under section 101, unless the conditions of the title are fulfilled." S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82–1923, at 6 (1952), *quoted in part in Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). As the Supreme Court stated, this oft-quoted sentence "is not to suggest that § 101 has no limits or that it embraces every discovery. The laws of nature, physical phenomena, and abstract ideas have been held not

patentable." *Id* (citations omitted). *See also Diamond v. Diehr*, 450 U.S. 175, 185 (1981). The Supreme Court further held that:

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none."

Chakrabarty, 447 U.S. at 309 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). *See also Parker v. Flook*, 437 U.S. 584, 593 n.15 (1978)

Thus, natural phenomena, such as gene sequences, are not patentable. The principle that one cannot patent natural phenomena is longstanding and predates the 1952 Patent Act. *See, e.g., Funk Bros. Seed Co.*, 333 U.S. at 130 ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end.")

Several Supreme Court decisions, both before and after the 1952 Patent Act, have specifically addressed the distinction between an unpatentable natural phenomenon or product of nature, and patentable subject matter. In *Funk Bros.*, the Supreme Court invalidated a patent of a mixture of several bacteria which could successfully inoculate many types of plants. 333 U.S. 127 (1948). The Court noted, "however ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants." *Id.* at 131. The Court also noted that the bacteria "serve the ends nature originally provided and act quite independently of any effort by the patentee." *Id.* In *Chakrabarty*, for example, the Supreme Court held that a human-made bacteria was patentable subject matter. 447 U.S. at 310. However, the bacteria in *Chakrabarty* were genetically engineered to exhibit

characteristics not found in any natural bacteria, and thus were not products of nature. In *American Wood-Paper v. Fibre Disintegrating Co.*, 90 U.S. 566 (1874), the Court invalidated a patent on a more pure version of cellulose than had been available at the time, stated that the cellulose was an extract, and an extract, "when obtained cannot be called a new manufacture." 90 U.S. at 594 (1874). "The substance of the products, therefore, was the same, and so were their uses." *Id.* In *Cochrine v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884), the Court invalidated a patent on a dye produced from a synthetic process that was identical to a dye obtained from a natural plant. The Court stated, "Calling [the dye] artificial alizarine did not make it a new composition of matter, and patentable as such, by reason of its having been prepared artificially." *Id*. at 311. As further discussed below, gene patents, unlike small chemical compound patents, are patents on unpatentable natural phenomena, *i.e.*, products of nature, not patentable man-made compositions of matter.

Similarly, laws of nature, such as bare correlations between a gene sequence and a disease, are not patentable. "[R]ecognition of a theretofore existing phenomenon or relationship carries with it no rights to exclude others from its enjoyment." *Parker v. Flook*, 437 U.S. 584, 593 n.15 (1978); *see also Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.").[4] Most recently, in *Lab. Corp of Am. Holdings v. Metabolite Labs. Inc.*, Justice Breyer, with whom Justice Stevens and Justice Souter joined, dissented from the Court's decision to dismiss the writ of certiorari, and argued

[4] The laws of other nations and patent systems likewise preclude patenting natural phenomena and laws of nature. *See, e.g.*, European Patent Convention Article 52(2) (excluding from patentability "discoveries, scientific theories and mathematical methods"), *available at* http://www.epo.org/patents/law/legal-texts/html/epc/1973/e/ar52.html; India, Patents Act, 1970 § 3(c) (excluding from patentability "mere discovery of a scientific principle or the formulation of an abstract theory"), *available at* http://ipindia.nic.in/ipr/patent/patents.htm; Japan, Examination Guidelines for Patent and Utility Model in Japan, Part II, Chapter 1 ("A law of nature as such"

that the patent claim in issue to "a simple natural correlation" between high levels of homocysteine in the blood and deficiencies of two essential vitamins was "an unpatentable 'natural phenomenon.'" 548 U.S. at 137-138.

Thus, in *Parker v. Flook*, for example, the Supreme Court held that a process for monitoring chemical reactions by using a mathematical formula is not patentable. 437 U.S. at 594. And in *Gottschalk v. Benson*, the Supreme Court held that a process related to converting decimal to binary numerals using a formula is not patentable. 409 U.S. at 71-72.

The distinction between the non-patentable and patentable subject matter in the case of method claims, like several claims at issue in this case, often turns on whether the claimed process is transformative. In analyzing the patentability of a claimed process, both *Diehr* (which upheld a claimed process) and *Gottschalk* (which struck down a claimed process) focused on the *end result* of the process: "Transformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Diehr*, 450 U.S. at 184; *Gottschalk*, 409 U.S. at 70. The issue of "transformation" is currently before the Supreme Court again in the context of business method patents. *In re Bilski*, No. 08-964 (U.S. 2008) . In "comparing" the DNA sequence from a patient's tissue sample against the wild-type sequence, as in the present claims, no patentable "transformation" occurs. Thus, based upon *Gottschalk*, as followed by the Federal Circuit in *Bilski*, claims to bare correlations between gene sequences and diseases (or susceptibility to a disease) – which do not involve a "transformation" – are nothing more than patents on unpatentable laws of nature.

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is "not considered to be a statutory invention.") (English translation available at Japanese Patent Office website at http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/1312-002_e.htm).

In sum, Supreme Court precedent clearly forbids patents on natural phenomena and laws of nature. For the reasons set out below, all the Myriad claims to gene sequences and bare correlations are unpatentable subject matter under this precedent.

B. The Myriad Patent Claims Improperly Assert Exclusive Rights To Natural Phenomena and Laws of Nature—Namely, Gene Sequences, Mutation Sequences, and the Correlations Between Certain Mutations and Susceptibility to Breast Cancer and Ovarian Cancer

The human genetic code is contained in twenty-three pairs of chromosomes, which are present in almost every cell of the human body. These chromosomes are passed on from generation to generation. The chromosomes comprise tightly wound bundles of the long, thin molecule called "DNA" ("deoxyribonucleic acid"). Along its length, DNA contains a sequence of four compounds called bases. This sequence of bases is a code that is the template for protein production in all cells. Every individual (except identical twins) has a slightly different sequence. Some of those differences or variations in the sequence reflect a person's susceptibility to a disease. These sequences are natural phenomena that are not created by mankind (including the present Myriad "inventors"), they are merely observed. Isolation and purification of the DNA sequences does not change the order of nucleotides and does not result in qualitative changes in the sequence.

In the present case, the sequences in issue are the BRCA genes. There is a relationship between these sequences and a probability that a person will develop a breast or ovarian cancer. That is, if a woman has a particular sequence in her BRCA genes, she is more likely to develop breast cancer. It cannot be disputed that these gene sequences and the relationship between the sequences and breast cancer is "the handiwork of nature" – they existed in nature long before the Myriad "inventors" did their work, and nothing these inventors did changed the relationship. Yet, it is precisely that natural genetic material and correlation – the genes called BRCA1 and

BRCA2, and the relationship between their sequences and the probability that a person will develop a cancer – that Myriad has claimed as its exclusive property.

Like the discoverers of a previously unknown plant in the wild, the inventors assert that they were the first to have uncovered these natural phenomena and laws of nature:

> It is a discovery of the present invention that the BRCA1 locus which predisposes individuals to breast cancer and ovarian cancer, is a gene encoding a BRCA1 protein, [. . .]. It is a discovery of the present invention that mutations in the BRCA1 locus [. . .] are indicative of a predisposition to breast cancer and ovarian cancer. Finally, it is a discovery of the present invention that somatic mutations in the BRCA1 locus are also associated with breast cancer, ovarian cancer and other cancers, which represents an indicator of these cancers or of the prognosis of these cancers.

'282 patent at col. 7, ll. 18-30. The BRCA genes were identified using well-known techniques of molecular biology. '282 patent at col. 7, l. 39 – col. 8, l. 14. Their relationship to cancer was mapped by testing cancer-prone families. '282 patent at col. 35, l. 39 – col. 36, l. 46.

The sequences of the BRCA genes that are now "owned" by Myriad existed in nature before Myriad discovered them. Both normal and mutant genes occur naturally in humans. Myriad did not invent these coding sequences, nor do Myriad's sequences have characteristics not found in nature. However, through their claims, such as claims 1 and 2 of the '282 patent, Myriad can exclude others from any use of the claimed sequences for the two BRCA genes, including use of those sequences present in an individual's own blood. Thus, if these claims on natural products are allowed to stand, physicians and scientists – other than Myriad – will continue to be prohibited from looking at these naturally occurring gene sequences in their patients until the patents expire, impeding both the diagnosis and treatment of patients, and interfering with the research into the disease and potential treatments. In turn this directly harms the patient Plaintiffs and patients represented by *Amici Curiae*.

The harm is particularly pronounced because BRCA genes are complex genes that are subject to a plethora of sequence variations of differing clinical significance. Genetic testing requires a database of clinical significance for known variants, because some variations affect susceptibility to cancer while others do not, that is, some variations or "mutations" of BRCA gene sequences give rise to a high probability of breast cancer, while other mutations result in a lower probability or have no effect. By suppressing virtually all external research related to BRCA genes, Myriad precludes others from building clinical significance databases. Myriad is able to use these patents to amass trade secrets which forestall competition after the patents expire, until alternative databases can be created. The Supreme Court has recognized that any attempt to extract profits after the expiration of a patent is illegal and contrary to public policy. *See, Scott Paper Co. v. Marcalus Co.*, 326 U.S. 249, 256 (1945) (". . . any attempted reservation or continuation in the patentee or those claiming under him of the patent monopoly, after the patent expires, whatever the legal device employed, runs counter to the policy and purpose of the patent laws.")

Furthermore, while Myriad has described some mutations that cause an increased likelihood of breast cancer, not all mutations have been studied (let alone disclosed by Myriad). Thus, in the case of Plaintiff Ms. Runi Limary, Myriad reported the outcome of her BRCA testing to be "of uncertain significance" – in other words, Myriad doesn't know and has not described in its patents what Ms. Limary's variation means as far a likelihood of breast cancer is concerned. If Myriad allowed more research by others, this outcome might be different.

Myriad's method claims are equally problematic. For example, claims such as claim 1 of the '857 patent, exclude others from performing a simple mental process of comparing a mutant sequence and a wild-type sequence. The method claims also attempt to monopolize applications

of this basic process to screening for potential cancer therapeutics (claim 20 of '282 patents), a method for detecting a mutation (claims 1 of '999, '001, '441 and '857 patents), and a method for diagnosing a predisposition to breast cancer (claim 1 of the '857 patent). Myriad's claims preempt these natural phenomena by precluding all others from testing and observing these phenomena. The basic method claimed by Myriad — comparing the patient's sequence to the non-mutated sequence, and thereby drawing a conclusion as to susceptibility to breast cancer — is nothing more than a law of nature.

Myriad's method claims are not limited to any particular kind of comparison or test. *Any* comparison of the BRCA sequences infringes. In fact, even just thinking about the results of the test – comparing the patient's sequence and the "wild-type" sequence – infringes the patent. Thus, for example, infringement might occur if a doctor sends a sample to a lab to be tested for BRCA1 and BRCA2 genes, and then receives the patient's sequence which he or she compares with the wild-type sequence. In this scenario, the doctor is an infringer even if the doctor had no idea how the sequencing was done. One may not even test one's own blood to observe the relationship without running afoul of these patents. The patents thus allow the patent holders to own a law of nature—the relationship between mutations in the BRCA1 and BRCA2 genes and an increased risk of breast or ovarian cancer.

In contrast to the patent claim upheld in *Diehr*, there are *no* other steps in the claimed process here. These patents cover every substantial practical application of the law of nature that BRCA gene mutations are correlated to breast cancer. Myriad's claims are similar to a method of estimating the risk of heart attack on the basis of measurements of blood pressure. Such a claim, like Myriad's methods claims here, preempts all uses of a particular law of nature.

In the language of *Diehr* and *Gottschalk*, the natural relationships between cancer and the BRCA genes have been "pre-empted" by the patent claims. Allowing Myriad to appropriate such a natural phenomenon and law of nature as their exclusive property would require departure from the Supreme Court's long-settled precedents.

II. THE MYRIAD PATENTS UPSET THE PATENT BALANCE CAREFULLY STRUCK BY CONGRESS AND THE COURTS, HARM RESEARCH AND INNOVATION IN THE LIFE SCIENCES, AND HARM PATIENTS AND OTHERS

The Constitution requires that patents "promote the *Progress* of Science and useful Arts." Art. I, § 8, cl. 8 (emphasis added). Fulfilling this constitutional purpose requires a balance between rewarding existing research and ensuring that other research may go forward freely in the future. Allowing a patentee to remove a natural phenomenon and laws of nature from the public sphere thwarts this constitutional purpose by impeding rather than promoting the progress of biochemical research, clinical diagnostics and medical treatments. Without access to testing and observing products of nature and laws of nature, medical researchers cannot build upon the discoveries of others.

Allowing patent claims such as those at issue here blocks medical information based on natural, biochemical relationships from appropriate further scientific use. This impediment is especially acute with respect to the field of genome analysis, which requires the study of multiple genes and multiple correlations. Disallowing claims such as these patents, by contrast, will cause little harm to scientific progress because a wide range of other appropriate claims would remain available to researchers and patentees like Myriad, such as patents on specific treatments that make use of genetic information about the predisposition to cancer. Thus, the balance struck in *Diehr* and similar cases on the scope of patentable subject matter should be preserved.

A. Existing Limitations On The Scope Of Patentable Subject Matter Reflect A Careful Balance Between Rewarding Existing Research And Ensuring Opportunity For Future Innovation

Patents are fundamentally a balance between allowing free competition and government-granted exclusive rights. "The Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Eldred v. Ashcroft*, 537 U.S. 186, 215 (2003) (citing *Bonito Boats*, 489 U.S. at 146). *See Mazer v. Stein*, 347 U.S. 201, 219 (1954) (noting that the patent system is based upon the "conviction that encouragement of individual effort by personal gain is the best way to advance public welfare through the talents of authors and inventors").

Patent law seeks to strike a balance between these competing interests. Some features of patent law ensure adequate returns for the costs of research and development. For example, Congress has decided upon a twenty-year term for patents. *See* 35 U.S.C. § 154. Other features of patent law seek to preserve opportunities for future innovation. There are the requirements that patentable inventions are new, inventive, definite, and adequately described, among other things. 35 U.S.C. §§ 102, 103, and 112. As another example, there is a statutory safe harbor for certain activities relating to the development of generic forms of patented drugs that would otherwise constitute patent infringement. *See, e.g.*, 35 U.S.C. § 271(e); *Merck KGAA v. Integra Lifesciences, Ltd.*, 545 US 193 (2005) (exemption applied to certain preclinical research).

The definition of what constitutes patentable subject matter likewise reflects a balance that has been struck by Congress in section 101 of the Patent Act and by case law in interpreting that section. The key to this balance — which distinguishes human-made inventions from products of nature and laws of nature — is the recognition that there are interests in promoting innovation on *both* sides of any patent. As the Supreme Court stated in a different context in

Bonito Boats, "from their inception, the federal patent laws have embodied a careful balance between the need to promote innovation and the recognition that imitation and refinement through imitation are both necessary to invention itself and the very lifeblood of a competitive economy." 489 U.S. at 146. As Justice Breyer noted in the related context of copyright law, in ensuring a balance between preserving incentives to intellectual property holders and protecting opportunities for others to develop new technologies, it is important to be sure that "the gains on the copyright swings would exceed the losses on the technology roundabouts." *Metro-Goldwyn-Mayer Studios, Inc. v. Grokster, Ltd*., 545 US 913, 960 (2005) (Breyer, J., concurring).

Here, permitting patent claims like the disputed claims, would cause serious "losses on the technology roundabouts," upsetting the balance that Congress and the Supreme Court have long struck with respect to patenting laws of nature. By precluding scientific inquiry (*i.e.*, the ability to test, observe and conclude) into naturally occurring phenomena, Myriad's sequence and correlation claims, and others like them, have and will remove the common tools accessible to all scientists that allow scientific progress to be made. Invalidating the disputed claims, by contrast, would still allow wide berth for patenting truly transformative human inventions that add to rather than subtract from the public domain.

There are further constitutional problems with the patent claims at issue in this case, and with all patents claiming exclusive rights to natural phenomena and laws of nature. The first problem is that patents on products of nature, like the copyright struck down in *Feist Publ'ns, Inc. v. Rural Tel. Serv. Co.*, 499 U.S. 340 (1991), deal with facts themselves. The corresponding lack of originality raises serious questions under Art. I, § 8, which gives Congress authority to issue patents that "promote the *Progress* of Science and useful Arts." Art. I, § 8, cl. 8 (emphasis added). Patents on products of nature, like gene sequence patents, take information *out* of the

public domain rather than putting ideas *into* the public domain as is the intention of the Constitution and of the patent disclosure provisions. A second constitutional difficulty with patent claims on products and laws of nature is that the claims have a significant chilling effect on publication, in violation of principles of freedom of speech protected by the First Amendment. That is because scientists and researchers are prevented from researching and publishing science using the patented genes. No scientist should need to undertake a patent analysis before publishing a research article on a direct correlation between a measurement and a natural phenomenon. But that is the effect of Myriad's claims here and others like them.

B. Permitting Myriad's Patent Claims To Stand Would Impede Future Biomedical And Genetic Research That Depends Upon Common Access To Natural Phenomena

Science has always proceeded in an incremental way in which one discovery builds upon another. Experts in the scientific method have accordingly noted that scientific progress requires that research results be open for all to "use, attempt to replicate, and evaluate."[5] Gene patents impede application of the scientific method of hypothesis generation, discovery and replication. In one survey, half of gene patent holders said they would require a license for researchers to study the prevalence of mutations in the patented gene in the population.[6] Even more troubling is the finding that 28% of geneticists surveyed reported that they were unable to duplicate published research because other academic scientists refused to share information, data, or materials.[7] For example, families affected by Canavan disease and *Amici Curiae* Canavan Foundation and NTSAD sued Miami Children's Hospital, when the hospital patented a genetic

[5] U.S. National Research Council Committee on Intellectual Property Rights in the Knowledge-Based Economy, A PATENT SYSTEM FOR THE 21 ST CENTURY 26 (2004) (citing Robert K. Merton, THE SOCIOLOGY OF SCIENCE: THEORETICAL AND EMPIRICAL INVESTIGATIONS (1973)).

[6] Timothy Caulfield, E. Richard Gold, and Mildred K. Cho, "Patenting Human Genetic Material: Refocusing the Debate," 1 *Nature Reviews Genetics* 227-231, 230 (2000).

[7] Eric G. Campbell, Brian R. Clarridge, Manjusha Gokhale, Lauren Birenbaum, Stephen Hilgartner, Neil A. Holtzman, and David Blumenthal, "Data Withholding in Academic Genetics," 287 *JAMA* 473, 478 (2002).

test and set up restrictive licensing agreements, capping the number of tests that each laboratory could perform. This aspect of scientific progress, a confirmation of scientific data through replication, would be impeded if patents could extend to natural phenomena. The Council of the [United Kingdom] Royal Society has drawn a parallel implication:

> [P]ure knowledge about the physical world should not be patentable under any circumstances. That it should be freely available to all is one of the fundamental principles of the culture of science. Only by having knowledge unencumbered by property rights can the scientific community disseminate information and take science forward. [8]

Whatever the effect of the scope of patentability on scientific research in the past, however, these principles are even more important to the next generation of biomedical and genetic research. Any holding that one may effectively own a natural biochemical relationship by excluding others from any and all testing of that relationship would have especially fundamental implications for future research in the field of DNA and human genetic conditions.[9] Further, the ability to own the underlying sequence and prevent others from examining it for relationships to other diseases, or even looking for additional mutations associated with the same disease, has direct implications for the health of patients, such as Plaintiffs and those represented by *Amici Curiae*, who may have, or be susceptible to, such diseases.

Amici Curiae's patients are particularly harmed because mutations in BRCA genes are only associated with about 5% of all breast cancers.[10] Doctors need to test for genetic mutations not only in the BRCA1 and BRCA2 genes, but in all the genes that are known to cause cancer in order to provide patients with full information about the risks and benefits of certain treatments.

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[8] Royal Society Working Group on Intellectual Property, KEEPING SCIENCE OPEN: THE EFFECTS OF INTELLECTUAL PROPERTY POLICY ON THE CONDUCT OF SCIENCE 8 (April 2003).

[9] The scope of preemption is significant, for it has been estimated that approximately one-fifth of all human genes are already patented. Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 Science 239 (2005).

When a doctor biopsies or removes a tumor, a small piece of tissue is sent for testing. But it is not practical to send multiple samples to separate laboratories to test for each cancer-associated sequence or correlation; it is more efficient to send it to one lab, which can test for everything at once. Ordinarily there should be several labs that could conduct the tests, located in different parts of the country. However, in this case there is only one lab where the doctor can have the BRCA genes tested – Myriad. Myriad's patents coupled with Myriad's refusal to license others in effect forces health care providers to order patented *and* unpatented tests from Myriad. But if a patentee possesses market power, as Myriad does, when it ties the purchase of a patented product to an agreement to buy unpatented goods, the Supreme Court has held that such tying is illegal. *See, e.g., Ill. Tool Works Inc. v. Indep. Ink, Inc.*, 547 U.S. 28 (2006), *and Morton Salt Co. v. G. S. Suppiger Co.*, 314 U.S. 488 (1942). Myriad's practice is akin to such a tie. Furthermore, if each of the cancer-associated sequences or correlations is eventually patented, there will simply not be enough tissue to send to all the different patent holders for complete testing.

Also, with no commercial incentives to research the clinical significance of rare sequence variants, Myriad reports "genetic variant of unknown significance" to some patients. Myriad does not follow up on these rare variants, and its refusal to license its patents prevents other laboratories, teaching hospitals and academic institutions from researching the clinical significance of rare sequence variants, even where others are willing and able to conduct research and to pay royalties. Consequently, Myriad suppresses research and development which otherwise could improve the standard of care for cancer patients.[11]

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[10] Fraz A. Malik et al., Contribution of BRCA1 germline mutation in patients with sporadic breast cancer, *Int. Seminars Surgical Oncol.*, 5(21) (2008).

[11] The same harm has been experienced by *Amicus Curiae* CAHF in connection with the SMA patent gene and patent claims covering it. *See,* CAHF Position Statement: Pan-Ethnic Population Based Carrier Screening and

As explained above, Myriad's claims in issue in this case cover natural phenomena – the gene sequences – and laws of nature – the bare correlations between the wild-type and mutant sequences that Myriad "discovered" indicate a predisposition to breast cancer. Myriad's claims preclude a person from testing their own genetic code, even though sequencing genes is so routine and straightforward that it is taught in high school. Yet testing for a relationship between a single gene mutation and a physical condition has demonstrated medical value and may even be life saving. The impediments to genetic research are compounded by the fact that modern genomic research has moved past one mutation/one function diseases to exploration of complex interrelationships among genes and genetic functions.[12] Without Myriad's basic blocking patents, science would advance more rapidly through competition and collaboration, resulting in increased benefits to patients.

C. Invalidating Myriad's Patent Claims Would Neither Eliminate Incentives To Invest In Research Nor Disrupt The Patent System

The unsettled state of the patent law with respect to ownership of genetic material and its relationship to disease has resulted in a well-documented "land-grab" mentality, in which patent attorneys seek gene patents at the outer boundaries of the line between human invention and natural phenomena.[13] This is not surprising, for without adequate guidance about the scope of patentable subject matter attorneys are obliged seek the broadest possible claims for their clients. *See Solomon v. Kimberly-Clark Corp*., 216 F.3d 1372, 1382 (Fed. Cir. 2000) (a patent attorney has a "professional responsibility ... to assist his or her client in defining her invention to obtain, if possible, a valid patent with maximum coverage").

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the SMA Patent, *available at* http://www.clairealtmanheinefoundation.org/pdf/CAHF_Final_Patent_Position_G_A.pdf (March 2009)

[12] An example is the U.S. National Human Genome Research Institute's Research Roadmap. *See* Francis S. Collins et al., *A Vision For The Future Of Genomics Research: A Blueprint For The Genomic Era*, 422 Nature 1 (2003).

[13] *See* Jensen & Murray, *supra* note 9.

These pressures have led patent attorneys to seek and often obtain patents that stretch the boundaries of patentability into the natural realm. However, such increased scope is not necessary to advances in science, and, as already described, in fact impedes science. This case presents a vital opportunity for this Court to curb this pressure on the outer boundaries of patentability, and to return the balance to the baseline set by the Supreme Court in *Diehr* and related decisions.[14] In so doing, there is little danger that genetic or other biomedical research will be harmed by reduced incentives for making discoveries of nature.

Nothing in the argument advanced by *Amici Curiae* here would impede patents in the genetic area if those patents involve more than the mere discovery of a product of nature or a law of nature. Consistent with the Supreme Court's test in *Diehr*, *Amici Curiae* do not oppose patent claims directed to innovative tests, or inventive pharmaceutical compositions, or new and useful therapies, or any number of products or methods that add human invention to a natural phenomenon. The issue is whether ownership rights should result from the mere *discovery* of a product of nature or a law of nature.

Myriad's sequence claims cover gene sequences, found in nature, that relate directly to susceptibility to breast cancer. Myriad's correlation claims are directed to the relationship between certain mutations and an increased risk for breast cancer, which exists in nature and was merely discovered by Myriad. Myriad did nothing to "invent" these sequences and correlations but merely discovered their existence. Myriad's sequence and correlation claims do not cover an application of the law of nature, but the law itself. Simply finding the DNA sequences and their

[14] Some guidance in this area might well be provided by developments in areas of patent law other than the scope of patentable subject matter. For example, the Federal Circuit struck down the validity of patent claims directed to short fragments of DNA sequences (called "Expressed Sequence Tags" or "ESTs") without a known function as lacking specific and substantial utility as required by the patent laws. *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005). *See also In Re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). But such approaches cannot be as systematic and useful as curtailing the "land grab" in patentable subject matter.

correlation with cancer, however, can readily be distinguished from inventive methods used to find the DNA sequences, or inventive therapies and tests that use those DNA sequences. The latter would be legitimately patentable under the principles set forth in *Diehr*, and ownership of rights to such tests and therapies is adequate to ensure research into products and laws of nature.

CONCLUSION

Amici Curiae appreciate the opportunity to add to the Court's understanding of the critical issues concerning patentable subject matter raised in this case. For the reasons set out herein, *Amici Curiae* respectfully submit that that Defendants' motions to dismiss be denied so that these vital patent issues can receive the full consideration that they deserve and that Plaintiffs' motion for summary judgment that the disputed claims are invalid be granted.

Dated: August 26, 2009

Respectfully submitted,

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