No. 11-725

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMICI BRIEF OF THE NATIONAL WOMEN'S HEALTH NETWORK, GENERATIONS AHEAD, THE PRO-CHOICE ALLIANCE FOR RESPONSIBLE RESEARCH, ASIAN COMMUNITIES FOR REPRODUCTIVE JUSTICE, THE CENTER FOR GENETICS AND SOCIETY, ALLIANCE FOR HUMANE BIOTECHNOLOGY, G. MICHAEL ROYBAL, MD, MPH AND ANNE L. PETERS, MD, IN SUPPORT OF PETITION FOR WRIT OF CERTIORARI

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INTEREST OF *AMICI CURIAE*

Amici Curiae include women's health and social justice advocates with expertise in policy issues relating to women's health, and health disparities for women of ethnic and racial backgrounds and socio-economically disadvantaged women and their families. Additionally, *Amici Curiae* include physicians with particular expertise in the clinical care and treatment of women in underserved populations. *Amici* advocate for just public policy, and educate community-based organizations about the implications of new technologies for women's rights and health. *Amici* physicians working within our burdened healthcare system understand the importance of genetic technologies for preventive medicine, treatment, and possible cures.

Amici are deeply concerned about the Federal Circuit's decision to allow the patenting of human genes, including the BRCA 1 & 2 genes and the sequences they embody. *Amici* have the expertise to illustrate to the Court how basic research on human genes, and research and access to quality genetic testing is restricted by these patents, thereby harming the health of women and their families, particularly those most in need of the benefits of genetic technologies.[1]

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1. The parties have consented to the filing of this brief and letters of consent to the filing of this brief were lodged with the Clerk of the Court. Counsel of record for all parties received timely notice of the *amici curiae's* intention to file this brief, per Supreme Court Rule 37. No counsel for a party authored this brief in whole or part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* and their members or their counsel made a monetary contribution to its preparation or submission.

Amicus Curiae **The National Women's Health Network** develops and promotes a critical analysis of women's health issues in order to affect policy and support consumer decision-making. The Network aspires to a health care system that is guided by social justice and reflects the needs of diverse women. The Network supports the integrity of individual decision-making by providing independently researched, evidence-based information. They have particular expertise in research and evaluation of newly-developed drugs, devices and treatments and their impact on women's health.

Amicus Curiae **Generations Ahead (GA)** is a nonprofit community-based organization that expands the public debate and promotes policies on genetic technologies that protect human rights and affirm our shared humanity. By looking at the benefits and risks of these technologies for diverse communities including African-Americans, Latinos, Asian-Pacific Islanders, Native Americans, and people with disabilities, GA promotes policies that ensure full respect and human rights for all people.

Amicus Curiae **The Pro-Choice Alliance for Responsible Research (PCARR)** is a coalition of reproductive rights and justice advocates, bioethicists, academics, and community leaders working to promote accountability, safety and social justice in bio-medical research, including developments in genetics and biotechnologies, from a women's rights perspective. PCARR provides research and legal analysis to policymakers and consumers, and engages with administrative agencies to ensure that women's health outcomes are protected.

Amicus Curiae **Asian Communities for Reproductive Justice (ACRJ)** is a nonprofit community-based organization that promotes and protects reproductive justice. ACRJ believes that reproductive justice includes the economic, social and political power and resources to make informed health decisions. ACRJ works in communities of color to ensure that women and adolescents have the information they need to improve their own health status.

Amicus Curiae **The Center for Genetics and Society (CGS)** is a nonprofit information and public affairs organization working to encourage responsible uses and effective societal governance of genetic, reproductive and biomedical technologies. CGS works with a growing network of civil society leaders, health professionals, scientists, and others who share a commitment to advancing the public interest in the development of policy regarding human biotechnologies.

Amicus Curiae **Alliance for Humane Biotechnology** (AHB) is a non-profit association working for a culture of science that places the health and welfare of people and the natural environment above financial interests. AHB conducts outreach and education on the social implications of developments in biotechnology, particularly human genetics.

Amicus Curiae **G. Michael Roybal, MD, MPH** is the creator and Medical Director of the Roybal Comprehensive Health Center (CHC) in underserved East Los Angeles, which provides over 80,000 yearly patient visits for mostly uninsured individuals. Dr. Roybal attended Harvard but returned to California in order to help improve health care

in underserved Latino communities. In addition to his MD he obtained an MPH and has spent his career working with the Department of Health Services for Los Angeles County. His focus has been on healthcare redesign and reform, attempting to lead the County towards improved healthcare delivery.

Amicus Curiae **Anne L. Peters, MD,** is a Professor at the USC Keck School of Medicine and the Director of the Diabetes Clinic at the Roybal Comprehensive Health Center (CHC). Dr. Peters has created a program for cost effective diabetes care that has been replicated at five additional safety net sites throughout Los Angeles County. Internationally known as an expert in the field, Dr. Peters is on the Board of the American Diabetes Association and has received numerous grants to improve the health environment in low income areas.

SUMMARY OF ARGUMENT

The work of the *Amici Curiae* depends upon their ability to obtain the most current and accurate scientific findings about the human genome, to be able to interpret its meaning, and to transmit this information and knowledge to the communities, women, and patients they serve. The patenting of human genes, including the BRCA 1 & 2 genes at issue in the case, severely limits this ability. The practice restricts access to the human genome, thereby reducing the quantity and affecting the quality of biomedical research in human genetics; it prohibits the dissemination of information regarding the human genome, affecting the opportunities of clinicians to provide the highest caliber of healthcare to patients; and it complicates and threatens the use of new methods of genetic analysis in diagnostics and treatments.

Significantly, the patenting of human genes has a deleterious effect on the health and well-being of women, particularly women of racial and ethnic minorities and socio-economically disadvantaged women and their families who are unable to benefit from the unique promise of genetics and its use in biomedical research and clinical care. *Amici* organizations, individuals, and clinicians who advocate, educate, and treat patients to improve the health of women and eliminate disparities in the quality of healthcare are impeded in their efforts as a result of the continued practice of patenting human genes and the information they embody.

In addition, the claims at issue do not meet the standard of patentability as defined by this Court in *Chakrabarty*. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). The Federal Circuit erred in characterizing the isolated BRCA gene sequences as, a "distinct chemical entity," and thus, patent eligible, and not "products of nature," exceptions to the statutory classifications. The supposed *distinction* is based upon a minute structural change that occurs when the gene sequence is removed from the chromosome. Despite this, the fundamental character and nature of the patented human DNA, whether the isolated molecule, or the cDNA is identical to the DNA in its native state. It does not have a "distinctive name, character and use" from the human gene as it exists in the body nor is it "markedly different" from the genes in their native state. *Chakabarty,* 447 U.S. at 309-310. The Federal Circuit's flawed characterization of the nature of an isolated gene sequence and cDNA will create uncertainty in several areas of the law and genetics.

The patenting of isolated sequences necessarily encompasses the patenting of the sequential patterns

of amino acids of which they are constructed. These sequences embody the function for which they are being patented, the ability to code for proteins. The resulting exclusivity of their use and control negatively impacts the current state of health care in our nation, affecting a multitude of people from all races and classes in our society, including those most in need of the benefits of genetic knowledge. If the Federal Circuit's decision is not overturned by this Court the practice of patenting gene sequences will continue to impede the use of promising new genetic technologies and a complex and tangled patent landscape will continue to serve as a barrier to innovation and progress in research and clinical care. *Prometheus v. Mayo Collaborative Services,* granting, vacating and remanding 130 S. Ct. 3543 (2010), and cert. granted, 131 S. Ct. 3027 (June 20, 2011) will not reach the question of the preemptive effect of patenting the structure of the BRCA gene sequences, the function for which they are being patented, and the universal knowledge they embody. It is for these reasons that *Amici* urge the Court to resolve the important question of the patentability of the BRCA genes.

ARGUMENT

I. Patenting Human DNA, including the BRCA 1 & 2 Genes Diminishes the Quality and Accessibility of Medical Care, Particularly for Women, Women of Ethnic and Racial Minorities and Socio-Economically Disadvantaged Women and their Families.

This Court has recognized that "laws of nature, physical phenomenon, and abstract ideas" are not suitable for patent protection. *Chakrabarty,* 447 U. S. at 309. The

rationale is clear. Phenomena of nature, even though just discovered, are the "basic tools of scientific and technological work." *See Gottschalk v. Benson*, 409 U. S. 67 (1972). As such they should remain part of "the storehouse of knowledge…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)).

Isolated human DNA is a product of nature, an exception to the categories of eligible subject matter. Myriad's claims to the BRCA 1 & 2 genes allows them to exclude anyone from using these genes or copies of these genes outside of the human body, and as such is patent protection that impedes scientific progress. The BRCA composition claims restrict basic biomedical research on the genes as well as research and development of alternative and improved methods of testing for susceptibility to breast and ovarian cancer. The restrictions on the use of these genes deny clinicians the opportunity to offer accessible and quality testing for breast and ovarian cancer. Patents on genes slow the progress of medical genetics, as researchers and clinicians who are anxious to proceed with modern technologies such as multiplex testing and whole-genome sequencing (WGS) are deterred by their fear of infringement liability.

These impediments to research and clinical care have detrimental effects on the health and well-being of women, particularly women representing ethnic and racial minorities, and socio-economically disadvantaged women and their families.

A. Patenting Human Genes, Including the BRCA Genes, Restricts Basic Biomedical Research and Research and Development of Alternative Genetic Testing Methods.

The patenting and exclusive licensing of human genetic materials has hindered research in the United States by negatively affecting basic cultural norms of science and medicine. See, Shobita Parthasarathy, Patent Docs: *Gene Patenting Debate Continues,* available at: http://www.patentdocs.org/2009/06/gene-patenting-debate-continues.html. Thirty-five percent of surveyed geneticists reported that the sharing of basic data and research material has decreased substantially from previous decades, and 21% claim that research projects have been abandoned as a result of data being withheld. Eric G. Campbell, et al., *Data Withholding in Academic Genetics*, 287 JAMA 473, 473-80 (2002). "Empirical evidence demonstrates...a real fear on behalf of clinical laboratory directors and researchers …that patent holders can and will prevent them from conducting their research." Richard Gold and Julia Carbone, *Myriad Genetics: In the Eye of the Policy Storm*, 12 Genetics in Medicine S39 (2010) [hereinafter "Gold"]. Although Myriad claims it does not enforce its patents against researchers, Myriad has never publicly stated this policy in a written form, one which acts as a basis for the actions of others and which includes activities Myriad would consider as infringing. *See Secretary's Advisory Committee on Genetics, Health & Society*: *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*, 4-2010, at A26-27 [hereinafter "*Report*"]. Thus, "[a]mbiguity may itself stifle basic or clinical research as researchers either avoid the work altogether or are wary of public reporting results." *Id.* at A27.

Gene patents negatively affect follow-on public research about those genes, where researchers forego about one in ten research projects (more precisely, research publications). *Id.* at 27. The negative effects of patents on knowledge production are greatest for immediately useful genes, those closely linked to human disease. *Id.*

Prior to the issuance of Myriad's patents, researchers and scientists were studying BRCA genes, but ceased doing so when alerted to potential infringement liability. Laboratories reported nine instances of Myriad having enforced their BRCA patents, *id.* at 7, citing Mildred K. Cho, et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. Molecular Diagnostics 3, 5 (2003), and two laboratories received 'cease and desist' letters, including one at the University of Pennsylvania, the Genetics Diagnostics Laboratory (GDL). Gold, *supra* at S44. In 1998, "Myriad asserted that even though the GDL limited testing to patients in NCI [National Cancer Institute] research protocols, GDL was performing a patent-infringing third-party service in which it charged other laboratories and rendered clinical services." *Report* at A-26. Scientists expressed concerns about contributing their research results on the BRCA genes to public databases as the basis for invoking patent infringement claims, and one researcher from the University of Alberta was specifically told not to contribute new mutations based upon this assumption. Gold, *supra* at S44.

As a result of their exclusive testing, Myriad accumulated significant amounts of data relating to previously unknown mutations, 'variations of unknown significance' (VUS), but denied access to this important

information. John Conley, Dan Vorhaus, Robert Cook-Deegan: Genomics Law Report, March1, 2011: *How Will Myriad Respond to the Next Generation of BRCA Testing?*, *available at* http://www.genomicslawreport.com/index.php/2011/03/01/how-will-myriad-respond-to-t. In November 2004 they stopped contributing this data to the NIH open access Breast Cancer Information Core (BIC) mutation database, and ceased publishing information regarding the VUS in peer-reviewed literature, creating a major impediment to significant research. *Id.*

Clinical laboratories decide not to develop new or improved genetic tests in light of patents, where 53% of surveyed laboratory directors did not develop alternative tests. *See e.g.*, Cho, *supra* at 3-5. Researchers have stated that Myriad prevented the development of improved BRCA 1 & 2 tests, the ability to assess the quality of Myriad's tests, and the development of treatments for breast and ovarian cancer. Gold, *supra* at S44.

B. Myriad's Patents on BRCA 1 & 2 Genes Restricts the Accessibility of Genetic Testing for Breast and Ovarian Cancer, and Diminishes the Quality of Those Tests.

Based upon its BRCA patents, Myriad is the sole provider of genetic testing for breast and ovarian cancer in the United States and has stopped other laboratories from conducting testing on the genes. *Report* at 40. Identifying and providing alternative testing methods by researchers other than Myriad is prohibited, restricting access to numerous testing methods. Robert Cook-Deegan, Subhashini Chandrasekharan & Misha Angrist, *The Dangers of Diagnostic Monopolies*, 458 Nature 405 (2009).

These include methods which might be more cost-effective or efficient: "When compared to the most cost-effective mutation detection strategy analyzed…the average cost per mutation using the Myriad approach was five times as high," more than tests that had been developed and were used in Europe. *Report* at A-27. European methods do not necessarily insist upon initially testing the whole gene sequence as in the BRCA test, therefore Myriad has unilaterally established the "standard of care" in the United States; arguably precluding the use of potentially more efficient testing methods. *Id.* at A-28.

Myriad's patents preclude the possibility of patients accessing a confirmatory test from a different laboratory, equivalent to a physician's independent second opinion. *Report* at 44. Patients for whom Myriad's initial test produced inconclusive results may be forced to accept those results, relying only upon Myriad's data. This lack of information greatly impairs the decision-making of both a patient and their physician. "The ability to obtain a confirmatory test from a second laboratory is important because genetic test results can have implications for major medical decisions, such as whether to have a mastectomy or surgical removal of the ovaries." *Id.*

The quality of genetic testing is diminished as a result of exclusive patenting practices. Testing for the BRCA genes is limited to Myriad's laboratories, thus the test's accuracy in identifying mutations in the BRCA genes (analytical validity) and predicting a patient's risk for breast or ovarian cancer (clinical validity) cannot be determined by clinical geneticists outside of Myriad's purview without risking infringement. One study by non-clinical researchers found 10-20% of false negatives

in patients at high risk. Walsh T., Casadei S, Coat KH et al., *Spectrum of Mutations in BRCA 1, BRCA 2, CHEK and TP53 in Families at High Risk of Breast Cancer* 295 JAMA 1379 (2006) [hereinafter "Walsh"]. However since clinical geneticists cannot participate in similar studies, the effectiveness of Myriad's test cannot be validated.

Myriad's patent-based restrictions on the development of quality testing have produced serious harms. A 2006 study used an alternative, molecular testing method and found that Myriad's test missed up to 12% of large genomic deletions or duplications. Walsh, *supra* at 1380. Because this more accurate method requires the use of Myriad's patented gene sequence, the performance of the test would be considered an infringement. Myriad's decision not to use an alternative testing method (paraffin-embedded tissue) has "hampered availability of that type of testing in instances where it might be clinically useful." *House Judiciary Subcommittee on Courts, the Internet and Intellectual Property,* Washington D.C.: 2007, Statement of Wendy Chung. Myriad has "little incentive to analyze samples other than blood samples, thereby leaving 'families at risk with no remedy.'" *Id.*

Following the publication relating to their flawed test, Myriad developed an additional test to its BRACAnalysis test, the BRAC Analysis Rearrangement Test (BART). BART was not included in their standard test, and it had to be specially ordered. Mary Beattie, *UCSF Cancer Risk Program: Updated Test Improves Detection for Breast and Ovarian Cancer Gene*, available at: http://www.ucsfhealth.org/newsletters/primary_care_connections/june_2008/cancer_genes/. In a competitive marketplace the delay in developing the BART test might not have

occurred and could potentially have been included in a standard sequencing test.

One story illustrates damaging consequences. Elizabeth Cohen, *When Breast Cancer Tests Gets it Wrong*, *available at* http://www.cnn.com/2011/10/27/health/brca-genetic-testing-ep/index.html?eref=rss_mostp. Eileen Kelly was diagnosed with breast cancer, and had tested negative for the BRCA gene using the original Myriad BRACAnalysis test. Nevertheless her sister Kathleen Maxian later developed ovarian cancer. When Maxian told her surgeon that her sister had tested negatively for the genes he regretfully suggested that her sister's test might have been incomplete, and to find out if she had had the BART test. Kelly had not. When both sisters had the additional test, they tested positive for the genetic abnormality, indicating a 50-80% risk for breast cancer, and a 10-40% risk for ovarian cancer.

Maxian would have had preventive surgery if she had taken the test. Because of the delay in detection due to Myriad's faulty test, she has a 20% chance of survival in five years. Kelly's initial genetic counselor did not suggest the BART test as "information from Myriad led her to believe that BART mutations were extremely rare among women like Kelly without an extremely strong history of breast or ovarian cancer." *Id.*

Further limitations on both the availability and the quality of genetic testing for breast and ovarian cancer have resulted from Myriad's exclusive patents. Walsh, Lee, Casadei, Thorton, Stray, Pennil, Nord, Mandell, Swisher, and Mary-Claire King; PNAS Early Edition, *Detection of Inherited Mutations for Breast and Ovarian*

Cancer Using Genomic Capture and Massive Parallel Sequencing, www.pnas.org/cg/10.1073/pnas [hereinafter "King"]. Myriad's patents prevent labs from offering more rapid and cost-effective testing such as genomic capture and massive parallel sequencing for multiple breast and ovarian cancer susceptibility genes. If Myriad's initial tests are negative then testing for other breast or ovarian cancer genes is done selectively, based upon specific family or personal histories or physical examinations. These extra tests cost thousands more dollars beyond the costs of both Myriad's standard ($3,300) and BART ($700.00) tests. *Id.* However, with new and improved technology not used in Myriad's test, "it is possible to identify mutations in the 21 known breast and ovarian cancer genes in one sample for a cost…less than $1500.00 … with further bar-coding and indexing strategies the costs could be reduced to less than $500.00 per sample." *Id.*

These new testing methods are also more accurate than Myriad's tests. A new method of evaluating multiple genes in addition to BRCA 1 & 2 "identified a wide range of mutations in a variety of genes in 100% of [] test cases with zero spurious mutations called." *Id.* Six large deletions and duplications were identified, which could have been missed by Myriad's standard test. *Id.* "By allowing comprehensive parallel testing of multiple cancer susceptibility genes, we will be able to confidently identify the fraction of women with breast and ovarian cancer who carry a germline alteration in a cancer susceptibility allele and the characteristics of the tumors of patients' inherited mutations in various genes." *Id.* Such tests, however, cannot be done on the BRCA1 & 2 gene sequences without infringing Myriad's patents.

C. Exclusive Patenting Practices Impedes the Use of Next-Generation Sequencing and Genetic Testing Methods.

The patenting of human genes complicates and threatens the development and use of improved diagnostic techniques. The findings that approximately 20% of human genes are referenced in patent claims, the ownership of which is spread over a large number of assignees, have significant implications for the current and future use of new technologies. *Report* at 50-51. "While new technologies enable simultaneous evaluation of multiple genes through multiplex testing, parallel sequencing, and whole-genome sequencing, fragmented ownership may create a host of problems such as patent thickets, blocking patents, high transaction costs, royalty stacking, and holdouts. Some of these problems have already come to light. In particular, some laboratories using multiplex tests have chosen not to report to patients or ordering clinicians the results for certain patent-protected genes for fear of being sued… In short, the evidence indicates that patents have already limited the potential of these tests." *Id.* at 89.

Varying interpretations of claim language contribute to the uncertainty regarding patent infringement. Myriad's attorney stated that "without an isolating procedure directed at gauging BRCA mutations, whole genome sequencing would not infringe Myriad's patents." Turna Ray, "*At Appeals Hearing, Myriad Outlines Stance on BRCA IP Rights for Whole-Genome Sequencing*, April 4, 2010, available at: http://www.genomeweb.com/dxpgx/appeals-hearing-myriad-outlines-stance-brca-ip-rights. However he did not specify the meaning of the term, 'isolating.' *Id.* Scholar Robert Cook-Deegan questioned the

limiting effect of the term 'isolating': "How do you do DNA sequencing without some purification step? Even nanopore or scanning-tunneling (electro-machining) means isolating some piece of DNA…That's an 'isolated' molecule you're measuring. It's a meaningless distinction." *Id*.

Thus it has been suggested that for the WGS industry "….an examination of the specific patent claims in light of a company's sequencing technology-may be required for all or many of the thousands of human genome sequences subject to patent protection." Dan Vorhaus and John Conley, Genomics Law Report, *Whole Genome Sequencing and Gene Patents Coexist (For Now*) August 11, 2009, available at: http://www.genomicslawreport.com/index.php/2009/08/11/whole-genome-sequencing-and. This represents the type of high transaction costs that patents on human genes, such as those on the BRCA 1 & 2 genes, create. Particularly where multiplex and whole genome sequencing analysis is necessary to assess for the risk or existence of disease, concerns have been voiced that these barriers and costs will risk patient care. National Society of Genetic Counselors, Position Statement on Human Gene Patents, available at: http://www.nsgc.org/Advocacy/PositionStatements/tabid/107/Default.aspx (2010).

D. The Exclusive Patenting of the BRCA 1 & 2 Genes Harms Women, Particularly Women of Racial and Ethnic Minorities and Socio-economically Disadvantaged Women and their Families.

Myriad's patenting of the BRCA genes threatens the potential for continued innovations in the field of breast and ovarian cancer research, testing, and clinical care; clearly

impacting women in the United States: breast cancer is the second most common cancer among women, nearly one in four of diagnosed cancers. American Cancer Society, *Breast Cancer Facts and Figures 2009-2011* [hereinafter "ACS"]. Ovarian cancer accounts for approximately 3% of all cancers for women, and although it is the ninth most common cancer for women, it is the fifth leading cause of cancer-related deaths. *Id.*

The provision of the best therapeutic practices available is threatened as a result of the BRCA 1 & 2 patents. Patients who have a relatively high pre-test probability of having a mutation in a given cancer susceptibility allele are chosen for testing. King, *supra* at 4. However, many breast and ovarian cancer patients with BRCA 1 & 2 mutations have a negative family history, and as such will not undergo Myriad's testing. *Id.* As a result of the advent of specific inhibitors, treatments which effectively kill BRCA 1 & 2 mutated carcinomas, understanding the genetic basis of human cancers has *therapeutic* as well as preventive implications. *Id.* The availability of these inhibitors has increased the clinical incentive to identify BRCA 1 & 2 mutations in women with breast and ovarian cancer through genetic testing, which is limited by Myriad's patents. *Id.*

Myriad's BRCA patents create particular harms for women of racial and ethnic minorities and socio-economically disadvantaged women and their families. Access to cancer genetic testing and counseling for women of underserved racial and ethnic minorities is less than those in the white population, leading to growing health care disparities. Armstrong K, Micco E., Carney A. et al, *Racial Differences in the Use of BRCA 1/2 Testing Among Women with a Family History of Breast or*

Ovarian Cancer, 293 JAMA 1729 (2005). For example, African-American women are 78 % less likely to use genetic BRCA testing than white women. *Id.* Although more white women are diagnosed with breast cancer, African-American women are more likely to die from the disease. ACS, *supra* at 1.

The disparity in genetic testing originates "from the same social, cultural and economic forces that produce all heath care disparities." Michael J. Hall, Olufunmilayo I. Olopade, *Disparities in Genetic Testing: Thinking Outside the BRCA Box*, 24 J. Clin Oncol 2197 (2006) [hereinafter "Hall"]. The price of Myriad's test is necessarily prohibitive. "Myriad, as a monopolist, maximizes its profit through price discrimination in which it charges the highest price to those women who most value the test." *Report* at A-32. Financial restraints including the lack of insurance, underinsurance, and incomplete Medicare/Medicaid reimbursements result in underserved populations having lesser access than whites to genetic testing services and is a significant barrier to comprehensive cancer care. Michael J. Hall, Olufunmilayo I. Olopade, *Confronting Genetic Testing Disparities*, 293 JAMA 1783 (2005). Previous coverage for BRCA testing has been inconsistent, and reimbursement is restricted to those at high risk. *Report* at 37-38. Because of its price, access to BRCA 1& 2 testing is severely limited for those without insurance or with policies lacking testing coverage. *Id.* at 38.

Myriad's policies regarding their supplemental BART test have deleterious effects for economically disadvantaged women and their families. K.M. Shannon et al., *Which Individuals Undergoing BRACAnalysis Need*

BART testing? 204 Cancer Genetics 416 (2011). Complete genetic testing (sequencing plus tests for genomic rearrangements) is indicated for *all* families with histories suggesting a BRCA 1 or BRCA 2 mutation. *Id.* However, if a patient's history does not meet Myriad's defined BART testing criteria, the test will be billed separately, costing $700.00. Although some companies will reimburse the costs, many do not, and for some insurers, BART is considered to be an investigational test, excluded from coverage and thus prohibited for those unable to afford the out-of-pocket costs. *Id.*

Women of underserved racial and ethnic minorities are also disproportionately affected by Myriad's patents in regards to the quality of the genetic tests being offered. Approximately 12% of patients with breast cancer and "severe" family history (defined as at least four cases of breast or ovarian cancer) who test negative for the BRCA 1 & 2 genes will be found to have a large genomic deletion or duplication in one of these genes, known as large genetic rearrangements. *Id.* Myriad's own data suggests that such large rearrangement BRCA mutations are over-represented and account for a larger percentage of mutations than previously thought in some populations, e.g., 20% of Latina women. *An Open Letter to Myriad Genetics*, Friday, July 22, 2011, *available at* http://yalecancergeneticcounseling.blogspot.com/2011_07_01_archive.html).

The lack of access to Myriad's test also diminishes the quality of tests in assessing risks for breast and ovarian cancers in underserved populations. "The majority of demographic and tumor-related data used to develop risk models comes from high-risk white families…their

applicability in the nonwhite population may be reduced and their performance suboptimal." Hall, *supra* at 2199. Models for risk assessment used in BRCA testing depend upon accurate estimates of population-specific prevalence to estimate probabilities in particularly high risk genotypes, however the prevalence of Ashkenazi groups in testing shows a 10 fold increased prevalence in this ethnic group compared with estimates for the remaining U.S. population. *Id.* Without accurate estimates of mutation prevalence in minority subgroups, the reliability of these models is compromised. *Id.*

II. The Federal Circuit Erred in its Characterization of the Composition Claims as Statutory Subject Matter.

Products of nature are exceptions to the statutory categories of patentable subject matter under §101. *Chakrabarty*, 447 U. S. at 313. The question is whether the claims are for a patentable "non-naturally occurring manufacture or composition of matter-a product of human ingenuity 'having a distinctive name, character [and] use' *Hartranft.v Wiegmann*, 121 U. S. 609, 615 (1887)" *Chakrabarty* at 309-310, or claims to 'hitherto unknown natural phenomenon,' which are not so qualified." *Id.* For the claim to be patentable the invention must possess "markedly different characteristics from any…found in nature." *Id.* at 310. The Federal Circuit erred in its determination that the BRCA composition claims are patent eligible.

The court relied on *Chakrabarty* and *Funk Brothers* to decide the patent eligibility of isolated DNA molecules. *Ass'n for Molecular Pathology v. U.S. Patent and*

Trademark Office, 653 F.3d 1329, 1351 (Fed.Cir.2011). What distinguished Chakrabarty's invention from the invention in *Funk Brothers* was "markedly different characteristics from any…found in nature." *Id*., citing *Chakrabarty*, 447 U.S. at 310. Thus, the patentability of isolated DNA "turns on a change in the claimed composition's identity compared with what exists in nature." *Id.*

Finding that DNA molecules exist in the body (native DNA) as part of a "large structural complex," (i.e., part of a chromosome), isolated DNA, is a "free-standing portion of a native DNA molecule, frequently a single gene." *Id* at 1352-1352.. Because it "had been cleaved (i.e., had covalent bonds in its backbone chemically severed) or synthesized," the number of nucleotides from the BRCA 1 & 2 genes as they existed in their native state had been greatly reduced. *Id.* The resulting isolated DNA became a distinctive chemical identity. *Id.* at 1351-1355. It is only the act of their being isolated, "portions of larger entities," which renders them distinctive and thus patent-eligible. *Id.* at 1353.

The Federal Circuit offers no further evidence of why the isolated or synthesized molecules have a distinctive name, character, or use, or why a minute change in physical structure makes the isolated or synthesized DNA markedly different from native DNA. Rather the court ignored arguments regarding the essential and fundamental characteristics of isolated and synthesized BRCA 1 & 2 genes which serve to prove they are not markedly different from those in their native state, by erroneously insisting that these arguments can be reduced to only one *similarity* to the genes in their native state,

as opposed to specifying differences: "the informational content contained in isolated and native DNAs' nucleotide sequence." *Id.* The informational content was found to be irrelevant: "We recognize the biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than their functions." *Id.*

This bifurcation of the gene into a hierarchy of structural and functional components dismisses biological facts (i.e., functionality) and ignores the unique informational content of isolated DNA molecules, thereby denying the essential qualities, the fundamental nature, or "identity" of the subject matter at issue. The claims indicate that their *biological* function, unlike other chemicals, is the conveyance of specific information as dictated by the sequential order of the nucleotides which direct the proteins, cells, and organs that make up the body. Unlike other chemicals, the patent claims describe the nucleotide sequence. This *biological* function is the defining and identical characteristic of DNA both before and after isolation or synthesis, thus isolated and synthesized DNA is not markedly different from native DNA, nor does it have a distinctive name, character, and use.

The name "isolated" does not impart special or distinguishing qualities from that of native DNA. The minute structural change, removal of the DNA molecule from the chromosome does not render the character of the isolated DNA *markedly* different, or distinctive enough to change its "identity," the fundamental nature, or character for which it is being patented. Despite a different chemical structure, cDNA connotes that the DNA is complementary,

not markedly different from native DNA, having been synthesized from and containing the same information as the template, the naturally occurring DNA sequence.

Judge Moore, concurring in judgment, reasoned that for some of the isolation claims, its additional utility is the basis for considering these molecules "markedly different." *See Id.* at 1363, Moore, Circuit Judge concurring in-part. Whereas the majority focuses on the physical structure of the gene and dismisses its functionality, i.e., its *biological* properties, Judge Moore's concurrence dismisses the importance of its basic underlying functionality, or usefulness, illuminated by biology: the gene's ability to transmit information inside a person's body. If isolated or synthesized DNA had a markedly different use from native DNA, their applications in research and diagnostics could not take advantage of the natural biological characteristics of DNA sequences to code for a protein and to anneal to its complementary nucleotide sequence.

The Federal Court's ruling is based upon a narrow and limited characterization of a human gene once excised from the human body, simply a man-made chemical separate from its biological nature. Although the court is concerned with "disrupt[ing] the settled expectations of the inventing community," it does not recognize the possible implications that the characterization might have for disrupting areas of law that rest upon the biological qualities of human genes. *Id.* at 1354-1355. Finding the informational content irrelevant could potentially disturb criminal forensic law, genetic privacy law, tort duties regarding the conveyance of the results of genetic testing, and genetic discrimination, such as the federal Genetic Information Non-Discrimination Act.

III. This Court's Ruling in *Prometheus v. Mayo* Will Not Decide the Important Issue in this Case.

Illustrated by the arguments presented above, patents on human genes such as Myriad's numerous and broad BRCA 1 & 2 claims impede scientific progress and imperil the health and well-being of woman and their families. The harms of patenting genes grow exponentially. When access and quality genetic testing for breast and ovarian cancer is limited, not only is the health of the woman in need of the test threatened, her children and family are also affected, creating a major impediment to exactly the type of preventive medicine needed to reduce our over-burdened and high-cost healthcare system.

Many of these important testing methods rest on patenting the underlying sequence information of the specific genes in question. Although this Court in *Prometheus v. Mayo Collaborative Services* will answer important questions regarding the patentability of natural phenomenon and scientific correlations involved in certain healthcare related technologies, it will not reach the issue of the patentability of human genes, genetic sequences, and the biological information so critical to the future of health and medicine, that they embody.

CONCLUSION

For the foregoing reasons the petition for writ of certiorari should be granted.

Respectfully submitted,

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