UNITED STATES DISTRICT COURT
FOR THE 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, Plaintiffs, -against- 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.	No. 09 Civ. 4515 (RWS) ECF Case DECLARATION OF DR. GREGORY C. CRITCHFIELD

I, Gregory C. Critchfield, declare:

1. I am President of Myriad Genetic Laboratories, Inc., a wholly owned subsidiary of Myriad Genetics, Inc. (referred together as "Myriad"). I have held this position since July 1998. I received my M.D. from the University of Utah, and my M.S. in Biophysical Sciences from the University of Minnesota. I am Board Certified in Clinical Pathology. Before joining Myriad, I served as Senior Vice President, Chief

Medical and Science Officer of Quest Diagnostics Inc. A copy of my curriculum vitae and a list of publications by me are provided in the **Exhibits 1 and 2**, respectively.

I. MYRIAD'S PATENT RIGHTS HAVE PROMOTED RESEARCH

2. Myriad was founded to conduct innovative research to discover and isolate disease genes, and to commercialize genetic testing based on the disease genes. Today Myriad is still active in research and discovery to develop prognostic, personalized, and predictive medicine testing products. It is in Myriad's own interest that neither basic nor clinical research be stifled by patents. In fact, Myriad has consistently promoted and encouraged both basic and clinical research on the *BRCA1* and *BRCA2* genes by others, by (1) allowing academic scientists to conduct research studies on the *BRCA1* and *BRCA2* genes freely; (2) providing direct assistance to researchers in their studies on the *BRCA1* and *BRCA2* genes; and (3) conducting its own research on the *BRCA1* and *BRCA2* genes, publishing the research results and actively disseminating information on the *BRCA1* and *BRCA2* genes.

Myriad Allows Research on the *BRCA1* and *BRCA2* Genes Freely

3. It has been, and still is, Myriad's policy and practice to allow scientists to conduct research studies on the *BRCA1* and *BRCA2* genes freely. This has been commonly understood by academic scientists in the field. For example, Plaintiff Wendy Chung acknowledges that researchers "could sequence the *BRCA1* and *BRCA2* genes for purely research purposes." D. Chung ¶ 15. In fact, Dr. Chung has been doing so. *See e.g.,* D. Chung ¶ 11 ("As part of my molecular genetics research, we sequence human genes, including the *BRCA1* and *BRCA2* genes of research subjects in my research lab. We look at the sequences to determine if there are any alterations and investigate whether

those alterations have clinical significance."). Indeed, tens of thousands of researchers have been conducting research on the *BRCA1* and *BRCA2* genes and published thousands of research papers on the *BRCA1* and *BRCA2* genes. *See* ¶ 13 below; *see also*, D. Parvin; D. Li; D. Baer; D. Sandbach.

Myriad Provides Direct Assistance to Researchers in Their Studies

4. Myriad and its collaborators published their landmark research on the *BRCA1* and *BRCA2* genes in 1994 and 1996, respectively. Since then, Myriad has provided assistance to researchers around the world in their independent studies on the genes.

5. Since 1994, Myriad has provided genetic materials such as cDNA clones of the *BRCA1* and *BRCA2* genes free to researchers at over 30 research institutions all over the world, including, among others, the University of Pennsylvania, Emory University, the University of Chicago, and the University of Rochester. These researchers have since published a total of 336 peer-reviewed scientific papers related to *BRCA1* and *BRCA2*.

6. Myriad also has a policy to collaborate with researchers on studies relating to the *BRCA1* and *BRCA2* genes. In fact, since the *BRCA1* and *BRCA2* genes were discovered, Myriad has collaborated with over 440 outside researchers and participated in more than 110 research programs/studies by outside researchers in further studies of *BRCA 1* and *BRCA2*.

7. For example, in 1999, to further encourage research on the *BRCA1* and *BRCA2* genes, I proposed to Dr. Richard Klausner, the then National Cancer Institute ("NCI") Director, for Myriad to provide *BRCA* testing services to researchers conducting

studies funded by NCI and other NIH Institutes. In December 1999, a Memorandum of Understanding (MOU) between Myriad and NCI was signed. Under the MOU, Myriad agreed to provide research testing services at a fraction of the commercial testing price to researchers conducting research funded by NCI or another Institute under the National Institute of Health. The MOU was renewed twice for a total of six years. During those six years, 178 scientists received the discounted research testing services and 5,932 individuals were tested for *BRCA* mutations under the MOU. This program provided support for a number of key research groups that led to important publications on *BRCA* mutation prevalence and the value of clinical intervention in *BRCA* mutation carriers.

8. In another important area, Myriad worked with noted researchers on efforts to classify genetic variants of uncertain clinical significance ("VUS"), making data available from our large sequence database.[1] In these studies, Myriad provided the researchers with information from its database of gene sequence information built upon the largest scale of clinical genetic testing on *BRCA1* and *BRCA2* in the world. This was critical to the researchers' studies. The published research results have the potential of improving the diagnostic testing for a number of other genes.

9. Myriad's contribution to research is also evidenced by the tens of millions of dollars in patent royalty payments made to research institutions such as the University of Utah, National Institute of Health, the University of Pennsylvania, the University of Toronto, and Laval University, all of which collaborated with Myriad in research to identify and isolate the *BRCA1* and *BRCA2* genes.

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[1] *See e.g.,* Abkevich *et al.*, *Analysis of Missense Variation in Human* BRCA1 *in the Context of Interspecific Sequence Variation*, J. MED. GENET., 40:492-507 (2004); Goldgar *et al.* & Breast Cancer Information Core (BIC) Steering Committee, *Integrated Evaluation of DNA Sequence Variants of Unknown Clinical Significance: Application to* BRCA1 *and* BRCA2, AM. J. MED. GENET., 75:535-544 (2004).

Myriad Actively Publishes Its Own Research and Disseminates Scientific Information on the *BRCA1* and *BRCA2* Genes

10. Besides assisting outside researchers in their research, Myriad also has been actively conducting its own research for a better understanding of the *BRCA1* and *BRCA2* genes. More importantly, Myriad has been actively publishing its research findings in peer-reviewed journals, and abstracts and posters in scientific meetings. To date, Myriad has made 128 publications on the *BRCA1* and *BRCA2* genes in peer-reviewed journals and scientific meetings.

11. Shortly after the discoveries of the *BRCA* genes by Myriad and its collaborators, Myriad, under no obligation to do so, worked with other researchers to build the Breast Cancer Information Core ("BIC") database (http://www.research.nhgri.nih.gov/bic/), a central repository for information regarding *BRCA* mutations. The BIC database is an open access on-line database that provides valuable information to scientists in their early research on the *BRCA1* and *BRCA2* genes. Myriad is the largest contributor to this database, and made more than 20,000 submissions to the database.

12. In addition, Myriad has published the most clinical data on mutation risk in the *BRCA1* and *BRCA2* genes based on its extensive experience from the largest scale of genetic testing ever conducted in the world.[2] The mutation risk data have been tabulated and posted on Myriad's website (http://www.myriadtests.com/provider/mutprevo.htm), and are frequently updated by Myriad and freely available to researchers and clinicians throughout the world. Using these mutation prevalence tables, researchers and physicians can readily determine an

[2] *See* Frank *et al.*, *Clinical Characteristics of Individuals with Germline Mutations in* BRCA1 *and* BRCA2: *Analysis of 10,000 Individuals*, J. CLIN. ONCOL., 20:1480-90 (2002).

individual's predicted risk of harboring a deleterious *BRCA* mutation based on his or her personal cancer history and family history. *See* Exhibit 3. These tables have been widely accessed by researchers and clinicians worldwide.

Significant Progress Has Been Made in Research on the *BRCA* Genes

13. Scientific research in *BRCA*-associated hereditary breast and ovarian cancers not only has been made possible by the landmark discoveries and publications by Myriad and its collaborators, but also has been significantly promoted by Myriad's policy and practice as summarized above. Indeed, a recent search of the PubMed medical literature database shows that since Myriad's publications of the discoveries of the *BRCA1* and *BRCA2* genes in October, 1994,[3] and March 1996,[4] respectively, more than 18,000 scientists have researched the *BRCA* genes, publishing more than 5,600 research papers on *BRCA1* and over 3,000 research papers on *BRCA2*. Many of these scientists are members of the institutional Plaintiffs in this suit including the Association for Molecular Pathology, American College of Medical Genetics, American Society for Clinical Pathology, and College of American Pathologists. Among these scientists are also members of *amici* supporting the Plaintiffs' case including the American Medical Association, American Society of Human Genetics, American College of Obstetricians and Gynecologists, American College of Embryology, and the Medical Society of the State of New York. Notably, the individual plaintiffs in this suit and their supporting

[3] Miki *et al.*, *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene* BRCA1, SCIENCE, 266:66-71 (1994).
[4] Tavtigian *et al.*, *The Complete* BRCA2 *Gene and Mutations in Chromosome 13q-Linked Kindreds*, NAT. GENET., 12:333-7 (1996).

declarants alone have published a total of 48 peer-reviewed research papers on the *BRCA1* and *BRCA2* genes. *See* Exhibit 4.

14. Thanks in part to Myriad's active effort in promoting research, scientists have made impressive progress in understanding and even harnessing the *BRCA1* and *BRCA2* genes. For example, when Myriad and its collaborators identified and isolated the *BRCA1* and *BRCA2* genes, the data showing their association with predisposition to cancer was generated from selected Caucasian family pedigrees. Researchers now know that mutations in the *BRCA1* and *BRCA2* genes confer high risk for hereditary breast and ovarian cancer in a variety of human population groups.[5] Also, when the genes were discovered, the biological mechanism underlying their association with cancer was unknown. Today, scientists understand that functional BRCA1 and BRCA2 proteins prevent mutations and cancer through homologous recombination by repairing double-stranded DNA damages.[6]

15. Importantly, extensive clinical research has uncovered various means to reduce the risk of breast and ovarian cancer once *BRCA* mutations carriers are identified. For example, the risk of breast cancer can be reduced by up to 90% by prophylactic mastectomy in *BRCA* mutation carriers.[7] The risk of breast cancer can be reduced as

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[5] *See* James D. Fackenthal & Olufunmilayo I. Olopade, *Breast Cancer Risk Associated with* BRCA1 *and* BRCA2 *in Diverse Populations*, NAT. REV. CANCER, 7:937-948 (2007).

[6] *See e.g.,* Gowen *et al.*, BRCA1 *Required for Transcription-Coupled Repair of Oxidative DNA Damage*, SCIENCE, 281:1009-12 (1998); Welcsh *et al.*, *Insights into the functions of* BRCA1 *and* BRCA2, TRENDS GENET., 16:69-74 (2000).

[7] *See e.g.,* Hartmann *et al.*, *Efficacy of Bilateral Prophylactic Mastectomy in* BRCA1 *and* BRCA2 *Gene Mutation Carriers*, J. NATL. CANCER INST., 93:1633-7 (2001); Rebbeck *et al.*, *Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in* BRCA1 *and* BRCA2 *Mutation Carriers: the PROSE Study Group*, J. CLIN. ONCOL., 22:1055-62 (2004).

much as 72% by prophylactic oophorectomy in *BRCA2* mutation carriers.[8] The risk for ovarian cancer is reduced by 85-96% by prophylactic risk- reducing oophorectomy in *BRCA* mutation carriers.[9] In addition, mortality risk can be significantly reduced by bilateral prophylactic risk-reducing salpingo-oophorectomy in *BRCA* mutation carriers.[10] Also, tamoxifen use in *BRCA* mutation carriers for five years reduces the odds of contralateral breast cancer by 50%.[11] Finally, researchers have also found that the use of oral contraceptives for at least six years is associated with a 60% decreased risk of ovarian cancer.[12]

16. Exciting research on the *BRCA* genes has also suggested improved and personalized chemotherapies in cancer patients. For example, scientists have found that breast cancer tumors must possess intact BRCA function in order to exhibit sensitivity to spindle poisons such as taxol and vinblastin, while tumors lacking BRCA function exhibit increased sensitivity to cytotoxic DNA-damaging agents such as cisplatin.[13]

17. Indeed, new drugs such as PARP1 inhibitors are being developed targeting the biological pathway centering around BRCA1 and BRCA2 proteins in cancer cells. Examples of such PARP1 inhibitor drugs in development include olaparib (also

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[8] *See e.g.,* Kauff *et al., Risk-Reducing Salpingo-Oophorectomy for the Prevention of* BRCA1- *and* BRCA2-*Associated Breast and Gynecologic Cancer: A Multicenter, Prospective Study*, J. CLIN. ONCOL., 26:1331-7 (2008).

[9] *See e.g.,* Rebbeck *et al., Prophylactic Oophorectomy in Carriers of* BRCA1 *or* BRCA2 *Mutations*, N. ENGL. J. MED., 346:1616-22 (2002).

[10] *See e.g.,* Domchek *et al., Mortality after Bilateral Salpingo-Oophorectomy in* BRCA1 *and* BRCA2 *Mutation Carriers: A Prospective Cohort Study*, LANCET ONCOL., 7:223-9 (2006).

[11] *See e.g.,* Narod *et al., Tamoxifen and Risk of Contralateral Breast Cancer in* BRCA1 *and* BRCA2 *Mutation Carriers: A Case-Control Study*, LANCET, 356:1876-1881 (2000).

[12] *See e.g.,* Narod *et al. Oral Contraceptives and the Risk of Hereditary Ovarian Cancer*, N. ENGL. J. MED., 339:424-428 (1998).

[13] *See e.g.,* Kennedy *et al., The Role of* BRCA1 *in the Cellular Response to Chemotherapy*, J. NATL. CANCER INST., 96:1659-68 (2004); Farmer *et al., Targeting the DNA Repair Defect in BRCA Mutant Cells as A Therapeutic Strategy*, NATURE, 434:917-21 (2005).

known as AZD2281) by AstraZeneca[14], BSI-201 by BiPar Sciences Inc.[15], ABT-888 by Abbott Laboratories, Inc.[16], and AG014699 by Pfizer[17]. Screening for *BRCA1* and *BRCA2* mutations can allow such drugs to be administered specifically to cancer patients harboring such mutations. This personalized approach provides patients with optimized treatment while avoiding wasteful spending on ineffective therapies. As a matter of fact, Myriad has been using its expertise in *BRCA* mutation screening to help AstraZeneca in its development of olaparib, which has shown great promise in clinical trials.

18. In summary, tremendous progress has been made in the field of *BRCA1* and *BRCA2* and hereditary breast and ovarian cancer. Because of all the research in this area, physicians today are able to conveniently estimate the risk of *BRCA* mutation in a given individual, and identify candidates for BRAC*Analysis*® testing. Moreover, once *BRCA* mutations are detected, effective options validated by research are available to reduce the risk of breast and ovarian cancer in healthy individuals or the risk of second cancer in cancer patients. In addition, tailored chemotherapy regimens can be selected for cancer patients based on the *BRCA* mutation status. More excitingly, effective PARP1 inhibitors targeting tumors with *BRCA* mutation are on the horizon. Myriad's discovery and publication of the *BRCA1* and *BRCA2* genes opened the doors to all of these advances in science. Myriad's policy and practice of promoting research has

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[14] Fong *et al., Inhibition of Poly(ADP-ribose) Polymerase in Tumors from BRCA Mutation Carriers*, N. ENGL. J. MED., 361:123-34 (2009).
[15] Kopetz *et al., First in Human Phase I Study Of BSI-201, A Small Molecule Inhibitor of Poly ADP-Ribose Polymerase (PARP) in Subjects with Advanced Solid Tumors*, J. CLIN. ONCOL., 26: 2008 (May 20 suppl; abstr 3577).
[16] Yang *et al., Immunohistochemical Detection of Poly(ADP-Ribose) Polymerase Inhibition by ABT-888 in Patients with Refractory Solid Tumors and Lymphomas*, CANCER BIOL. THER., 8:2002-7 (2009).
[17] Plummer *et al., Phase I Study of the Poly(ADP-Ribose) Polymerase Inhibitor, AG014699, in Combination with Temozolomide in Patients with Advanced Solid Tumors*, CLIN. CANCER RES., 14:7917-23 (2008).

facilitated such significant progress in science and medicine. The notion advanced by the Plaintiffs that research has been stifled by the patents at issue in this lawsuit is contradicted by the evidence.

Myriad Has Never Stopped Scientists from Doing Research

19. In the late 1990s, Myriad sent cease and desist letters to the University of Pennsylvania regarding the commercial (not research) *BRCA* testing activities of Drs. Haig Kazazian and Arupa Ganguly at the Genetic Diagnostic Laboratory on the campus. The purpose of these letters was to request that Drs. Haig Kazazian and Arupa Ganguly cease their commercial diagnostic testing. Myriad has never requested Drs. Kazazian and Ganguly, or anyone else, to not conduct research.

20. Plaintiffs Haig Kazazian and Arupa Ganguly at the Genetic Diagnostic Laboratory of the University of Pennsylvania were very quick in rushing to commercially exploit the fruits of the hard-earned discoveries by Myriad and its collaborators. The commercial nature of their *BRCA* testing services in the 1990s has been admitted by Plaintiff Kazazian. *See e.g.,* D. Ganguly ¶ 4; D. Kazazian, ¶¶ 3, 4, 8 and 10 ("At the time we were forced to stop offering BRCA genetic services, we were charging patients less than Myriad was charging.") (emphasis added). As Dr. Kazazian stated, "[t]hrough the Genetic Diagnostic Laboratory, Dr. Ganguly and I provide state-of-the-art DNA-based diagnostic testing for a variety of genetic conditions and diseases, as well as prenatal and predictive testing and genetic counseling services." D. Kazazian, ¶ 3 (emphasis added). The commercial nature of the lab is also confirmed by the information on its website.[18] For example, billing (CPT) codes are associated with every genetic test the lab offers.

[18] *See* Penn Medicine: The Genetic Diagnostic Laboratory, http://www.med.upenn.edu/gdl/ (last visited December 8, 2009).

For any testing by their lab, "[p]ayment is required with sample submission. Patients may choose to pay for their testing on a major credit card or submit a money order or personal check payable to the Genetic Diagnostic Laboratory."[19] *See id.*; *see also* Exhibit 5.

21. The *BRCA* testing by Dr. Ganguly offered to the Cancer Genetics Network Project in 1998-1999 was also commercial in nature. D. Ganguly ¶¶ 12 & 13. The principal involvement by Dr. Ganguly in the Project was conducting DNA testing on the *BRCA1* and *BRCA2* genes for fees. *See id.* Dr. Ganguly's lab was acting as a central core lab for researchers much like other commercial core labs. In a meeting in late 1999 at the National Cancer Institute ("NCI") with Dr. Kazazian and Dr. Richard Klausner, the then NCI director, Dr. Klausner clearly told Dr. Kazazian that the *BRCA* testing Drs. Kazazian and Ganguly were conducting was clearly commercial and did not qualify as research.

22. Moreover, during a personal meeting with Plaintiff Dr. Haig Kazazian sometime between 1999 and 2000, I told him that he was free to do academic research on the *BRCA1* and *BRCA2* genes including sequencing the genes and detecting mutations in the genes.

23. There is simply no evidence that Myriad has stopped or deterred any scientists from conducting research.

II. PATENTS HAVE PROMOTED PATIENT ACCESS TO *BRCA* TESTING

24. I believe broad "patient access" to a genetic test requires that (1) there be significant awareness and understanding of the test by patients and their healthcare

[19] *Id.*

providers, and as a result, there is a desire for the test by those patients who may benefit from the test, (2) the test be of high quality and readily available when patients need it and test results are obtained in a timely manner, and (3) the test be affordable to most patients.

25. To date, Myriad has performed over 400,000 BRAC*Analysis*® tests for *BRCA* mutations. We receive tests from all 50 states. Over 40,000 healthcare providers have ordered and used the test. Presently, test results are typically available within two weeks. More than 90% of the BRAC*Analysis*® tests ordered by healthcare providers are covered by insurance, and the average reimbursement rate is over 90% of the cost of the test. There are more than 2,600 insurance payors who reimburse for the BRAC*Analysis*® test. There are more than 80,000 insurance plans that cover the BRAC*Analysis*® test. This undeniable "patient access" is the very result of Myriad's enormous investment in research, development, insurance coverage, and more importantly in raising patient and physician awareness and understanding of the test. Myriad would not have made the investment of more than 200 million dollars in raising patient and physician awareness alone without the protection provided by the exact patents the Plaintiffs are challenging. Myriad's story stands as a clear example of societal benefit due to patent protection. I am not aware of any diagnostic or pharmaceutical company that has made, or would be willing to make, this enormous investment without the benefit of a limited period of exclusivity engendered by patent rights.

The Awareness Barrier

26. When Myriad launched the commercial BRAC*Analysis*® test in late 1990s to screen for mutations in the *BRCA1* and *BRCA2* genes, knowledge about the genes was

largely limited to genetic researchers in universities. Moreover, the greatest benefit of the test is to find healthy carriers of *BRCA* mutations who have not developed cancer, so that early surveillance and preventive measures can be offered to these individuals. Without a good understanding of the role that *BRCA* mutations play in hereditary breast and ovarian cancer and genetic testing, there is little motivation for healthy individuals to even seek advice on genetic testing or their risks for predisposition to hereditary cancer.

27. To bring genetic testing, or the BRAC*Analysis*® test, to those patients who can benefit from it, Myriad had to invest significant time and money to raise the awareness and understanding of genetic testing to patients and their healthcare providers, and to educate and convince the insurance industry of the pharmacoeconomics of the test. For example, Myriad has established a 300-person sales force calling on oncologists and OBGYN doctors all over the country. Our sales representatives, genetic counselors and medical specialists are well-trained and well-versed on our tests. They meet personally with physicians, nurses and genetic counselors, providing them with research papers and educational materials, answering questions on our tests, and helping in testing logistics. Our large team of in-house genetic counselors and medical experts provide their expertise to help healthcare providers understand *BRCA* mutations, the BRAC*Analysis*® test and hereditary breast and ovarian cancer. In addition, Myriad organizes hundreds of educational meetings for physicians to learn about *BRCA* testing and hereditary breast and ovarian cancer from thought leaders who share their experience with their peers ("speakers programs"). For example, during the July – September, 2009 quarter alone, Myriad organized more than 300 such speakers programs all over the country.

28. Direct proactive approaches in patient education have been shown in research studies to be especially important in getting the message across to healthy family members of cancer patients about the benefit of undergoing *BRCA* mutation screening.[20] Significantly, we have invested millions of dollars in patient awareness promotions on TV and other popular media to raise the awareness of hereditary breast and ovarian cancer and BRAC*Analysis*® testing. Such promotions introduce hereditary breast and ovarian cancer and encourage people who may be at risk for hereditary cancer to speak to their healthcare providers about their personal and family history of cancer to determine if genetic testing is appropriate for them. Our patient and physician outreach has made *BRCA* mutation testing available even in more remote rural areas. Without patent exclusivity, Myriad would not have made these investments.

29. Indeed, because of Myriad's efforts, we now routinely receive patient samples from everywhere in all 50 states. More than 40,000 physicians and genetic counselors have used the BRAC*Analysis*® test. Over 400,000 patients who meet testing criteria have been tested at Myriad for mutations in the *BRCA1* and *BRCA2* genes. To say that Myriad's patent rights have limited patient access is simply ignoring the facts. To the contrary, patient awareness and access to important genetic testing has been significantly enhanced as a result of the patent grants at issue in this case.

30. The diagnostic labs run by the geneticists plaintiffs such as those by Drs. Kazazian and Ganguly (the Genetic Diagnostic Laboratory at the University of

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[20] *See e.g.,* Evans *et al.*, *Comparison of Proactive and Usual Approaches to Offering Predictive Testing for* BRCA1/2 *Mutations in Unaffected Relatives*, CLIN. GENET., 75:124-32 (2009); *see also* Suthers *et al.*, *Letting the Family Know: Balancing Ethics and Effectiveness When Notifying Relatives about Genetic Testing for A Family Disorder*, J. MED. GENET., 43:665-670 (2006).

Pennsylvania), Dr. Harry Ostrer (the Genetic Lab at NYU Langone Medical Center) and Drs. David Ledbetter and Stephen Warren (at Emory Genetics Laboratory) are all within major universities typically serving only patients within the major teaching hospitals affiliated with their respective universities. None of them would have been able to make the substantial capital investment to do what Myriad has done in raising awareness and understanding of *BRCA* testing and reaching individuals who need these test services most, even in rural communities.

The Cost Barrier

31. Insurance reimbursement is a major barrier for patient access to any medical product. Myriad has invested significantly in building a strong marketing department including a team of experts specialized in working with insurance payors (private insurance companies, state-run Medicaids and Medicare) for reimbursement agreements to cover the cost of genetic testing. Today, Myriad has in place over 400 contracts with private insurance payors that cover over 130 million lives in the US. Additional lives are covered under Medicaid and Medicare plans. In fact, between July 2007 and now, more than 2,600 insurance payors have reimbursed the BRAC*Analysis*® test under more than 80,000 insurance plans.

32. To reduce the out-of-pocket expense for patients, Myriad has set up a large Billing and Customer Service Department. Almost 150 individuals in this department interact daily with patients, their doctors, and their insurance companies to help patients work through the complexities of insurance coverage that could potentially prevent patients from receiving important testing services. Due to their efforts, over 90% of the tests Myriad performs are covered by insurance at over 90% of the test cost. As a

result, for the 90% of testing covered by insurance, the weighted average out-of-pocket cost to each patient is less than $100.

33. At Myriad, we also understand that there are patients in our country who do not have insurance and need help. Since 1996 when BRAC*Analysis*® was launched, Myriad has had a financial assistance program directly providing free testing to low-income, uninsured patients. Just in the last four years, more than 3,000 patients have received free *BRCA* testing under this program (about 55 tests a month). In addition, Myriad also makes free testing available to needy patients through independent non-profit organizations such as the Cancer Resource Foundation ("CRF") in Massachusetts. *See* http://www.breastcancerma.org/helping-hand/#genetic. In fact, through the CRF, MassHealth patients such as Plaintiff Ceriani may receive BRAC*Analysis*® testing at no charge.

34. Plaintiffs also alleged that the cost of the BRAC*Analysis*® test is too high because of patent exclusivity. However, the HHS Secretary's Advisory Committee on Genetics, Health, and Society ("SACGHS") in March 2009 released a Public Consultation Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests. This Draft Report clearly stated: "One surprising finding from the case studies was that the per-unit price of the full-sequence *BRCA* test, which often is cited as being priced very high, was actually quite comparable to the price of other full-sequence tests done by polymerase chain reaction (PCR), at both nonprofit and for-profit testing laboratories."[21]

[21] SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, AND SOCIETY (SACGHS), PUBLIC CONSULTATION DRAFT REPORT ON GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS 114 (2009),

35. In fact, the relative price of BRAC*Analysis*® is actually lower than the gene sequencing-based genetic tests offered by those diagnostic labs run by the geneticist plaintiffs Kazazian and Ganguly (the Genetic Diagnostic Laboratory at the University of Pennsylvania), and Ledbetter and Warren (Emory Genetics Laboratory). For example, for full sequencing of the *APC* gene to detect mutations predictive of familial adenomatous polyposis (FAP), a type of hereditary colon cancer, Drs. Kazazian and Ganguly charge $1,360 per test, while Drs. Ledbetter and Warren charge $1,675. Full sequencing genetic tests typically are done exon by exon.[22] The *APC* gene has 15 coding exons, and their prices on a per exon basis are $90.6/exon and $111.7/exon, respectively. In contrast, the *BRCA1* and *BRCA2* genes have 48 total coding exons. The price of Myriad's comprehensive BRAC*Analysis*® test on a per exon basis is less than $70/exon, and this price also includes additional testing for common large genomic rearrangements, which Plaintiffs' tests do not include. *See* Exhibits 5 & 6.

36. Protected by patent exclusivity, Myriad has also made tremendous investment in its clinical laboratory facilities and processes, resulting in great efficiency which is translated into extremely sensitive and accurate test results which are rendered in a prompt timely fashion to allow health care practitioners to make immediate medical management decisions. Plaintiffs' allegation that patents increase genetic testing cost is simply baseless.

III. PATENTS HAVE PROVIDED INCENTIVE TO IMPROVE TEST QUALITY

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http://oba.od.nih.gov/oba/SACGHS/SACGHS%20Patents%20Consultation%20Draft%203%209%202009.pdf.

[22] An exon is a segment of a gene that corresponds to a portion of an mRNA which encodes part of a protein. In contrast, an intron is the "junk" DNA between two exons. Intron sequences are not in an mRNA and thus do not encode protein sequence.

37. Myriad is the pioneer and leader in genetic testing. At Myriad, we understand the importance of the quality of our tests better than anyone in the field. That is why from the very beginning Myriad adopted the full sequencing method in our BRAC*Analysis*® test, the most reliable and sensitive approach, even though it was more expensive. Our method has been independently validated and is recognized throughout the field as the "gold standard."[23] Even so, we have continuously invested in improving the BRAC*Analysis*® test.

Myriad's Full Sequencing Approach in BRAC*Analysis*®
Has Been Recognized as the Gold Standard

38. In mid-1990s, Myriad and its collaborators identified the *BRCA1* and *BRCA2* genes, isolated them, and discovered that mutations in the genes are predictive of a predisposition to breast and ovarian cancers. A mutation is an alteration at a chemical unit or units (nucleosides) of a DNA molecule representing a gene.[24]

39. Each of the *BRCA1* and *BRCA2* genes includes segments of DNA called exons and introns. An intron is an intervening segment between two adjacent exons. When a gene is expressed inside cells, the gene is transcribed into a RNA molecule based on the nucleotide structure of one strand of the genomic DNA of the gene. The transcribed RNA molecule is then "spliced" by cutting out the introns and connecting the adjacent exons together producing a messenger molecule called "mRNA." Thus an mRNA only contains exons but not introns. A protein is encoded by an mRNA. Therefore, a mutation in the genomic DNA of a gene can cause a corresponding change

[23] *See* Eng *et al.* on behalf of the Steering Committee of the Breast Cancer Information Core (BIC) Consortium, *Interpreting Epidemiological Research: Blinded Comparison of Methods Used to Estimate the Prevalence of Inherited Mutations in* BRCA1, J. MED. GENET., 38:824–833 (2001).
[24] There are four different chemical units in DNA molecules: deoxyadenosine ("A"), deoxythymidine ("T"), deoxycytidine ("C") and deoxyguanosine ("G").

in the mRNA, which may lead to an alteration in the structure of the encoded protein. Some mutations are "insertion or deletion" of a small number of nucleotide units in an exon. Other mutations are "substitutions" of one type of nucleotide unit to a different type of nucleotide unit (e.g., deoxyadenosine to deoxythymidine). Still other mutations are a deletion or duplication of one or more exons, also known as "large genomic rearrangements" or "large rearrangements." Large rearrangements in the *BRCA1* or *BRCA2* gene almost invariably cause major structural alterations in the encoded protein and a loss of function of the protein. They are usually associated with a predisposition to breast and ovarian cancer, i.e., they are "deleterious." Many insertions, deletions, and substitutions result in a frameshift or stop codon causing a truncation of the encoded protein. These kinds of insertions, deletions or substitutions are also deleterious.

40. To detect a mutation in the *BRCA1* and *BRCA2* genes, a tissue sample (e.g., blood) is obtained from a patient. The genomic DNA-containing cells in the sample are broken up, and a sufficient amount of the genomic DNA corresponding to the *BRCA1* and *BRCA2* genes is obtained from the sample. This step typically involves enzymatic synthesis to connect different nucleotide molecules into a DNA chain using a genomic DNA molecule from the patient sample as a template. To obtain a sufficient quantity of the genomic DNA, the enzymatic synthesis is performed by PCR (polymerase chain reaction) to duplicate the DNA molecule exponentially. However, there is a limit in the size of the genomic DNA fragment that can be made by PCR (about several hundred base pairs). The *BRCA1* and *BRCA2* genes are large in size each being over 70,000 base pairs long, and can not be amplified or duplicated into a single DNA fragment. Under the current state of the art, the only practical way to obtain a sufficient amount of *BRCA1* or

BRCA2 genomic DNA for mutation detection purpose is to PCR amplify the genomic DNA in segments. Typically, each coding exon (an exon that codes for part of the protein sequence) of the *BRCA1* and *BRCA2* genes, including a small adjacent portion of the flanking introns, is separately amplified by PCR into one or more amplified DNA fragments, also called "amplicons." The *BRCA1* and *BRCA2* genes have a total of 48 coding exons containing over 15,700 nucleotide base pairs. More than 50 amplicons are typically produced, and each is subsequently interrogated for the presence or absence of mutations.

41. A mutation can occur in virtually every one of the more than 15,700 nucleotides in the amplicons. Thus, a mutation detection method must be able to identify tens of thousands of mutations distributed along the lengths of the amplicons. There are a number of different methods in the art for mutation detection in the amplicons. At Myriad, we have been using direct nucleotide sequence analysis or "full sequencing." That is, the identity of every single nucleotide unit in the amplicons is determined by sequencing all of the more than 50 amplicons. Moreover, each amplicon is a double-stranded DNA molecule, and the sequence of one strand can be used to deduce the sequence of the other strand. We determine the sequences of both strands for each amplicon. Additionally, each person has two copies of the *BRCA* genes, and our tests can determine the sequences of both copies. Thus, we have built-in quality control and confirmatory components for every amplicon. Moreover, once a mutation is detected in an amplicon, the entire amplification and sequencing process is repeated for that amplicon to further confirm the mutation. Understandably, the cost associated with this method is high because of the large amount of reagents for sequencing all amplicons as

well as the labor required to analyze the more than 30,000 (>15,700 x 2) sequencing data points generated. However, Myriad believes and researchers concur that this method is required to produce a "gold standard" test.

42. In contrast, many other laboratories use shortcut methods. Many of these shortcut methods cost less than the full sequencing approach by Myriad, but have been shown to be inferior in test quality.[25] In many of these methods, all the nucleotide identities in the amplicons are not determined. That is, the methods do not closely examine each nucleotide in the amplicons. Instead, they take a quick and cursory review of each amplicon by an indirect approach. Specifically, they try to predict the presence or absence of mutations in each amplicon based on whether there are any specific physical property changes in the amplicon as a whole. For example, in the CSGE (Conformation-Sensitive Gel Electrophoresis) approach used by Plaintiffs Kazazian and Ganguly in the late 1990s for mutation detection in *BRCA1* and *BRCA2*, the amplicons are run through gel electrophoresis to identify amplicons exhibiting an abnormal migration pattern compared to a normal amplicon. Only those particular amplicons are then sequenced to specifically identify the mutations in the amplicons if any. If no amplicon is detected with an abnormal migration pattern in a patient's sample, no sequencing is performed at all.

43. Because few, if any, of more than 50 amplicons are sequenced, the CSGE method is less expensive. However, the method is significantly less sensitive. In fact, in one comparative study by the Breast Cancer Information Core (BIC) Consortium, the CSGE laboratory participating in the study missed as many as 40% of mutations in

[25] Eng *et al.*, *supra* note 23.

BRCA1 and *BRCA2*.[26] In that study, four different less expensive methods were compared to Myriad's method. Myriad's full sequencing approach was recognized as the "gold standard" for mutation detection for *BRCA1* and *BRCA2*.[27]

Myriad Has Been Continuously Improving Its Testing Process

44. Relying on strong patent protection, Myriad invested significantly in its testing facilities and testing process from the very beginning. All our tests are done in a highly automated and CLIA-compliant laboratory with utmost quality. Indeed, quality control is one of the most important functions in our testing labs, and we have a large team of quality specialists vigilantly scrutinizing the quality of all our tests. Myriad participates in the College of American Pathologist (CAP) Proficiency Test every year, and has consistently excelled in theses tests.

45. In our process, all tests must be ordered through healthcare providers, and genetic counseling and patient informed consent are prerequisites of all of our *BRCA* mutation testing. These measures have ensured that patients receive the best services from Myriad and develop the best understanding about their test results.

46. The high quality of Myriad's BRAC*Analysis*® test is even more remarkable in view of the very rapid turn-around time required for clinical decision-making. Test results are typically available for patients and healthcare providers within about 2 weeks after the samples are released to Myriad's laboratories. This is in stark contrast to the poor turn-around in *BRCA* testing in Europe. For example, in the UK, it has been reported that some women have to wait up to 2 years for their *BRCA* testing

[26] *Id.*
[27] *Id.*

results.[28] Another problem in European *BRCA* testing is that the test criteria for selecting candidates for *BRCA* testing are much more restrictive than those in the US.[29] As a result, it is estimated that more than 50% of individuals carrying harmful *BRCA* mutations can be missed.[30]

47. Relying on strong patent protection, Myriad has also continuously invested in its testing laboratory to improve the testing process. For example, Myriad has a large in-house team of software programmers and bioinformaticists continuously optimizing our automation process and software.

Large Rearrangement Mutations

48. As explained above in Paragraphs 40 and 41 above, full sequencing analysis requires separate PCR amplification and DNA sequence analysis of each exon and the flanking intronic sequences. The *BRCA1* and *BRCA2* genes have 48 coding exons. In some patients, one or more full exons are deleted or duplicated in one copy of the gene, while the other copy is normal. Because of the normal copy, the deletion or duplication of exons ("large rearrangement") is undetectable by full sequencing.

49. In the late 1990s, Myriad and the research community recognized the need for testing "large rearrangements" in the *BRCA1* and *BRCA2* genes. Large genomic

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[28] *See* Laura Barton, *Genetic Testing for Breast Cancer Varies across UK*, LANCET ONCOL., 7:113 (2006); *see also*, BBC News: Health, *Long Wait for Cancer Test Results*, BBC NEWS, Dec. 14, 2005, http://news.bbc.co.uk/2/hi/health/4525260.stm.

[29] *See* Wylie Burke, *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care*, N. ENG. J. MED. 358:318 (2008) (reviewing Plantiff's declarant Shobita Parthasarathy's book on the commercial development of BRCA testing, and characterizing certain claims as "unsubstantiated" and declaring the book to be "unconvincing"); *see also* Balmaña *et al., BRCA in Breast Cancer: ESMO Clinical Recommendations*, ANN. ONCOL., 20(4):iv19-iv20 (2009) (outlining the European clinical *BRCA* testing criteria).

[30] *See* Moller *et al.*, *Genetic Epidemiology of* BRCA *Mutations – Family History Detects Less Than 50% of the Mutation Carriers*, EUR. J. CANCER, 43:1713-1717 (2007).

rearrangements occur in a small percentage of all patients tested for hereditary breast and ovarian cancer. Nevertheless, Myriad immediately began researching and developing a commercially viable high quality process for detecting large rearrangements in the genes. As a result, in 2002 Myriad supplemented its full sequencing analysis with a large rearrangement panel (LRP) for detecting five common large rearrangement mutations. Since then, Myriad has included the LRP panel in every comprehensive BRAC*Analysis*® test it performs.

50. In the meantime, Myriad continued its research and development work with a goal to provide a test that could detect all large rearrangement mutations, even those extremely rare ones. The commercially available MLPA (Multiplex Ligation-dependent Probe Amplification) kit often used by academic researchers is for research use only and not approved for clinical testing by the FDA. Moreover, it is incapable of detecting certain rearrangements with smaller sizes, and may yield false positive results for apparent deletions due to nucleotide changes at probe binding sites.

51. After much research and development, Myriad launched in 2006 the BART™ (BRAC*Analysis*® Rearrangement Test) assay which can detect virtually all large rearrangement mutations in the *BRCA1* and *BRCA2* genes. BART™ is a complex quantitative multiplex PCR assay examining every single coding exon and promoter of the *BRCA1* and *BRCA2* genes for large rearrangements. It incorporates an automated and computerized analysis, includes quality control processes to confirm positive results, and has been fully validated and is performed in our CLIA certified, CAP accredited laboratory. In studies by outside researchers, BART™ has exhibited superior

performance over other methods including MLPA.[31] Since 2004, Myriad has been sharing information on BART™ with researchers and clinicians in numerous scientific meetings of the Association for Molecular Pathology, the American Society of Human Genetics, and the American Society of Clinical Oncology, among others.

52. BART™ is a complex test with a high cost, and large genomic rearrangements occur in a small percentage of all patients tested for hereditary breast and ovarian cancer. Nevertheless, Myriad has made BART™ available to all patients who want to be tested. At the present time, for high risk patients, BART™ is performed together with our full sequencing analysis and LRP (for common large rearrangements) at no additional charge. For low risk patients who do not meet certain clinical criteria developed based on published literature, BART™ is still available at a reasonable cost.

53. Today, Myriad is still investing heavily to develop a new version of BART™ with a significantly lowered cost and increased efficiency. In these efforts, Myriad is working to provide an improved BART™ that is commercially viable to all patients at little cost. Without patent protection, Myriad would not have made such investments.

Variants of Uncertain Clinical Significance

54. Genetic variants of uncertain clinical significance, also known as "VUS", are mostly missense changes and variants that occur in intronic regions whose clinical significance has not yet been determined. Many nucleotide substitutions in the coding exons of the *BRCA* genes result in a change from one amino acid residue to another in the encoded protein. Given the current state of scientific knowledge, it may not yet be

[31] *See* Palma *et al.*, *The Relative Contribution of Point Mutations and Genomic Rearrangements in* BRCA1 *and* BRCA2 *in High-Risk Breast Cancer Families*, CANCER RES., 68: 7006-14 (2008).

possible to determine whether such an amino acid substitution will result in enough changes in protein function to confer an increased risk of breast and ovarian cancer, requiring further scientific research and analysis. There are also other nucleotide substitutions or small insertions or deletions in the *BRCA* genes that occur in an intron. Again, given the current state of science, it can be difficult to determine whether they result in sufficient changes in the protein so as to confer an increased risk of breast and ovarian cancer. All of these mutations are called "variant of uncertain significance" or "VUS."

55. When Myriad detects a VUS, it reports the variant to the patient as a "genetic variant of uncertain significance." The uncertainty about the cancer risk of such variants at the time of their detection arises not because of any limitation in the test, but because of the limits of current scientific knowledge. This is independent of the testing method. Any lab uncovering the same variant, such as those of Plaintiffs Ledbetter or Ganguly, would need to report the exact same result because of limited scientific knowledge.

56. In fact, there is widespread consensus among cancer geneticists that the VUS problem is challenging. It has been estimated that about one-third of the genetic variants in *BRCA1* and 50% of those found in *BRCA2* reported by the Breast Cancer Information Core (BIC) Consortium are or have been considered genetic variants of unknown clinical significance.[32] Also, the VUS problem is not unique to *BRCA* testing. It is also common in many other genetic tests such as sequencing analysis of the *CFTR*

[32] Gómez-García *et al.*, *A Method to Assess the Clinical Significance of Unclassified Variants in the* BRCA1 *and* BRCA2 *Genes Based on Cancer Family History*, BREAST CANCER RES., 11:R8 (2009), http://breast-cancer-research.com/content/11/1/R8.

gene (for cystic fibrosis),[33] the *MLH1* and *MSH2* genes (for hereditary nonpolyposis colorectal cancer),[34] the *CDKN2A* gene (for hereditary melanoma),[35] and the *APC* gene (for familial adenomatous polyposis or FAP)[36].

57. Over the years, Myriad has continuously invested significant resources in solving the VUS problem. In this regard, Myriad's enormous centralized mutation database based on clinical testing of hundreds of thousands of patients has proven to be critical. Myriad has also made critical data available to noted international researchers and helped them analyze their VUS models in their research.[37] The published research results have the potential of improving the diagnostic testing for the other genes discussed above.

58. Myriad has an in-house review committee for variant classification, and has developed a systematic approach to provide clinical interpretations for detected sequence variants based on generally accepted scientific data and analysis of its own database. We also continuously improve upon this approach based on research advances and accumulated experience. Because of all these efforts, the VUS reporting rate at Myriad has decreased markedly, as we reported recently.[38] In particular, between 2002 and 2006, a decrease of almost 50% was accomplished in major ethnic minority groups.[39]

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[33] Oca *et al.*, *Amniotic Fluid Digestive Enzyme Analysis Is Useful for Identifying* CFTR *Gene Mutations of Unclear Significance*, CLIN. CHEM., 55:2214-7 (2009).
[34] Arnold *et al.*, *Classifying* MLH1 *and* MSH2 *Variants Using Bioinformatic Prediction, Splicing Assays, Segregation, and Tumor Characteristics*, HUM MUTAT., 30:757-70 (2009); *see also,* Chan *et al.*, *Interpreting Missense Variants: Comparing Computational Methods in Human Disease Genes CDKN2A,* MLH1, MSH2, MECP2, *And Tyrosinase* (TYR), HUM MUTAT. 28:683-93 (2007).
[35] Chan *et al.*, *supra* note 34.
[36] Aretz *et al.*, *Familial Adenomatous Polyposis: Aberrant Splicing Due to Missense or Silent Mutations in the* APC *Gene*, HUM MUTAT. 24:370-80 (2004).
[37] *See e.g.,* Abkevich *et al.*, *supra* note 1; Goldgar *et al. supra* note 1.
[38] *See* Hall *et al.*, *BRCA1* and *BRCA2* Mutations in Women of Different Ethnicities Undergoing Testing for Hereditary Breast-Ovarian Cancer, CANCER, 115(10):2222-33 (2009).
[39] *See id.*

Myriad's extensive *BRCA* testing experience and its centralized clinical data have made large-scale VUS reclassification possible. Today, the overall VUS reporting rate in our *BRCA* testing is below 6.6%, which is significantly lower than that in other tests such as those for the *MLH1* and *MSH2* genes.

59. In addition, Myriad constantly reexamines all remaining VUS previously reported to patients in an attempt to clarify the clinical significance of the variants based on new information gained in research and clinical testing. As soon as a clarification is accomplished for a patient, we generate and send an updated report to the patient's healthcare provider, thus providing the doctor and patient with the most up-to-date scientific information about that patient's particular hereditary cancer risk. In fact, it is estimated that Myriad has in total clarified about 850 VUS for about 21,000 patients, all of whose physicians have been notified with an updated report. Just between the beginning of 2008 and the present, we have thus reclassified 502 VUS for 13,127 patients.

60. Clearly, without strong patent protection, Myriad would not have made these enormous investments and would not have been able to make such significant contributions to the progress of science in VUS. Nor would Myriad have been able to accomplish the significant improvement on test quality, particular the reduction of VUS reporting rate and the clarification of test results for tens of thousands of patients.

IV. SECOND OPINION

61. Plaintiffs raised the hypothetical issue of "second opinion." However, in reality, since Myriad launched its BRAC*Analysis*® in 1996, I am not aware of a single request (or even the suggestion) made to Myriad by anyone to seek "second opinion"

repeat testing at another lab. In fact, physicians using our test for their patients do not feel the need for a "second opinion" testing. *See* D. Frieder, ¶ 11; D. Bone, ¶ 8. I believe this is largely attributable to the excellent quality of the BRAC*Analysis*® test that patients and their doctors trust. As I discussed in Paragraph 41 above, all BRAC*Analysis*® tests at Myriad already include multiple built-in confirmatory components. Moreover, it simply does not make good economic or medical sense for patients to routinely obtain second opinion testing. Finally, nothing prevents patients from seeking second opinions with genetic counselors and physicians on their test results.

62. In any event, the argument made by the Plaintiffs Girard and Limary, that they cannot get a second test to confirm their *BRCA* mutations, is disingenuous. There are multiple laboratories available for confirmatory testing under patent licenses from Myriad. Many of these labs have been performing testing for specific *BRCA* mutations for the past ten years. For example, testing for specific *BRCA* mutations is available in both the University of Chicago Genetic Services Laboratories and Yale DNA Diagnostic Laboratories.[40] Information on their testing services for *BRCA* mutations is readily accessible on Internet.[41] Both could provide a confirmatory test for the *BRCA* mutations Plaintiffs Girard and Limary had previously received.

63. If the plaintiffs are still not happy after such second opinion testing, there are also other options for second opinion testing: At any given time, there are a number

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[40] Indeed, it is rather disingenuous for plaintiffs to make the allegation of lack of second opinion testing when one of the plaintiffs, Ellen Matloff, the Director of the Cancer Genetic Counseling Program at Yale, works closely with Yale DNA Diagnostic Laboratories from which the hypothetical second opinion testing would be available.

[41] *See* Yale DNA Diagnostic Services: BRCA, http://info.med.yale.edu/genetics/DNA/BRCA-Familial.html (last visited Dec. 17, 2009); *and* Department of Human Genetics, University of Chicago: BRCA Sample Submission Form, http://genes.uchicago.edu/LabPDF/01BRCA.pdf (last visited Dec. 17, 2009).

of research studies going on in the US and abroad by researchers outside Myriad. Plaintiffs can always participate in such research studies for second opinions.

64. Myriad has never prohibited a "second opinion" on *BRCA* mutation testing, which has been available to patients like Plaintiffs Girard and Limary since late 1990s. In reality, the need for a second opinion is extremely rare and the problem of getting second opinions simply does not exist. It is merely plaintiffs' conjecture for the sole purpose of attacking the US patent system in this suit.

V. CONCLUSION

65. In summary, Myriad's discovery of the *BRCA1* and *BRCA2* genes made clinical testing possible to detect genetic predispositions to breast and ovarian cancers. Early detection of such cancer risks enables patients to utilize various available means to reduce the risks or even possibly prevent cancer. Myriad has consistently encouraged, promoted and subsidized research on the *BRCA* genes, and Myriad's patent rights have not stifled research. As evidence, Myriad has provided *BRCA1* and *BRCA2* cDNA clones free to researchers at over 30 research institutions, and conducted collaborative research with more than 440 scientists all over the world. Overall, more than 18,000 scientists have researched on *BRCA1* and *BRCA2*, and published more than 7,000 papers on the genes since Myriad's publication of the genes. These include 4 plaintiffs in this suit and their supporting declarants publishing a total of 48 papers on *BRCA1* and *BRCA2*.

66. Myriad has performed over 400,000 BRAC*Analysis*® tests for *BRCA* mutations for patients in all 50 states. Over 40,000 healthcare providers have ordered the test. Test results are typically available within two weeks. More than 90% of the BRAC*Analysis*® tests are covered by insurance. There are more than 2,600 insurance

payors who reimburse for the BRAC*Analysis*® test. There are more than 80,000 insurance plans that cover the BRAC*Analysis*® test. The average reimbursement rate is over 90% of the cost of the test. All these accomplishments are directly attributable to Myriad's investment of more than 200 million dollars in insurance coverage, and more importantly in raising patient and physician awareness and understanding of the test. Myriad would not have made the investment without the protection by the exact patents plaintiffs are challenging. Myriad's patent rights have clearly promoted patient access to the BRAC*Analysis*® test.

67. Patent rights have also provided incentives for Myriad to continuously invest significantly in its testing facilities and testing process. Testing services are available at Myriad for detecting all mutations in the *BRCA1* and *BRCA2* genes, including rare large rearrangement mutations. Myriad also has the best resources and capability in classifying variants of uncertain clinical significance. Myriad's full sequencing test has been recognized as the "gold standard" for *BRCA* mutation testing. In contrast, the CSGE method used by Plaintiffs Kazazian and Ganguly in the late 1990s has been shown to be unreliable, missing 40% of mutations in *BRCA1* and *BRCA2*.

68. Clearly, Myriad's patent rights have encouraged research on the *BRCA* genes, promoted patient access to *BRCA* testing, and improved the quality of *BRCA* testing at Myriad. For these reasons, Myriad cherishes and respects the US patent system and firmly believes that patent protection for landmark inventions such as the *BRCA1* and *BRCA2* and their use in diagnostic testing, stimulates innovation and encourages the commercialization and wide dissemination of valuable products and services, and thus provides great benefit to both individuals and society.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Gregory C. Critchfield, M.D., M.S.

Executed on December 18, 2009

CERTIFICATE OF SERVICE

This is to certify that on December 23, 2009, a true and correct copy of the foregoing document has been served on all counsel of record via the court's ECF system.

/s/ Brian M. Poissant
Brian M. Poissant