

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
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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.

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

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); Welch *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

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 AstraZeneca¹⁴, BSI-201 by BiPar Sciences Inc.¹⁵, ABT-888 by Abbott Laboratories, Inc.¹⁶, and AG014699 by Pfizer¹⁷. 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 BRACAnalysis[®] 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

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 BRACAnalysis[®] 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 BRACAnalysis[®] 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 BRACAnalysis[®] test. There are more than 80,000 insurance plans that cover the BRACAnalysis[®] 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 BRACAnalysis[®] 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 *BRCAAnalysis*[®] 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 *BRCAAnalysis*[®] 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 *BRCA*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 *BRCA*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

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 Medicaid 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 BRCA[®] 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 *BRACAnalysis*[®] 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 *BRACAnalysis*[®] testing at no charge.

34. Plaintiffs also alleged that the cost of the *BRACAnalysis*[®] 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 *BRACAnalysis*[®] 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 *BRACAnalysis*[®] 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

<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 BRACAnalysis[®] 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 BRACAnalysis[®] test.

Myriad’s Full Sequencing Approach in BRACAnalysis[®]
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 ($>15,700 \times 2$) 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 these 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 *BRCAAnalysis*[®] 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

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 Plaintiff’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 BRACAnalysis[®] 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[™] (BRACAnalysis[®] 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

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 *BRCAAnalysis*[®] 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 BRACAnalysis[®] test that patients and their doctors trust. As I discussed in Paragraph 41 above, all BRACAnalysis[®] 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

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*.

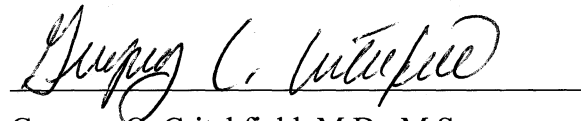
66. Myriad has performed over 400,000 BRACAnalysis[®] tests for *BRCA* mutations for patients in all 50 states. Over 40,000 healthcare providers have ordered the test. Test results are typically available within two weeks. More than 90% of the BRACAnalysis[®] tests are covered by insurance. There are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

payors who reimburse for the BRACAnalysis[®] test. There are more than 80,000 insurance plans that cover the BRACAnalysis[®] 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 BRACAnalysis[®] 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

EXHIBIT 1

**CRITCHFIELD DECLARATION
EXHIBIT 1**

CURRICULUM VITAE

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

PROFESSIONAL ADDRESS

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EDUCATION

1985: M.S., Biophysical Sciences, University of Minnesota
1980: M.D., University of Utah College of Medicine
1976: B.S., Microbiology, Brigham Young University

MILITARY SERVICE

1970-74: United States Army National Guard, Honorable Discharge

BOARD CERTIFICATION

1981: Diplomat of National Board of Medical Examiners
1986: Diplomat of American Board of Pathology , Clinical Pathology

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HONORS, AWARDS, AND FELLOWSHIPS

- 2004: vSpring Capital Top 100 Venture Entrepreneurs
- 2002: Lazarow Lecturer, University of Minnesota, Department of Laboratory Medicine, April 25, 2002, Minneapolis, MN
- 1985: Young Investigator Award, Academy of Clinical Laboratory Physicians and Scientists
- 1984: Young Investigator Award, Academy of Clinical Laboratory Physicians and Scientists
- 1981-83: National Library of Medicine Training Grant in Health Computer Sciences
- 1980: Dean's Award for graduating class in medical school
- 1979: Special honors in Internal Medicine, Surgery, Obstetrics/Gynecology, and Pediatrics, junior year in medical school
- 1979: Alpha Omega Alpha, junior year in medical school
- 1976: Phi Kappa Phi
- 1973-76: Academic Scholarships, Brigham Young University
- 1973: Leadership Scholarship, Brigham Young University

PROFESSIONAL EXPERIENCE

- 1998-: President, Myriad Genetic Laboratories, Inc.
- 1996-98: Senior Vice President, Chief Medical & Science Officer, Quest Diagnostics Incorporated (formerly Corning Clinical Laboratories), Teterboro, NJ/San Juan Capistrano, CA. Responsible for all Science, Medicine and Innovation for Quest Diagnostics, reporting to Chairman/CEO, Quest Diagnostics
- 1995-96: Corporate Vice President, Clinical Pathology; Chief Laboratory Officer, Corning Clinical Laboratories/Corning Nichols Institute. Member of Strategic Leadership Team. Responsibilities: medical, technical, scientific and business direction.

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Page 3

- 1995: Director of Clinical Pathology, IHC Laboratory Services, Salt Lake City, Utah.
- 1993–95: Member, Laboratory Management Guidance Team, IHC Laboratory Services, Salt Lake City, Utah. Executive committee charged with management of all laboratory services and coordination with managed care, physician and hospital divisions of Intermountain Health Care.
- 1994: Faculty, American Society of Clinical Pathologists/College of American Pathologists Workshop, "Oral Anticoagulant Management and the International Normalized Ratio Reporting System," October 26, 1994, Washington D.C.
- 1994–95: Chairman, Multidisciplinary Review Study Section, SBIR (R43/R44), STTR (R41), R01 Grant Reviews, National Institutes of Health, November 14, 1994; March 30-31, 1995; October 25-26, 1995; April 11-12, 1996.
- 1994–95: Member, Technical Advisory Group on Quality Improvement, Governor's Commission on Health Care, State of Utah
- 1994–95: Chairman, Chemistry Guidance Team, IHC Laboratory Services, Salt Lake City, Utah
- 1992–95: Creator and Grant Writer for 3 NIH-funded projects: Intelligent Refrigerated Automatic Storage System (IRASS), a robotic storage/retrieval system for laboratories, 1991-SBIR Phase I, 1992-SBIR Phase II; COAGS: Computerized Oral Anticoagulation Guidance System, an expert probabilistic modeling system for standardization, interpretation and understanding the International Normalized Ratio for laboratories and clinicians, 1995-SBIR Phase I.
- 1992–95: Chairman, Laboratory Information Systems Committee, IHC Laboratory Services, Salt Lake City, Utah
- 1992–95: Chairman, Department of Pathology, Utah Valley Regional Medical Center, Provo, Utah.
- 1992: Consultant, Intermountain Health Care Information Systems. Laboratory information system, Intermountain Health Care, Salt Lake City, Utah.
- 1992—: Reviewer, *Clinical Chemistry* journal.

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Page 4

- 1992–93: Substance Abuse Mental Health Services Administration (formerly NIDA, now SAMHSA/HHS)-certified Laboratory—Responsible Person for certified forensic urine drug testing laboratory according to *Mandatory Guidelines for Federal Workplace Testing Programs*.
- 1991–95: Consultant, Automated Control Systems, Inc., Provo, Utah. Robotics and medical informatics.
- 1990–92: Collaborative toxicology analytical methods research with Center for Human Toxicology, University of Utah.
- 1990–95: College of American Pathologists (CAP) Inspector in toxicology, general laboratory laboratory, nuclear medicine, and chemistry.
- 1988–93: Director, IHC Laboratory Services Forensic Toxicology (a NIDA-certified laboratory), Utah Valley Regional Medical Center. Duties: scientific, technical and administrative responsibility for development and operation of the laboratory, including application for and completion of the NIDA certification process.
- 1987–95: Clinical Pathologist, Utah Valley Regional Medical Center, Provo, Utah. Primary Duties: Toxicology, Clinical Chemistry, Blood Banking, Computer.
- 1985-96: National Institutes of Health Reviewer for Small Business Innovation Research Grants (R43, R44), Shared Instrument Grants (S10), Research Grant Applications (R01), Biomedical Research Resource Grants. Member of numerous special study sections SSS-9 over last twelve years (frequency ranging from 3-5 times/year), reviewing computer applications in biomedical research and medicine.
- 1986–87: Associate Director for Health Studies, Center for Health Policy Research and Education, Duke University, Durham, North Carolina. Development of quantitative policy models for health care various health care entities.
- 1985–86: Chief of Laboratory Medicine, Hutzel Hospital, 4707 St. Antoine Blvd, Detroit, Michigan 48201.
- 1984–85: Chemistry Fellow, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota. Primary duties: toxicology, clinical chemistry.

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Page 5

1981–84: Medical Fellow, Department of Laboratory Medicine and Pathology, University of Minnesota, 198 Mayo, 420 Delaware St. SE, Minneapolis, Minnesota 55455.

1980–81: Resident, Department of Pathology, University of Michigan.

APPOINTMENTS

2003—: Board of Directors, American Clinical Laboratory Association

2001—: Member, Utah Governor's Science Advisory Committee

1996—: Member, Informatics Committee, College of American Pathologists

1997: Corporate Recruit Chair, Bergen County Juvenile Diabetes Foundation, Bergen County, NJ

1996—: Adjunct Professor of Microbiology, Brigham Young University, Provo, Utah.

1995—: Senior Leadership Team, Corning Clinical Laboratories/Corning Nichols Institute, Teterboro, NJ.

1992–95: Chairman, Department of Pathology, Utah Valley Regional Medical Center, Provo, Utah.

1993–94: Member, Board of Directors, Central Utah Health Care Foundation

1992–95: Member, Board of Directors, Automated Control Systems, Inc. Orem, Utah

1992–95: Member, Parent Advisory Committee, The Waterford School, Sandy, Utah

1987—: Adjunct Associate Professor of Microbiology, Brigham Young University, Provo, Utah.

1986–87: Assistant Professor, Center for Health Policy Research and Education, Duke University, Durham, North Carolina.

1985–86: Assistant Professor of Pathology, Wayne State University, Detroit, Michigan.
 1985: Organization Management User Task Force Committee for Computerization, Detroit Medical Center.

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Page 6

- 1983–84: Chief Resident, Department of Laboratory Medicine and Pathology,
University of Minnesota, Minneapolis, Minnesota
- 1981–85: Medical Fellow, Department of Laboratory Medicine and Pathology,
University of Minnesota, Minneapolis, Minnesota.

RESEARCH

- 2002: Clinical characteristics of hereditary breast/ovarian cancer syndrome.
- 1999: Predictive value of genetic testing.
- 1996: Predictive models for prostatic carcinoma.
- 1993–96: Mathematical models for oral anticoagulation management.
- 1993–94: Seroprevalence of chronic viral infections in emergency department patients.
- 1992–93: Statistical validation of drug identification using gas chromatography/mass spectrometry.
- 1990–91: Antibody-mediated interference of homogeneous immunoassays. Bayesian and nonparametric statistical models for assessing linearity of GC/MS assays.
- 1988–89: Principal Investigator, Grant from Association of Western Regional Hospitals, "A Computerized Information Network for Rural Hospitals in Southern Utah." Effective algorithms for screening blood donors for infectious diseases.
- 1987: Effectiveness of screening for osteoporosis by photon absorptiometry and computer tomography, success rates of percutaneous transluminal angioplasty in femoral-popliteal athleroscleotic peripheral vascular disease, the effectiveness of screening neonates for maple syrup urine disease.
- 1986: Effectiveness of chemical treatment of alcoholism, analysis of uncertainty in decision models based upon quantitative laboratory data, pharmacokinetics of intravenous induction anesthetics in follicular fluid.
- 1985: Decision analysis: Probabilistic modeling of decision trees using Monte Carlo simulation and symbolic algebra.
- 1985: Variance estimation of compartmental analysis parameters.
- 1984: Time series analysis model of platelet requirements in a large hospital.

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1983–84: Improved methods of reference range estimation in laboratory data.

TEACHING EXPERIENCE

1988–89: Lecturer, Clinical Microbiology 503, Brigham Young University.

1987: Course Director, Medical Decision Analysis, Duke University.

1986: Laboratory Lecturer, Wayne State University.

LICENSURE

1987—: Utah

1985–91: Michigan

1981–85: Minnesota

PROFESSIONAL SOCIETIES (PAST AND CURRENT)

American Medical Association

American Society of Clinical Pathologists

Association for Molecular Pathology

Society for Medical Decision Making

College of American Pathologists

Utah State Medical Association

American Association for Clinical Chemistry

Utah Association of Pathologists

American Association of Blood Banks

PRESENTATIONS (selected)

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December 21, 2009

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"Bioinformatics for the Practicing Pathologist", College of American Pathologists Annual Meeting, September 21, 2004, Phoenix, AZ.

"The Growth of Predictive Medicine", June 8, 2004, Bio Industry/FDA Panel, San Francisco, CA.

"Genomics, Pharmacogenomics & Proteomics in 21st Century Medicine," Lazarow Lecture, University of Minnesota, April 25, 2002, Minneapolis, MN

"Are Pharmacogenomics, Genomics, and Proteomics Fast-tracking to Clinical Diagnostics?", 2001 Executive War College, May 10, 2001, Cincinnati, OH.

"The Emerging Role of Information Technology in the Commercial Laboratory", Automated Information Management in Clinical Laboratories, May 5, 1997, Ann Arbor, MI.
"Calibration verification of the International Normalized Ratio," Corning Life Sciences, Inc. Science Expo, May 9, 1996, Chicago, IL.

"Prothrombin Time Reporting and the International Normalized Ratio (INR) System," American Society of Clinical Pathologists National Meeting, April 22, 1996, Boston, MA.

"Prothrombin Time Reporting and the International Normalized Ratio (INR) System," American Society of Clinical Pathologists National Meeting, September 19, 1995, New Orleans, LA.

"Predictive Value and Laboratory Testing," Family Practice Seminar, Cottonwood Hospital, February 14, 1995, Salt Lake City, UT.

"Robotic Storage and Retrieval Systems," Emerging Technologies in Informatics Conference, Tucson, AZ, January 22, 1995.

"Infectious Disease Testing," Small Hospitals Seminar, November 4, 1994, Provo, UT.

"Oral Anticoagulant Management and the International Normalized Ratio Reporting System," October 26, 1994, Washington D.C.

"Using Quality Management in the Selection of a Laboratory Information System." Utah State Medical Technologists Society Annual Meeting, March 1994.

"The International Normalized Ratio and Uncertainty," Department of Pathology, Wayne State University, Detroit, Michigan, February 19, 1993.

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"Emergency and Forensic Toxicology", Brigham Young University McDonald Health Center, October 16, 1991.

"Medical Decision Analysis", Brigham Young University McDonald Health Center, April, 1991.

"Viral Hepatitis", Utah Society of Medical Technologists, March 8, 1991, Salt Lake City, Utah.

"Computer Networks and Robotics", Symposium on Computer Applications in Medical Care, Washington, D.C., November 4, 1990.

"Emergency and Forensic Toxicology", McKay-Dee Hospital, Ogden, Utah, August 2, 1990.
"The Hepatitis C Virus", Utah Society of Medical Technologists, Salt Lake City, May 17, 1990.

"An Analysis of Sequential Testing for Infectious Diseases in Blood Donors, "American Association of Blood Banks, Annual Meeting, October 12, 1988, Kansas City, Missouri.

"A Confidence Profile Analysis of the Effectiveness of Disulfiram in the Treatment of Chronic Alcoholism." Invitational Conference on Applications of Quantitative Analytic Methods to Mental Health, Boston, Massachusetts, April 2, 1987.

"Medical Decision Analysis." Department of Family Practice Faculty Development Seminar, Wayne State University School of Medicine January 23, 1986.

"Improved Sensitivity Analysis Using Monte Carlo Simulation." Society for Medical Decision Making Meeting, Asilomar, California, October 22, 1985.

"Automatic Prediction of Platelet Utilization by Time Series Analysis." Academy of Clinical Laboratory Physicians and Scientists Annual Meeting, Charleston, South Carolina, June 7, 1985.

"Improved Reference Range Estimation by Smoothed Splines." Academy of Clinical Laboratory Physicians and Scientists Annual Meeting, Salt Lake City, Utah, June 1984.

"Anatomy and Physiology of Microcomputers." Minnesota Medical Society September 1982.

EXHIBIT 2

**CRITCHFIELD DECLARATION
EXHIBIT 2**

LIST OF PUBLICATIONS

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

Articles

Frank TS, Critchfield GC: Hereditary risk of women's cancers. *Best Pract Res Clin Obstet Gynaecol.* 2002 Oct; 16(5):703-13. Review.

Frank TS, Critchfield GC: Inherited risk of women's cancers: what's changed for the practicing physician? *Clin Obstet Gynecol.* 2002 Sep; 45(3):671-83; discussion 730-2. Review. No abstract available.

Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumpfer, KL, Scholl T, Tavtigian SV, Pruss DR, Critchfield GC: Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: Analysis of 10,000 individuals. *J Clin Oncol* 2002 Mar 15; 20(6):1480-90.

Critchfield GC, Frank TS: Identifying and managing hereditary risk of breast and ovarian cancer. *Clinics in Perinatol.* 2001 Jun; 28(2):395-406. Review.

Bansal A, Critchfield GC, Frank TS, Reid JE, Thomas A, Deffenbaugh AM, Neuhausen SL: The predictive value of BRCA1 and BRCA2 mutation testing. *Genetic Testing* 2000; 4:45-48.

Critchfield GC. The future of DNA diagnostics. *Dis Markers* 1999 Oct ; 15(1-3):108-11.

Feldman B, Yaron Y, Critchfield GC, Leon J, O'Brien JE, Johnson MP, Evans MI. Distribution of neural tube defects as a function of maternal weight: no apparent correlation. *Fetal Diagn Ther* 1999 May-Jun; 14 (3):185-9.

Evans MI, O'Brien JE, Critchfield GC. Detection of anomalies: alternatives to ultrasound. *Ann N Y Acad Sci* 1998 Jun 18; 847:191-9. Review

Bazzett LB, Yaron Y, O'Brien JE, Critchfield GC, Kramer RL, Ayoub M, Johnson MP, Evans MI. Fetal gender impact on multiple-marker screening results. *Am J Med Genet* 1998 Apr 13; 76(5):369-71.

List of Publications—Gregory C. Critchfield
December 21, 2009

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Yaron Y, Hamby DD, O'Brien JE, Critchfield G, Leon J, Ayoub, M, Johnson, MP, Evans, MI. Combination of elevated maternal serum alpha-fetoprotein (MSAFP) and low estriol is highly predictive of anencephaly. *Am J Med Genet* 1998 Jan 23; 75(3):297-9.

Kramer RL, Yaron Y, O'Brien JE, Critchfield GC, Ayoub M, Johnson MP, Qualls CR, Evans MI. Effect of adjustment of maternal serum alpha-fetoprotein levels in insulin-dependent diabetes mellitus. *Amer J Med Genet* 1998 Jan 13; 75(2):176-8.

Critchfield GC, Bennett ST, Swaim, WR. Calibration verification of the international normalized ratio. *Am J Clin Pathol* 1996 Dec; 106(6):786-94. Erratum in: *Am J Clin Pathol* 1997 Mar; 107(3):379.

Critchfield GC, Bennett ST. The influence of the reference mean prothrombin time on the International Normalized Ratio. *Am J. Clin Pathol* 1994 Dec; 102(6): 806-11.

Bennett ST, Critchfield GC. Examination of International Normalized Ratio imprecision by comparison of exact and approximate formulas. *J Clin Pathol* 1994 July; 47(7):635-8.

Critchfield GC, Bennett S. The International Normalized Ratio and uncertainty: validation of a probabilistic model. *Am J Clin Pathol* 1994; 102(1):115-22.

Critchfield GC, Urie PM, Bennett ST, Cox C, Nelson L, Shields L, Clark EC, Grandia LD. Using quality management techniques to select an LIS. *Healthcare Informatics* 1993 Sept; 10(9):46-54.

Critchfield GC, Wilkins DG, Loughmiller DL, Davis, BW, Rollins DE. Antibody-mediated interference of a homogeneous immunoassay. *J Anal Toxicol* 1993 Mar-Apr; 17(2):69-72.

Critchfield GC, Wilkins DG, Loughmiller DL, Rollins DE. Nonparametric assessment of toxicologic assay linearity by bootstrap analysis. *J Anal Toxicol* 1992 Mar-Apr; 16(2): 125-131.

Evans MI, Bottoms SF, Critchfield GC, Greb A, LaFerla JJ. Parental perceptions of genetic risk: correlation with choice of prenatal diagnostic procedures. *Int J Gynaecol Obstet* 1990 Jan; 31(1): 25-8.

Adar R, Critchfield GC, Eddy DM. A confidence profile analysis of the results of femoropopliteal percutaneous transluminal angioplasty in the treatment of lower-extremity ischemia. *J Vasc Surg* 1989 Jul; 10(1):57-67.

Critchfield GC, Eddy DM. A confidence profile analysis of the effectiveness of disulfiram in the treatment of chronic alcoholism. *Med Care* 1987 Dec; 25(12), supp: 66-75.

List of Publications —Gregory C. Critchfield
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Critchfield GC, Willard KE, Connelly DP. Probabilistic sensitivity analysis methods for general decision models. *Comput in Biomed Res* 1986 Jun; 19(3):254-65.

Critchfield GC, Willard KE. Probabilistic analysis of decision trees using Monte Carlo simulation. *Med Decis Making* 1986 Apr-Jun; 6(2):85-92.

Willard KE, Critchfield GC. Probabilistic analysis of decision trees using symbolic algebra. *Med Decis Making* 1986 Apr-Jun; 6(2):93-100.

Shultz EK, Willard KE, Rich SS, Connelly DP, Critchfield GC. Improved reference interval estimation. *Clin Chem* 1985 Dec; 31(12):1974-8.

Critchfield GC, Connelly DC, Ziehwein M, Olesen L, Nelson C, Scott E. Automatic prediction of platelet utilization by time series analysis in a large tertiary care hospital, *Am J Clin Pathol* 1985 Nov; 84(5):627-31.

Anderson MW, Haug P, Critchfield G. Dermatoglyphic features in myocardial infarction patients, *American Journal of Physical Anthropology* 1981 Aug; 55(4):523-7.

Reports

Gerber KA, Critchfield, GC, Bennett ST, Udall MR. Low Seroprevalence of Human Immunodeficiency, Hepatitis B and Hepatitis C Viruses in a Suburban Emergency Department. Report to the Central Utah Health Care Foundation, August 1994.

Critchfield GC, Urie PM. A Computerized Information System for Rural Hospitals in Southern Utah. Report to Association of Western Regional Hospitals/The Health Care Forum, April 1989.

Hasselblad V, Critchfield GC. An Analysis of Neonatal Screening for Maple Syrup Urine Disease. Working Paper TR #87-005. Center for Health Policy Research and Education, Duke University.

Eddy DM, Critchfield GC, Eddy JF: Screening for Osteoporosis. Report to Blue Cross Blue Shield Association, May 1987.

List of Publications —Gregory C. Critchfield
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Critchfield GC, Eddy DM: A Confidence Profile Analysis of the Effectiveness of Disulfiram Treatment for Alcoholism. Report to the North Carolina Hospitals Foundation, August 1987.

Chapters

Critchfield GC: Data entry for computer-based patient records. In *Aspects of the Computer-based Patient Record*, Ball MJ Cohen MF, (eds), Springer-Verlag, New York, pp. 140-5, 1992.

Critchfield GC: Perinatal and Pediatric Changes. Neonatal and Pediatric Laboratory Assessment, Chapter 37, In *Clinical Chemistry: Concepts and Application*, S. Anderson and S. Cockayne, Eds. W.B. Saunders, New York, (1992). Chapter discusses toxicology (including forensic toxicology) of the newborn.

Invited Contributions

Critchfield GC, Loughmiller DL: Drug war. *Medical Bulletin Utah Valley Regional Medical Center*. 1990; 5(1): 11.

Critchfield GC, Johnson EV: Blood supply. *Medical Bulletin Utah Valley Regional Medical Center*. 1990; 5(1): 10-11.

Critchfield GC: Interpretation of tests: What if any are the indications for a two-hour oral glucose tolerance test (OGTT): three-hour OGTT? or five-hour OGTT? Peter JB, Solloway H, eds. *Diagnostic Medicine* 1985; 8:11-2.

Selected Abstracts

Critchfield GC, Laub M: An Analysis of sequential testing for infectious diseases in blood donors. American Association of Blood Banks, Annual Meeting, October 12, 1988, Kansas City, Missouri.

Critchfield GC, Eddy DM: A confidence profile analysis of the effectiveness of disulfiram in the treatment of chronic alcoholism. Invitation Conference on Quantitative Methods in Mental Health, Boston, Massachusetts, April 1987.

List of Publications —Gregory C. Critchfield
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Endler GC, Stout M, Magyar DM, Hayes MF, Moghissi KS, Sacco A, Critchfield G: Follicular fluid levels of sodium thiamylal during laparoscopy for oocyte retrieval. Society of Anesthesiologists, Salt Lake City, Utah, April 1986.

Critchfield GC, Willard KW: Improved sensitivity analysis using symbolic algebra. Society for Medical Decision Making Annual Meeting, Asilomar, California, October 1985.

Willard KW, Critchfield GC: Improved sensitivity analysis using Monte Carlo simulation. Society for Medical Decision Making Annual Meeting, Asilomar, California, October 1985. Academy of Clinical Laboratory.

Oleson L, Ziehwein M, Ward N, Nelson C, Critchfield G, Scott E: A computer model to predict daily platelet usage and inventory levels. American Association of Blood Banks Annual Meeting, Miami, Florida, October 1985.

Critchfield, GC, Connelly DC, Ziehwein MS, Olesen L, Nelson CE, Scott EP: Automatic prediction of platelet utilization by time series analysis. Academy of Clinical Laboratory Physicians and Scientists Annual Meeting, Charleston, South Carolina, June 1985.

Critchfield GC, Shultz ES, Willard KW, Rich SS, Connelly DP: Improved reference range estimation of smoothed splines. Academy of Clinical Laboratory Physicians and Scientists Annual Meeting, Salt Lake City, Utah, June 1984.

Letters

Critchfield GC. Letter to the Editor. *Mol Diagn* 1996 Dec; 1(4):357.

Critchfield GC, Connelly DP: Re: Predictive Value of a Positive Test. *JAMA* 1986; 255-1438.

Critchfield G, Shultz E, Willard K; Prevalence and predictive value, *Am J Clin Pathol* 1984 Mar; 81(3):408.

Critchfield GC. Xenotransplantation. *Molecular Diagnostics* 1996; 1(4): 357.

EXHIBIT 3

Exhibit 3

Myriad Genetic Laboratories
Mutation Prevalence Tables


Last Update: Spring 2006

The following tables, which will be updated periodically, represent observations of deleterious mutations by Myriad Genetic Laboratories through its clinical testing service. Data obtained through testing performed under specific research protocols is not included here. The information included in these tables was obtained from a routine laboratory requisition form and has not been independently verified by Myriad Genetic Laboratories. Patients for whom relevant information was not provided were not included in this tabulation. Table 2 includes patients tested only for three prevalent founder mutations as well as patients tested by full sequence analysis. The method used to develop the prevalence tables has been published in, Frank TS et al: Clinical Characteristics of Individuals With Germline Mutations in BRCA1 and BRCA2: Analysis of 10,000 Individuals. Journal of Clinical Oncology. 20: 1480-1490, 2002. Please contact clinresearch@myriad.com or call 1-800-469-7423 with any questions or comments.

1. The Prevalence of Deleterious Mutations in BRCA1 and BRCA2 (Excludes Individuals of Ashkenazi Ancestry)

Patient's History	Family History (Includes at least one first or second degree relative)					
	No breast cancer <50, or ovarian cancer, in any relative. [†]	Breast cancer <50 in one relative; no ovarian cancer in any relative.	Breast cancer <50 in more than one relative; no ovarian cancer in any relative.	Ovarian cancer at any age in one relative; no breast cancer <50 in any relative.	Ovarian cancer in more than one relative; no breast cancer <50 in any relative.	Breast cancer <50 and ovarian cancer at any age. ^{††}
No breast cancer or ovarian cancer at any age	2.8%	4.5%	8.7%	5.6%	9.6%	12.2%
Breast cancer ≥ 50	2.9%	5.3%	11.4%	6.4%	12.2%	15.9%
Breast cancer <50	6.8%	15.8%	30.1%	16.9%	27.3%	39.2%
Male breast cancer	12.8%	21.8%	41.9%	20.0%	40.0%*	61.9%
Ovarian cancer at any age, no breast cancer	8.8%	23.1%	42.3%	21.1%	33.2%	46.5%
Breast cancer ≥50 and ovarian cancer at any age	17.6%	26.1%	46.2%	30.3%	46.2%	60.0%
Breast cancer <50 and ovarian cancer at any age	39.1%	53.9%	67.2%	66.0%	70.8%	79.0%

[†] May include families with breast cancer ≥50 (in women or men).

Number of observations in Table 1 is 49149

^{††} Includes family members with either or both diagnoses.

*N<20

2. The Prevalence of Deleterious Mutations in BRCA1 and BRCA2 in Individuals of Ashkenazi Ancestry

Patient's History	Family History (Includes at least one first or second degree relative)					
	No breast cancer <50, or ovarian cancer, in any relative. [†]	Breast cancer <50 in one relative; no ovarian cancer in any relative.	Breast cancer <50 in more than one relative; no ovarian cancer in any relative.	Ovarian cancer at any age in one relative; no breast cancer <50 in any relative.	Ovarian cancer in more than one relative; no breast cancer <50 in any relative.	Breast cancer <50 and ovarian cancer at any age. ^{††}
No breast cancer or ovarian cancer at any age	6.9%	13.7%	19.9%	15.6%	23.6%	27.5%
Breast cancer ≥ 50	4.4%	9.4%	11.3%	15.8%	20.0%	19.9%
Breast cancer <50	12.0%	24.2%	38.3%	38.8%	59.2%	51.4%
Male breast cancer	15.0%	30.8%	0.0% *	40.0% *	100.0% *	70.0% *
Ovarian cancer at any age, no breast cancer	22.2%	37.0%	60.6%	42.0%	43.2%	72.3%
Breast cancer ≥50 and ovarian cancer at any age	29.5%	64.3% *	50.0% *	50.0% *	100.0% *	63.6% *
Breast cancer <50 and ovarian cancer at any age	71.1%	88.9% *	80.0% *	90.9% *	100.0%*	75.0% *

[†] May include families with breast cancer ≥50 (in women or men).

Number of observations in Table 2 is 15345

^{††} Includes family members with either or both diagnoses.

*N<20

Table 2 includes individuals that tested for MultiSite3, which may have been for a known mutation in the family

EXHIBIT 4

**CRITCHFIELD DECLARATION
EXHIBIT 4**

Research Papers on *BRCA* by Plaintiffs and Plaintiff's Declarants

Name	Plaintiff/Declarant	Affiliation	Number of Published Research Papers
Arupa Ganguly	Plaintiff/Declarant	University of Pennsylvania School of Medicine	5
Ellen T. Matloff	Plaintiff/Declarant	Yale University School of Medicine	17
Wendy Chung	Plaintiff/Declarant	Columbia University	2
Harry Ostrer	Plaintiff/Declarant	New York University School of Medicine	1
Elizabeth Swisher	Declarant	University of Washington School of Medicine	16
Wayne W. Grody	Declarant	UCLA School of Medicine	2
Mark Sobel	Declarant	Association for Molecular Pathology	2
Jeffery A. Kant	Declarant	University of Pittsburgh	3
		Total:	48

EXHIBIT 5

Exhibit 5
PRICING INFORMATION ON GENETIC TESTS OFFERED BY
PLAINTIFFS KAZAZIAN & GANGULY

Name of Test	Turnaround Time	Cost	Billing (CPT) Codes
Familial Adenomatous Polyposis (FAP):APC gene Full Sequencing	10 weeks	\$1,360	83891, 83894x10, 83898x27, 83904x24, 83909x2, 83912
FAP: MYH Full Sequencing	6 weeks	\$600	83891, 83894x8, 83898x15, 83909x2,83912
FAP: APC or MYH Familial Mutation	3 weeks	\$340	83891, 83898x6, 83904x6, 83912
FAP: APC or MYH Prenatal Diagnosis of Known Familial Mutation	1-3 weeks	\$340	83891x2, 83898x4, 83904x5, 83912
Fibrodysplasia Ossificans Progressiva (FOP)	3 weeks	\$380	83891, 83898x7, 83904x5, 83909x2,83912
Hemophilia A: Inversion Analysis	3-4 weeks	\$260	83891, 83892x2, 83894, 83896, 83897, 83912
Hemophilia A: Full Sequencing	6-8 weeks	\$1,240	83891, 83894x14 83898x17, 83904x24, 83909x2, 83912
Hemophilia A: Deletion/Duplication	2-3 weeks	\$500	83891, 83900, 83901x5, 83909x2,83912
Hemophilia A: Familial Seq. Mutation	2-3 weeks	\$340	83891, 83898x6 83904x6, 83912
Hemophilia A: Prenatal Diagnosis of Inversion	1-3 weeks	\$340	83891x3, 83892x2, 83909, 83896, 83897, 83912
Hemophilia A: Prenatal Diagnosis of Known Sequencing Mutation	1-3 weeks	\$340	83891x2, 83898x4, 80904x5, 83912
Hemophilia A: Linkage Analysis	3-4 weeks	\$640	83891x3, 83894x10, 83898x11, 83912
Hereditary Hemorrhagic Telangiectasia (HHT): Full Sequencing with automatic reflex to Deletion/Duplication Analysis	10-16 weeks	\$1,720	83891, 83894x21, 83898x21, 83904x21, 83900, 83901x4, 83909,83912x2
HHT: Deletion/Duplication Analysis	4-6 weeks	\$500	83891, 83900, 83901x5, 83909x2,83912
HHT: Known Familial Mutation	2-3 weeks	\$340	83891, 83898x6, 83904x6, 83912

Exhibit 5
PRICING INFORMATION ON GENETIC TESTS OFFERED BY
PLAINTIFFS KAZAZIAN & GANGULY

HHT: Prenatal Diagnosis of Known Familial Mutation	1-3 weeks	\$340	83891x2, 83898x4, 83904x5, 83912
HNPCC: MLH1, MSH2 Known Familial Mutation	2-3 weeks	\$340	83891, 83898x6, 83904x6, 83912
HNPCC: Prenatal Diagnosis of MLH1 or MSH2 Known Familial Mutation	1-3 weeks	\$340	83891x2, 83898x4, 83904x5, 83912
Li-Fraumeni Syndrome (TP53): Sequencing of exons 3-9	5-6 weeks	\$560	83891, 83894x5, 83898x8, 83904x8, 83909x2, 83912
Li-Fraumeni Syndrome: Sequencing of exons 2,10, and 11	2-3 weeks	\$320	83894x2, 83898x5, 83904x5, 83909x2, 83912
Li-Fraumeni Syndrome: Known Familial Mutation	2-3 weeks	\$340	83891, 83898x6, 83904x6, 83912
Li-Fraumeni Syndrome: Prenatal Diagnosis of Known Familial Mutation	1-3 weeks	\$340	83891x2, 83898x4, 83904x5, 83912
Retinoblastoma: Full Sequencing of DNA from Frozen Tumor and/or Blood with automatic reflex to deletion/duplication analysis	8-12 weeks	\$1,720	83891, 83894x21, 83898x21, 83904x21, 83900, 83901x4, 83909, 83912x2
Retinoblastoma: Full Sequencing of DNA from Paraffin-embedded Tumor and Blood with automatic reflex to deletion/duplication analysis	12-15 weeks	\$1,840	83891x3, 83894x21, 83898x21, 83904x21, 83900, 83901x4, 83909, 83912x2
Retinoblastoma: Deletion/Duplication Analysis of DNA from blood	4-6 weeks	\$500	83891x3, 83894x21, 83898x21, 83904x21, 83900, 83901x4, 83909, 83912x2
Retinoblastoma: Known Familial Mutation sequencing mutation or deletion/duplication	2-3 weeks	\$340	83891, 83898x6, 83904x6, 83912
Retinoblastoma: Prenatal Diagnosis of Known Familial Mutation – sequencing mutation or deletion/duplication	1-3 weeks	\$340	83891x2, 83898x4, 83904x5, 83912
SMAD4: Full Sequencing	8-10 weeks	\$560	83891, 83894x5, 83898x8, 83904x8, 83909x2, 83912
SMAD4: Known Familial Mutation	2-3 weeks	\$340	83891, 83898x6, 83904x6, 83912
SMAD4: Prenatal Diagnosis for Known Familial Mutation	1-3 weeks	\$340	83891x2, 83898x4, 83904x5, 83912
Uveal Melanoma: Micro-satellite Analysis of Chromosome 3	8-10 weeks	\$1,000	83891, 83900x4, 83901x9, 83907, 83909x3, 83912
X-Inactivation Studies: Individual	3-4 weeks	\$360	83891, 83900x2, 83901, 83907, 83909, 83912
X-Inactivation Studies: Individual and Parent(s)	3-4 weeks	\$520	83891x3, 83900x2, 83901, 83907, 83909x3, 83912

EXHIBIT 6



EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Emory Genetics Laboratory (EGL)

(800) 366-1502 or (404) 778-8500

2165 N. Decatur Rd., Decatur, GA. 30033

Department of Human Genetics | Division of Medical Genetics | www.geneticslab.emory.edu

Familial Adenomatous Polyposis: APC Full Gene Sequencing

Synonyms: APC-Associated Polyposis Condition; Attenuated FAP (AFAP); Turcot Syndrome; Gardner Syndrome;

Test Codes: TV

Condition Description:

APC-associated polyposis conditions result from a mutation in the *APC* gene and cause a predisposition for colon cancer. Disorders in this category include familial adenomatous polyposis (FAP), attenuated FAP (AFAP), Gardner syndrome, and Turcot syndrome.

FAP is an autosomal dominant disorder characterized by the development of hundreds to thousands of adenomatous colonic polyps, usually beginning during early adolescence. 95% of affected individuals develop polyps by age 35; without surgical intervention, these polyps will inevitably progress to colorectal cancer by the early forties. Extracolonic manifestations may occur, including:

- dental anomalies
- polyps of the gastric fundus and duodenum
- congenital hypertrophy of the retinal pigment epithelium (CHRPE)
- osteomas
- desmoid tumors
- soft tissue tumors
- other associated cancers

Attenuated FAP differs in that the overall polyp burden tends to be less (average of 30) and polyps are also more proximally located. Colorectal cancer generally occurs at a later age. Gardner syndrome is associated with colon polyps typical of FAP in conjunction with osteomas, desmoid tumors, and other neoplasms. Turcot syndrome consists of colon polyps and central nervous system tumors.

The diagnosis of APC-associated polyposis conditions relies primarily on clinical findings. Molecular genetic testing of *APC* detects disease-causing mutations in up to 90% of individuals with typical FAP. Molecular genetic testing is most often used to confirm the diagnosis of FAP or attenuated FAP in individuals with equivocal findings (e.g., more than 100 adenomatous polyps) and to provide early diagnosis of at-risk family members. Phenotype variations may correlate with the specific location of the *APC* gene mutation. APC-associated polyposis conditions are inherited in an autosomal dominant manner. Approximately 75%-80% of individuals with APC-associated polyposis conditions have an affected parent.

The *APC* gene (5q21-q22) has 15 exons. The specific function of the *APC* gene is the object of much research and tumor suppressor activity is suspected.

Sequencing of the *APC* gene is recommended after a clinical diagnosis consistent with FAP or an APC-associated polyposis condition, and provides a complementary method to confirm the presence of mutations in a proband, identify at-risk individuals among the proband's relatives, and provide prenatal diagnosis in families with known mutations. For patients with suspected FAP or an APC-associated polyposis condition, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

Please [click here](#) for the GeneTests summary on this condition.

Indications:

This test is indicated for:

- Confirmation of a clinical diagnosis of FAP or an APC-associated polyposis syndrome.
- Individuals at-risk for FAP or an APC-associated polyposis syndrome due to family history.

Related Tests:

- Familial Adenomatous Polyposis: APC Gene Deletion/Duplication (QP) is available for those individuals in whom

sequence analysis is negative.

•MYH-Associated Polyposis: MYH Common Mutation Panel (TW), MYH-Associated Polyposis: MYH Gene Sequencing (QV), and MYH-Associated Polyposis: MYH Gene Deletion/Duplication (QW) may be indicated for individuals with a clinical diagnosis of FAP or AFAP who do not have a detectable APC mutation.

•Known Mutation Testing (KM) is available to family members if mutations are identified by sequencing.

Prenatal Custom Diagnostics (KM) is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.

Methodology:

PCR amplification of 15 exons contained in the APC gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

Reference Ranges:

Detection:

Clinical Sensitivity:

Sequence analysis of the APC gene detects disease-causing mutations in approximately 90% of individuals with typical FAP. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations, and large deletions cannot be detected by this analysis.

Analytical Sensitivity: ~99%.

Results of molecular analysis should be interpreted in the context of the patient's clinical presentation and/or tumor pathology.

TAT: 4 weeks

Samples Accepted: Monday - Friday 8:30AM - 5:00PM

Special Instructions:

Please submit copies of pedigree or other family history information along with the sample. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

Specimen Requirements

Specimen Type	Specimen Requirements	Specimen Shipping
Whole Blood	In EDTA(purple top)/ACD(yellow top) tube: Children under 1 year: 1ml. Children over 1 year: 3-5ml. Older children & adults: 5-10ml.	Refrigerate sample until shipment. Send sample at room temperature with overnight delivery within 5 days of collection.
Saliva	Preferred sample: Whole blood. Please contact laboratory for saliva collection kit for patients who cannot provide blood sample.	

CPT Codes: 83891, 83898x29, 83894, 83904x58, 83909x58, 83912

Pricing: \$1,675