

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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ASSOCIATION FOR MOLECULAR PATHOLOGY;
AMERICAN COLLEGE OF MEDICAL GENETICS;
AMERICAN SOCIETY FOR CLINICAL PATHOLOGY;
COLLEGE OF AMERICAN PATHOLOGISTS;
HAIG KAZAZIAN, MD; ARUPA GANGULY, PhD;
WENDY CHUNG, MD, PhD; HARRY OSTRER, MD;
DAVID LEDBETTER, PhD; STEPHEN WARREN, PhD;
ELLEN MATLOFF, M.S.; ELSA REICH, M.S.;
BREAST CANCER ACTION; BOSTON WOMEN'S
HEALTH BOOK COLLECTIVE; LISBETH CERIANI;
RUNI LIMARY; GENAE GIRARD; PATRICE FORTUNE;
VICKY THOMASON; KATHLEEN RAKER,

09 Civ. 4515 (RWS)

ECF Case

Plaintiffs,

v.

DECLARATION OF
ELIZABETH SWISHER,
M.D.

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.

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I, Elizabeth Swisher, M.D., declare under penalty of perjury:

1. I am an Associate Professor of Obstetrics and Gynecology at the University of Washington School of Medicine, as well as the Medical Director of the Breast and Ovarian Cancer Prevention Program of the Seattle Cancer Care Alliance. My research and clinical specialty is focused on the genetics and treatment of gynecologic cancers, which include ovarian, cervical, uterine, vaginal, and vulvar cancers.

2. My laboratory is studying how ovarian cancer starts in order to determine better methods for prevention and early detection of ovarian cancer. I also study mechanisms of chemoresistance in ovarian cancers, and how the BRCA1 and BRCA2 genes influence response to chemotherapy.

3. My research interests have led me to become a member of the Steering Committee for the Breast Cancer Information Core (BIC). The BIC gathers information on BRCA genetic mutations, which are correlated with ovarian and breast cancer, to further the scientific community's ability to research the genetics of these cancers.

4. I am aware that Myriad Genetics controls patents on the BRCA1 and BRCA2 gene sequences. In this declaration, based on my professional knowledge and expertise, I describe two of my concerns with these patents: 1) the excessive control these patents give to the patentholder over genetic information, including information about genetic variants, that impedes scientific inquiry, research, and clinical practice; and 2) the barriers presented by the patents to physicians in the U.S. who want to offer patients the international standard of care with respect to BRCA genetic testing.

Background

5. I completed my undergraduate studies at Yale University and earned my medical degree from the University of California, San Diego, in 1992. Following completion of my residency in obstetrics and gynecology at the University of Washington in 1996, I did a post-graduate fellowship in gynecologic oncology at Washington University. During my fellowship, I published several papers on the role of genetic mutations in endometrial cancers. I was then awarded a Research Training Scholar Award from the Women's Reproductive Health Research Career Development Program at the University of Washington.

6. I am currently an Associate Professor of Obstetrics and Gynecology at the University of Washington School of Medicine and an Adjunct Associate Professor in the Department of Medicine's Division of Medical Genetics at the University of Washington. I also am the Medical Director of the Breast and Ovarian Cancer Prevention Program of Seattle Cancer Care Alliance, an Affiliate Investigator for the Division of Public Health Sciences for the Fred Hutchinson Research Center, and a member of the University of Washington's Advisory Board on Women's Reproductive Health Research.

7. I am a physician, surgeon, and researcher. I treat women who have been diagnosed with gynecologic cancers, advise women regarding monitoring, prevention, and hereditary susceptibility, and research potential treatments for BRCA-positive ovarian cancers. Much of my work has investigated the links between BRCA genetic mutations, hereditary risk for ovarian cancer, and chemotherapy. My recent publications are listed in detail in my attached curriculum vitae and include, "Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum research," "Management of Women with Inherited BRCA1 and BRCA2 Mutations," and "Genomic structure of chromosome 17 deletions in BRCA1 associated ovarian cancers."

8. I have taught numerous undergraduate and graduate classes, engaged in extensive resident and fellow teaching, and offered continuing medical education courses. Examples of my classes include "Ovarian Cancer Risk Management," "BRCA-Positive Ovarian Cancer: Can Cisplatin Resistance be Predicted and Can PARP be Therapeutically Targeted?," "Oncogenes/Tumor Suppressor Genes," and "Recognition and Testing for Hereditary Cancer Risk."

9. I am a leader and member of numerous professional organizations, as noted fully in my curriculum vitae. I serve on the Steering Committee for the Breast Cancer Information Core (BIC) and on the Cancer Genetics Education Committee of the American Society of Clinical Oncology. I am also a member of the American Association of Cancer Research, the American College of Obstetricians and Gynecologists, and the Society of Gynecologic Oncologists.

BRCA1/2 Genes and Ovarian Cancer

10. Ovarian cancer is the eighth most common cancer in women and causes more deaths in the Western world than any other gynecologic cancer.

11. Between 10 and 15% of ovarian cancers are inherited genetically. For women who are diagnosed under the age of 50 years old, approximately 80% of inherited ovarian cancers are caused by BRCA1 mutations, and approximately 20% are caused by BRCA2 mutations. Women with inherited BRCA1 mutations have a 40-52% cumulative risk of ovarian cancer by the time they reach 70 years old. For women with inherited BRCA2 mutations, the risk is approximately 15- 25%.

12. The existence of BRCA1/2 mutations is an important factor in clinical care. If a patient is positive for a mutation, doctors frequently recommend ovarian cancer risk-reducing strategies that might include increased surveillance, chemoprevention through oral contraceptives, and/or oophorectomy (ovarian surgery). Bilateral salpingo-oophorectomy (removal of both ovaries and the fallopian tubes) is associated with an 80-90% reduction in ovarian and fallopian tube cancer and a 50-60% reduction in breast cancer.

13. The BRCA1 and BRCA2 genes are not only cancer susceptibility genes, but also are critical determinants of clinical sensitivity to chemotherapy. Some of my recent work has

focused on the use of platinum compounds to treat BRCA1/2-mutated carcinomas. Patients with BRCA1/2-mutated ovarian cancer consistently have a better prognosis compared with noncarriers if they receive platinum-based chemotherapy. Thus, BRCA1/2 genetic status can be a vital factor in deciding course of treatment.

Breast Cancer Information Core (BIC)

14. The scientific community has long recognized the importance of sharing data about genetic mutations in centralized, public databases. While publication of genetic information in medical and scientific journals increases scientific knowledge, a more efficient way of providing researchers with broad access to mutation data is through centralized databases. These databases can aggregate reports of findings of various genetic variants, and thus can have substantial value to the scientific community.

15. A steering committee of the National Human Genome Research Institute (NHGRI), a part of the National Institutes of Health, engaged in an international effort to develop a clearinghouse for information on the BRCA1 and BRCA2 genes. In 1995, the BIC was formed as a result of this worldwide effort. The BIC is an open access, on-line database that is a central repository for information regarding mutations and polymorphisms in the BRCA genes. It helps facilitate identification of deleterious mutations (mutations associated with a higher risk of cancer) and provides a mechanism to collect and distribute data about genetic variants. The BIC also provides technical support in the form of detection protocols, primer sequences, and reagent access. Beginning in 2005, the BIC began to post expert evaluations of some of the BRCA1 and BRCA2 variants recorded in its database.

16. The BIC is run by staff members who work on a volunteer basis. Since 2004, I have served on the BIC Steering Committee, which consists of ten to twelve investigators who

work in the field of cancer genetics. We meet monthly via teleconference to discuss issues of relevance to the database.

17. The BIC's data are derived from both published literature and direct online entries made by contributors all over the world. Laboratories submit data, and once reviewed by members of the steering committee to ensure that they meet certain quality standards, the data are added to the database. The value of the BIC comes from the amount and quality of data provided by the scientific community.

18. The BIC is used by researchers in a number of ways. A researcher anywhere in the world can access the BIC and look up information on a particular variant. A researcher can incorporate data regarding mutations and variants reported to BIC into studies he or she is conducting. Many of the studies that have been performed that involve BRCA-affected individuals draw on BIC data. In recent years, there has been special attention paid to determining the meaning of variants of uncertain significance, which are variants on the BRCA genes whose connection to cancer is unknown. Variants of uncertain significance pose a difficult clinical problem, as we cannot easily advise patients who have such variants about health decisions. By gathering information about variants of uncertain significance in one place, the BIC plays an important role in helping to elucidate these variants.

19. For several years, Myriad Genetics, like other laboratories around the world, submitted mutation and variant data to the BIC. Because Myriad controls clinical testing of the BRCA genes in the United States, and because more testing occurs in the U.S. than any other country, Myriad was the largest contributor of data to the BIC. It provided a majority of the reports regarding variants. However, Myriad stopped contributing its data approximately two years ago. As far as I know, it did not give any reason for its decision to the Steering

Committee. For that reason, the U.S. essentially does not provide any data regarding BRCA variants identified in Americans.

20. The patents granted on the genes allow one entity in the U.S. to exercise enormous control over BRCA1 and BRCA2 mutation data. While Myriad has shared its data in the past, it now does not do so, to the detriment of the scientific community, patients, and public health. Once Myriad stopped contributing data, the BIC became a much less useful tool, both to researchers in the U.S. and globally. It is true that researchers do not have a formal obligation to contribute variant data to the BIC. However, each laboratory has an incentive to do so in order to benefit from the data contributed by others and to further scientific progress. This incentive evaporates when one laboratory controls most of the data about a gene.

21. Scientific researchers need access to more information about the BRCA1/2 genes, not less. Genes are so fundamental to medicine and science that any restriction that prevents researchers from analyzing genes or examining the effects of genes is contrary to our efforts to promote scientific knowledge and improve medical practice.

Standard of BRCA1/2 Genetic Testing Provided to Patients in the United States

22. The BRCA1 and BRCA2 genes are large genes. 5,400 base pairs make up the nucleotide sequence that codes for the BRCA1 protein, and 10,200 base pairs make up the nucleotide sequence that codes for the BRCA2 protein. Mutations or variants can occur at any position along these sequences, taking the form of a substituted base, a small deletion or addition of one or more bases, or deletions and duplications of large sections of the gene.

23. Full sequencing is often the method used to identify when a base has been substituted at a single point in the sequence or where insertions or deletions of a small number of bases have occurred, because this method determines the order of bases in a sequence. However,

full sequencing can miss large genomic rearrangements, where whole sections of the gene have been deleted or moved to a different part of the sequence.

24. A number of tests have been developed by researchers to better detect large rearrangements. The test that is now frequently relied upon is the multiplex ligation-dependent probe amplification (MLPA). MLPA was developed in Holland and can be applied to amplify any targeted gene sequence. MLPA is a high-resolution, simple, and relatively low cost test. It is used widely around the world and has been validated through numerous studies. MLPA kits for analyzing the BRCA1 and BRCA2 genes have been developed and are offered commercially. The difference between using full sequencing and a test like MLPA to analyze a gene is analogous to the difference between proofreading a page for single letter typos and for misplaced paragraphs.

25. In 2006, I co-authored a study examining the frequency and types of undetected cancer-predisposing mutations in BRCA1 and BRCA2 that was published in the Journal of the American Medical Association (JAMA).¹ The study focused on cancer patients with severe family histories of breast or ovarian cancer who had tested negative for BRCA mutations under Myriad's commercial full sequencing test. We used MLPA as one alternative mode of analysis.

26. The study concluded that genetic testing, as carried out in the United States by Myriad, did not provide all available information to women at risk. The data indicated that "12% of those from high-risk families with breast cancer and with negative (wild-type) commercial genetic test results for BRCA1 and BRCA2 nonetheless carry cancer-predisposing genomic deletions or duplications in one of these genes."

¹ Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 JAMA (12) 1379-1388 (2006).

27. We recommended MLPA followed by confirmation of the points along the sequence where the genomic sections of the sequence had been moved as the best mode of analysis for identifying BRCA1/2 large rearrangements in patients who had tested negative for BRCA1/2 by conventional sequencing. Our study reinforced a number of other studies that previously had come to the same conclusion: full sequencing, while an important analytical method, misses significant BRCA1/2 large rearrangements.² As such, all women with significant family history who receive negative test results should undergo testing for large rearrangements.

28. Our recommendation cannot be carried out by any clinical laboratory that might wish to do so. Because of the U.S. patents on the BRCA1/2 gene sequences, Myriad Genetics has the exclusive right to offer genetic testing to patients. Myriad has granted some limited licenses to a few laboratories and allows researchers to conduct genetic testing. However, to the best of my knowledge, Myriad has not allowed any other laboratory in the country to perform clinical full sequencing of the BRCA1 and BRCA2 genes or to offer large rearrangement testing.

29. In response to the numerous studies published over the years documenting the inadequacy of full sequencing, Myriad began to offer a new test. Myriad's standard test, Comprehensive BRACAnalysis, consists of full sequencing of the BRCA1/2 genes and detection of five specific large rearrangements on the BRCA1 gene. In late 2006, Myriad began to offer the BRACAnalysis Rearrangement Test (BART), which looks for additional large rearrangements in the coding sequences of both BRCA1 and BRCA2.

² Some of these studies include: S. Agata et al., *Large genomic deletions inactivate the BRCA2 gene in breast cancer families*, J. Med. Genet. 2005;42:e64; C. Hartmann et al., *Large BRCA1 Gene Deletions Are Found in 3% of German High-risk Breast Cancer Families*, Human Mutation 2004;24:534; M. Montagna et al., *Genomic rearrangements account for more than one-third of the BRCA1 mutations in northern Italian breast/ovarian cancer families*, Human Molecular Genetics 2003;12:1055-1061; I. Tournier et al., *Significant contribution of germline BRCA2 rearrangements in male breast cancer families*, Cancer Research 2004;64:8143-8147; S. Gad et al., *Barcode screening on combed DNA for large rearrangements of the BRCA1 and BRCA2 genes in French breast cancer families*, J. Med. Genet. 2002;39:817-821.

30. The BART test is not available to many women who should have access to it. Myriad has strict criteria – that Myriad determines – for which patients should receive concurrent BART testing. BART will be run concurrently, at no additional cost, for patients who have personally experienced breast cancer before the age of 50 years, ovarian cancer at any age, or male breast cancer at any age, but only if the patient has at least two relatives on the same side of the family who were diagnosed with breast cancer before age 50 or ovarian cancer at any age.³ Patients who do not meet these criteria must pay an additional \$650 to order BART. Many insurance policies will not cover BART including Medicare. Approximately one-third to one-half of my patients for whom I request genetic testing do not meet Myriad’s criteria; yet, I think most should receive this additional testing.

31. One recent study examined Myriad’s criteria for automatic BART testing.⁴ Myriad provides automatic BART testing for people with an estimated risk of having a BRCA1/2 mutation of more than approximately 30%.⁵ The study authors concluded that these criteria are too strict, and that large genomic rearrangement screening should be offered to all non-Ashkenazi Jewish women whose estimated risk of having a BRCA1/2 mutation is greater than 10%, based on medical history, family history, and other factors. Their suggested criteria for offering BART testing are similar to previous criteria used to determine who should get gene sequencing. Therefore, if an individual has a personal and family history that suggests she would be offered genetic testing for BRCA1 and BRCA2, she probably should be offered both sequencing and testing for gene rearrangements.

³ Myriad’s criteria for including BART concurrently with BRCAAnalysis are available at <http://www.myriadresourceguide.com/pdfs/Myriad-Resource-Guide-BART-Criteria.pdf>.

⁴ M.D. Palma et al., *The Relative Contribution of Point Mutations and Genomic Rearrangements in BRCA1 and BRCA2 in High-Risk Breast Cancer Families*, *Cancer Research* 2008;68:7006-7014. The study found rearrangements using MLPA, a subset of which were confirmed by an alternate test, and also sent to Myriad for confirmation by BART.

⁵ *Id.* at 7012.

32. Because it is a test performed exclusively by Myriad, not much is known in the scientific community about BART. It is my understanding that the sensitivity and specificity of BART has never been fully and independently validated.

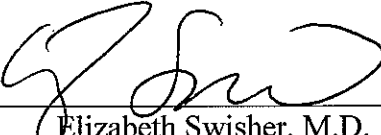
33. In other parts of the world, where the BRCA1/2 gene patents appear not to be enforced or have been limited, the standard of care includes large rearrangement testing using MLPA. To the best of my knowledge, MLPA on the BRCA1/2 genes is widely performed in Canada, Australia, and Europe. Myriad Genetics has published no formal comparison of BART with MLPA.

34. As a physician in the United States, I find myself unable to offer the international standard of care for my patients. Because I specialize in ovarian cancer, many of my patients are appropriate candidates for BRCA genetic testing. If they choose to go forward with testing, I must order the test through Myriad. However, the vast majority of them will not qualify for BART under Myriad's criteria even though my professional opinion is that large rearrangement testing should be done. For those who do not have the financial resources to pay for BART separately, neither I nor they can access that piece of information about their genes to help make medical decisions. For those who might be able to come up with the funds to pay for BART, I still cannot be confident that I am acting on the highest quality information because BART has not been fully and independently validated or compared to MLPA. I fear that I am ordering a second-rate test for my patients. More generally, I am concerned on behalf of my patients that the current system creates no incentive to create better and cheaper BRCA1/2 testing methods.

35. Today, I cannot offer my patients what I believe to be the best care related to BRCA1/2 genetic testing: a validated test that combines both full sequencing and large rearrangement analysis for all patients who are appropriate candidates for genetic testing. As a

result of the BRCA1/2 gene patents and the restrictions placed on genetic testing, this standard of care cannot be extended to patients in the United States. If the patents were invalidated, I have strong reason to believe that additional laboratories would offer large rearrangement BRCA1/2 testing, and I would order such testing for my patients.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.



Elizabeth Swisher, M.D.

Executed on August 19, 2009