UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

----------x

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,

v.

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.

----------x

09 Civ. 4515 (RWS)

ECF Case

DECLARATION OF DAVID H. LEDBETTER, Ph.D.

I, David H. Ledbetter declare under penalty of perjury:

1. I am Director of the Division of Medical Genetics and am the Robert W. Woodruff Professor of Human Genetics at Emory University School of Medicine. The Chair of our Department at Emory is plaintiff Stephen Warren.

2. My training and expertise are in the field of genetic testing. I received a PhD in Behavioral Genetics from the University of Texas at Austin in 1981.

3. Following completion of my PhD, I joined the faculty at Baylor College of Medicine in Houston as Assistant Professor and Director of the Kleberg Cytogenetics Laboratory, rising to the rank of full Professor in 1990. From 19993-1996, I served in the Senior Executive Service (SES6) of the federal government as Branch Chief of the Diagnostic Development Branch at the National Center for Human Genome Research (now the National Human Genome Research Institute). From 1996-2003, I served as the founding Chair of the Department of Human Genetics at the University of Chicago and held the Marjorie I. and Bernard A. Mitchell Professor of Human Genetics. Since 1992, I have served on the faculty of the Short Course in Medical and Experimental Mammalian Genetics in Bar Harbor, Maine.

4. I am a diplomat of the American Board of Medical Genetics (Clinical Cytogenetics) and a Founding Fellow of the American College of Medical Genetics (ACMG), an organizational plaintiff in this case. I have served on the Board of Directors of the American Society of Human Genetics and the American College of Medical Genetics. While on the Board of Directors for the American College of Medical Genetics, a position statement against the patenting of human genes was developed and approved by the Board and remains in effect today.

5. In 1995, I was awarded the 12th Carter Lecturer and Medal Recipient from the British Clinical Genetics Society.

6. A full copy of my current curriculum vitae is attached as an Exhibit.

7. My research has focused on the molecular characterization of human developmental disorders. As a graduate student, I discovered the chromosome 15 deletion that causes Prader-Willi syndrome (obesity and mental retardation). Shortly thereafter, I described the deletion of chromosome 17 that causes Miller-Dieker lissencephaly ("smooth brain"), a neuronal migration disorder causing profound mental retardation. My lab developed improved techniques for diagnosing these and other microdeletion syndromes (fluorescence in situ hybridization or FISH diagnostic tests, which were more accurate than high-resolution chromosome banding techniques that were used previously).

8. As Director of the Division of Medical Genetics, I am responsible for very large genetic testing laboratories at Emory University School of Medicine. These laboratories provide clinical testing services to a large number of patients and families with genetics diseases (over 28,000 tests performed per year) and include biochemical genetics, cytogenetics and molecular genetics testing.

9. Our genetic testing laboratory is a state-of-the-art clinical laboratory that offers full gene sequencing and testing for structural mutations. Test results are initially analyzed by experienced technologists and, where deleterious mutations are identified, these are interpreted, or correlated with disease risk. Our lab directors review the detailed results of all of our genetic tests and determine the final interpretation which is entered into a report.

10. Our genetic testing laboratory has the all of the personnel, expertise, equipment and facilities necessary to do comprehensive mutation analysis (including full gene sequencing and high-resolution deletion/duplication analysis) of any human gene, including sequencing of the BRCA1 and BRCA2 genes.

11. As an academically based genetics testing laboratory, a central part of our mission is to develop and implement new, better genetic tests that are more powerful, sensitive and accessible to patients. All of my research and most of the research of the faculty in my Division is "translational research" – research that aims to move new gene discoveries and technologies into clinical practice. In the last 3 years our molecular genetics laboratory has developed new gene sequencing tests for over 200 rare genetic diseases, many of which were previously unavailable as clinical tests. This work has depended upon our close collaboration with basic scientists at Emory and elsewhere.

12. Our program has developed several other techniques that are helping to revolutionize cytogenetics in research in clinical diagnostic laboratories. We are leaders in the development of microarray and high-throughput sequencing for clinical genetics testing.

13. For the past twenty-five years of my professional career, I have been aware of the detrimental impacts of gene patents, exclusive licensing, and genetic testing monopolies on clinical care. While at Baylor College of Medicine, I worked to discourage colleagues in my department from participating in an exclusive licensing practice. I was working at NIH with Dr. Francis Collins during the "race" to identify the BRCA genes by multiple groups, primarily funded by U.S. federal funds (National Institutes of Heatlh). I was quite aware of the "winning team" being a collaboration of investigators at the University of

Utah, Myriad and U.S. government labs and the subsequent patenting of and exclusive licensing of the BRCA 1 and BRCA2 genes that followed.

14. When I moved into doing translational research at the University of Chicago in 1996, the impact that the patenting and exclusive licensing of genes can have on research were made especially clear to me. Here, our quest to find new genes and undergo disease research was heavily directed by the patent landscape. We felt forced to design our research and business model so as to avoid genes that had been patented and exclusively licensed, since it had been made clear to us that we would not be able to obtain licenses to offer testing in those areas. Similarly, any enthusiasm we had for working on a particular disease was at risk of being deflated by announcements that a gene associated with that disease had been patented and exclusively licensed. For us, this meant that we could not participate in developing and improving tests associated with those diseases and that we could not work to make such tests accessible to our patients.

15. At Emory, we have also had to design our research and business plan around gene patents. Because of the interdependence of our translational research with our clinical testing activities, we are only able to invest in research for those diseases in which we will be free to offer genetic testing when we are successful in developing a new or improved clinical test. When a gene patent and exclusive licensing situation creates a genetic testing monopoly, we are forced to avoid performing research for this particular disease and therefore cannot contribute our cutting-edge technologies to the improvement of clinical testing for this patient population. This strong disincentive to perform translational research applies to many other academically based genetics testing

laboratories, thus depriving patient populations from the active research involvement of some of the best scientists and institutions in the world.

16. Our lab explicitly avoided the BRCA1 and BRCA2 genes even though we could have developed a better test than Myriad was offering. For example, we have understood for some time that simply sequencing the coding regions of the two genes does not find all known causative mutations that have been associated with an increased risk of developing breast and/or ovarian cancer. Sequencing will only uncover approximately 70% of the causative mutations. A significant portion of the remaining 30% of known mutations are structural mutations – primarily large rearrangements -- in the gene that disrupt its function. Testing for these requires applying alternative methods. The existence of these structural mutations and the methods for looking for them were known for a long time before Myriad started to test for them. Instead, Myriad employed a partial testing strategy. That means that a significant number of women were receiving false negative testing results. Still today, Myriad does not reflexively test for these additional structural mutations in the event of a negative sequencing test result.

17. By contrast, our lab offers comprehensive genetic analyses. In the event that we do not find known genetic alterations through gene sequencing, we automatically offer to look for structural mutations using cutting-edge microarray technologies to detect copy number. We offer this for all of our genetic testing. Our lab's leadership in microarray analysis means that we can conduct this additional testing more efficiently than most other labs.

18. If the BRCA 1 and BRCA2 patents were invalidated, our lab would immediately begin offering comprehensive BRCA1 and BRCA2 testing. I estimate that we could have

a BRCA testing program up and running within one month's time. We have all of the personnel and expertise that we need to offer comprehensive BRCA testing. Our leadership in developing high-throughput sequencing assays means that we have access to some of the most advanced equipment and techniques that would allow us to offer a highly efficient testing program. As we do for other whole gene tests, we would offer full sequencing, and for each case where standard sequencing does not reveal a pathogenic mutation, we would recommend and offer testing for structural mutations, utilizing our state-of-the art microarray technology. We would sequence and analyze the BRCA1 and BRCA2 genes for the named plaintiffs.

19. Our lab is of the view that clinical testing data should be contributed to a public, open database on a quick turnaround basis. The sharing of data benefits the entire clinical community whereas private, proprietary database inhibit the development of knowledge. If we were to offer BRCA testing, we would contribute all of our research and clinical data as we do in the case of all of our genetic testing.

20. One of the reasons data sharing is so essential in molecular diagnostics is that often we see genetic alterations that are difficult to interpret. These are referred to as "variants of unknown significance." Developing an understanding of which of these variants are pathogenic and which are benign requires large datasets. These can best be obtained by pooling data from many labs. When one party hoards all of the clinical data for a particular gene, it prevents the greater genetic community from being able to analyze this data and come to conclusions about the significance of these variants. If Myriad had been sharing its data and permitting other labs to analyze the genes, it is quite possible that researchers or clinicians in other labs would have been able to understand

the significance of some variants that Myriad now labels "unknown significance." That is why we routinely share such data. It is also why the participants of the Human Genome Project shared their sequence data, without restriction.

21. Our method for looking at structural mutations is different from the method that Myriad currently employs. Where multiple labs offer multiple methods of testing, it becomes possible to compare these different methods, and this ultimately may lead to improved testing quality.

22. After we sequence a gene we look at it to see if it has variants. That is, we compare it to the normal or wild-type gene to see if there are any differences. If there are differences, we try to determine if any of those differences have clinical significance. This process, of looking at a gene to see if there are variants and analyzing it to determine the clinical significance of those variants is routine and done by literally hundreds of labs all over the world every day. Indeed, analyzing the results of a sample taken from a patient to determine if it varies from the norm and if that variance has significance is the entire point of clinical laboratory work and is done not only with genes but in a huge variety of contexts.

23. By vigorously enforcing its patents and maintaining a monopoly on clinical diagnostic testing, Myriad is depriving women of an opportunity for a second opinion. Women who receive a negative result cannot know for certain what the rate of false negatives might be. Women who receive a positive result cannot confirm the lab's findings or seek a second opinion on the interpretation of those results. In addition to second opinions, proficiency testing and sample exchange programs are other aspects of

quality control that are jeopardized when a single laboratory controls all diagnostic testing for a disease gene.

24. Gene patents can directly interfere with our ability to investigate complex diseases. It is the case with most diseases that multiple genes play a causative role. For example, more than ten genes have thus far been associated with autism. Microarray technologies have brought us the ability to examine multiple genes at one time. But if one or more of these genes is patented, we are not able to develop a comprehensive, cost-efficient test for the full panel of genes.

25. Similarly, BRCA1 and BRCA2 may be associated with cancers other than breast and ovarian cancer, or even other diseases. But so long as the patents on these genes remain, no one will be able to include these genes in tests for other disease predispositions.

26. Gene sequencing involves purifying the DNA from the body and from at least some surrounding cellular material and making copies of the gene of interest, but the resultant sequence is functionally identical to the sequence that nature made in the body. The alterations or mutations in the gene that we are able to identify after sequencing the gene were made by nature, not by the process of sequencing or by me or other scientists, and the effect of those alterations or mutations is dictated by nature, not by any scientist.

27. Genes are products of nature and not inventions of man. They are so basic to science that any restriction that prevents scientists from looking at the genes themselves or examining the effects of the genes is fundamentally inconsistent with the advancement of human knowledge.

28. There is absolutely no need for patent protection in the diagnostic field of use. For any disease gene identified, there are a large number of academic and private diagnostic laboratories prepared to establish clinical testing at very modest investment, which will increase access to clinical testing services, and provide incentives for test improvement in the form of greater sensitivity and cost-effectiveness.

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.

David H. Ledbetter, Ph.D.

Executed on August 20, 2009