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)
Plaintiffs,	ECF Case
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,	DECLARATION OF EMANUEL PETRICOIN, Ph.D.
Defendants.	

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I, Emanual Petricoin, declare under penalty of perjury as follows:

1. Since 2005, I have served as a Professor in the College of Sciences at George Mason University. During this time, I have served as Co-Director of the Center for Applied Proteomics and Molecular Medicine. From 2006-2007, I was Chair of the Department of Molecular and Microbiology at George Mason University. My qualifications, publications and experience are described in my *curriculum vitae* attached hereto as Exhibit 1 ("Ex. 1").

2. In 1985, I received a B.S., and in 1990, I received a Ph.D. in Microbiology from the University of Maryland at College Park. Subsequently, I was a National Research Council

Post-Doctoral Fellow at CBER-FDA. From 1995 to 2003, I was a Senior Staff Fellow and Senior Investigator at the FDA, where my research focused on development of mathematical and bioinformatics approaches for molecular network elucidation and protein-protein interaction analysis as well as the identification and discovery of biomarkers for early stage disease detection. From 2001-2005, I served as Co-Director of the FDA-NCI Clinical Proteomics Program.

3. During the course of my research career I have received numerous awards including the University of Louisville, Kentucky Colonel 2006, faculty of 1000 in Medicine (2005, 2006 and 2007), Harvard University and Children's Hospital Leading Edge Award 2004, Nancy Terner Berman Award and Lecture 2004, American Society of Cytopathology Basic Research Award 2003, Clinical Ligand Assay Society Distinguished Scientist Award 2003, NIH Director's Award 2002, University of North Carolina School of Medicine Ralph Landes Award 2002, FDA Scientific Merit Award for Outstanding Intercenter Collaboration 2001, CBER Director's Distinguished Service Award 2001 and National Research Council Fellowship Award 1990.

4. I have served as Editor or Senior Editor of numerous publications including Cancer Epidemiology Biomarkers and Prevention, Expert Opinion in Molecular Diagnostics, Pharmacogenomics, Proteomics: Clinical Applications, Biomarkers in Medicine, Practical Proteomics, Biomedical Microdevices, Expert Opinion in Drug Discovery, Clinical Proteomics, Cancer Epidemiology Biomarkers and Prevention, and Journal of Proteome Research.

5. I have served as a reviewer of articles for publication in numerous scientific journals including Cancer Research, Molecular Cancer Therapeutics, Lancet, Lancet Oncology, Nature, Nature Medicine, Nature Biotechnology, Science, Journal of the American Medical

Association (JAMA), Journal of Proteome Research, Analytical Chemistry, Biotechniques, Proteomics and Clinical Cancer Research.

6. I have served on the Board or Scientific Advisory Board of several companies including: Ceres Nanosciences, SuperArray, Inc. and Theranostics Health, Inc.

7. I am familiar with patents and the patent process because I am an inventor on numerous U.S. and foreign patents and patent applications, including U.S. Patent Nos. 7,333,896; 6,969,614 and 6,925,389.

8. My scientific research has focused on the development of mathematical and bioinformatics approaches for molecular network elucidation and protein-protein interaction analysis; identification and discovery of biomarkers for early stage disease detection and treatment through personalized medicine; and development of techniques for improved imaging, monitoring and treatment of disease.

9. I have reviewed the following documents: Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment ("Plaintiffs' SJM"), Plaintiffs' Rule 56.1 Statement of Material Facts, ("Plaintiffs' SMF"), Declaration of Sir John Sulston, Ph.D. dated August 17, 2009 ("Sulston Decl."), Declaration of Christopher E. Mason of August 20, 2009 ("Mason Decl."), Declaration of Myles W. Jackson of August 18, 2009 ("Jackson Decl."), U.S. Patent Nos. 5,753,441 ("'441 patent"); 5,747,282 ("'282 patent"); 5,710,001 ("'001 patent"); 5,709,999 ("'999 patent"); and 5,693,473 ("'473 patent") which contain claims directed to *BRCA1* technology ("the *BRCA1* patents") and U.S. Patent Nos. 6,033,857 ("'157 patent") and 5,837,492 ("'492 patent") which have claims directed to *BRCA2* technology ("the *BRCA2* patents"). I refer herein to the *BRCA1* and *BRCA2* patents collectively as "the Myriad Genetics' patents."

10. I have been asked to review the above-identified documents and provide my opinion as to whether the description of the technology claimed in the Myriad Genetics' patents and implicated in this litigation, is accurately set forth in Plaintiffs' SJM and Dr. Sulston's Declaration.

I. Isolated DNA Is Not A Product Of Nature And Has Unique Properties Not Found Associated With Naturally-Occurring Nucleotide Sequences

11. I disagree with the assertion in Plaintiffs' SJM that the Myriad Genetics' patents "seek to patent natural ("wild type") human genes, mutations in those genes caused by nature . . . ." Plaintiffs' SJM, 1. Furthermore, Dr. Sulston misconstrues the claims of the Myriad Genetics' patents when he broadly asserts that "[g]enes and human genetic sequences are not inventions. They are naturally occurring." Sulston Decl. ¶10. To the contrary, the Myriad Genetics' patent claims are directed to isolated genes and genetic sequences which are not found in nature. Isolated genes and genetic sequences have a different chemical structure and unique properties not associated with naturally-occurring chromosomally located nucleotide sequences.

12. The Myriad Genetics' patents provide a scientifically acceptable definition of the terms "isolated DNA" and "isolated DNA molecule." The patents define "isolated DNA" or "isolated DNA molecule" as that "which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems." *See*, for example, the '282 patent, col. 19:14-18 and the '492 patent, col. 18:1-5.

13. Genes and human genetic sequences are comprised of DNA. The term DNA is an acronym for a chemical compound which is also known as deoxyribonucleic acid. DNA comprises repeating units known as nucleotides. These nucleotides each contain one of four different bases known as adenine or "A," thymine or "T," guanine or "G," and cytosine or "C."

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The bases are linked together by a sugar-phosphate backbone to form a single-stranded or double-stranded polymer.

14. The human genome comprises about 3 billion nucleotides organized into 23 chromosome pairs. Each chromosome comprises DNA and protein. The DNA found in the chromosomes contains two complementary polymers or strands of nucleotides that form a double helix. The complementary strands form because A associates with T and C associates with G. About 1.5% of the nucleotides in the human genome are organized into genes. A gene is the basic unit of heredity in all living organisms. Most genes in the human genome comprise a nucleotide sequence on one strand of the double helix that codes for a protein. When the gene is active or expressed, the nucleotide sequence is transcribed into messenger RNA (mRNA). DNA and RNA are different chemical compounds. RNA is an acronym for ribonucleic acid. The mRNA may then be then translated into protein. mRNA and protein are responsible for development and functioning of each cell that makes up a living organism.

15. The regulation of gene expression, and the production of mRNA and protein, is complex. The regulation of gene expression may involve nucleotide sequences within the gene and outside the gene. For example, a human gene may include introns, and genomic BRCA1 and BRCA2 genes for example, contain introns. An intron is a DNA region that may not be translated into protein. The human gene may be transcribed into precursor mRNA (pre-mRNA) and then introns are removed from the pre-mRNA by a process called splicing. The process of splicing produces an mRNA that differs both chemically and structurally from the (complement of the?) DNA that codes for it. Furthermore, the splicing of a pre-mRNA may be regulated such that different mRNAs and proteins may be produced from the same gene.

16. Gene expression may be controlled in many other ways. As noted above, chromosomes comprise DNA and protein. The protein/DNA complex is called chromatin. The structure of the chromatin regulates access to genes of molecules required for transcription and gene expression. Furthermore, the DNA may be methylated. During the process of DNA methylation an enzyme adds methyl groups to certain nucleotides in the DNA. The presence or absence of methyl groups attached to nucleotides can affect gene transcription.

17. As noted above, the Myriad Genetics' patents define the terms "isolated DNA" and "isolated DNA molecule" as DNA that "has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems." *See*, for example, the '282 patent, col. 19:14-18 and the '492 patent, col. 18:1-5. In the context of patent claims to isolated DNA comprising the *BRCA1* and *BRCA2* genes, the isolated DNA has a very different structure from that which occurs naturally. The isolated sequences are no longer located on a human chromosome and therefore are not necessarily assembled in the native chromatin structure.

18. The environment of a DNA molecule dictates both its structure and its function. For example, DNA can be influenced by factors within its naturally-occurring environment that affect expression of DNA, such as methylation which may epigenetically silence a gene. When obtaining DNA from its naturally occurring environment, these factors no longer influence the isolated DNA. Accordingly, the isolated DNA may not be methylated, or have a very different pattern of methylation than the naturally-occurring gene. Thus, contrary to Dr. Sulston's assertions, a genetic sequence is not just the biological information itself, and a genetic sequence

in one medium is a different chemical compound than a genetic sequence in a different medium. Sulston Decl. ¶16.

19. If the isolated DNA is a complementary DNA (cDNA), it may have a very different nucleotide sequence than the corresponding and naturally-occurring DNA. A cDNA is produced as a complementary copy of an mRNA. As discussed above, a mature mRNA may be produced by splicing and removing introns from the pre-mRNA. Consequently, cDNA may have fewer nucleotides than the gene to which it corresponds. It is my understanding that both the *BRCA1* and *BRCA2* genes contain introns. Consequently, the isolated *BRCA1* cDNA claimed in claim 2 of the '282 patent, a nucleotide sequence which does not contain introns, has a different nucleotide sequence than the naturally-occurring *BRCA1* gene. Likewise, the isolated *BRCA2* cDNA claimed in claim 2 of the '492 patent, a nucleotide sequence which does not contain introns, has a different nucleotide sequence than the naturally-occurring *BRCA2* gene. Accordingly, several of the recited DNA sequences in the Myriad patents do not include introns that are present in genes naturally occurring in cells, nor additional endogenous regulatory sequences.

20. Isolated DNA, by definition, cannot act independently of human intervention. In other words, without the hand of man, an isolated DNA sequence has no function or use.

21. Isolated DNA has unique properties and uses that are not associated with naturally-occurring DNA. I could enumerate a vast number of these unique properties and uses but I will provide three important examples. Unlike naturally-occurring DNA, isolated DNA may be used as a primer for synthesis of DNA in the polymerase chain reaction (PCR). PCR is an enzymatic technique used to make millions of copies of a target DNA sequence. A critical step in PCR is annealing of a primer to the target DNA sequence. A primer is a short fragment

of an isolated nucleic acid sequence that contains a nucleotide sequence complementary to the target DNA sequence or part of it and therefore the primer will anneal or attach to the target DNA. Once the primer is annealed to the target DNA sequence, an enzyme is used to make a copy of the target DNA. As PCR progresses, the DNA produced is itself used as a target DNA, resulting in selection and repeated amplification of the target DNA. The Myriad Genetics' patents contemplate using isolated DNA sequences from the *BRCA1* and *BRCA2* genes to amplify and analyze these genes to determine if a patient carries one or more mutations associated with breast and/or ovarian cancer. *See*, for example, the '282 patent at col. 28, ln. 9-39 and the '492 patent, col. 27, ln. 11-43.

22. Unlike naturally-occurring DNA, isolated DNA can be used to produce large quantities of a protein coded by the DNA. Production of large quantities of a protein may be very important if the protein can be used as a pharmaceutical, such as human growth hormone, or as substrate for research and development of therapies for treatment of malfunctioning protein. Isolated DNA can be cloned into a plasmid. A plasmid is an extra-chromosomal DNA molecule that is separate from chromosomal DNA and is capable of replicating independently of chromosomal DNA. In bacteria, for example, hundreds of copies of a plasmid may be present. By cloning an isolated DNA into a plasmid, and inserting that plasmid into a bacterium, thousand of copies of a gene can be produced, resulting in production of large quantities of the protein encoded by that gene. Furthermore, the isolated and cloned human DNA may be expressed in the absence of some or all of the mechanisms that normally control its expression in the human body. Consequently, the isolated and cloned DNA can be made to express much larger quantities of mRNA and protein than would normally occur in the human body. Prior to production of human growth hormone through cloning of isolated DNA, this protein was

extracted from the pituitary glands of cadavers and therefore there was a very limited supply of growth hormone for treatment of human disorders. The Myriad Genetics' patents contemplate cloning of isolated DNA comprising the *BRCA1* and *BRCA2* genes for production of large quantities of the proteins encoded by these genes. *See*, for example, the '282 patent at col. 62, ln. 5-33 and the '492 patent, col. 48, ln. 48-67.

23. Isolated DNA can also be used in a vector system to create a transgenic animal, *i.e*., an animal having a deliberate man-made modification in its genome. Transgenic animals have many uses, such as in agriculture and medicine. For example, a mouse expressing a human gene of interest can be created by preparing a transgenic construct containing an appropriate promoter (regulatory sequence) and the human gene (e.g., isolated DNA sequence) to be studied. The resulting transgenic animal can be used to study the regulation of the gene, as well as the effect of over- or underexpression of the gene. Accordingly, isolated DNA enables the function of a particular gene to be explored, which is something not possible with DNA in its naturally-occurring environment .

24. Thus, isolated and genomic DNA are distinct for at least the following reasons: (1) isolated DNA is different in size and composition from a corresponding gene contained in a chromosome in a body; (2) isolated DNA is not regulated by its natural environment; it is in a medium that is different from that of genomic DNA; (3) isolated DNA has unique properties and uses that are not associated with naturally-occurring DNA and because of these unique properties, isolated DNA can be used to perform different, additional functions that would not occur naturally; and (4) introns, which, amongst other functions, may regulate the timing of transcription of genomic DNA, contain enhancer sequences for normal gene expression, or just facilitate their own removal, may be absent in cDNA.

II. The Human Body Does Not Have A Means Of Isolating DNA And Therefore Scientists Had To Skillfully Undertake This Task

25. Contrary to the contention in Plaintiffs' SJM on page 25, citing Jackson ¶¶ 26-29 and Mason ¶¶ 11-12, the human body does not have a mechanism for isolating genes. More specifically, Plaintiffs contend on page 25 of their SJM that "the human body does possess a natural process for isolating and purifying genes Jackson ¶¶ 26-29 and Mason ¶¶ 11-12." This statement, however, is scientifically inaccurate.

26. The Jackson and Mason declarations contend that the process of gene expression is analogous to isolating DNA. Gene expression, however, involves the production of mRNA through the process of transcription and the production of protein through the process of translation. These processes occur in the naturally-occurring environment of the cell. At no time during either of the process of transcription or translation is DNA "removed from its naturally occurring environment" as "isolated DNA" is defined in the Myriad patents. *See*, for example, the '282 patent, col. 19:14-18 and the '492 patent , col. 18:1-5.

27. While a human body does transcribe a gene into mRNA, which is then translated into a protein, the human body does not isolate or purify an "isolated DNA". Genes naturally exist on two strands of DNA in chromosomes, where a single strand remains intact during cellular processes, such as transcription or DNA replication. Genes exist on chromosomes as DNA transcription units, which contain the sequence that is transcribed (the coding sequence), as well as regulatory sequences that exist upstream and downstream the coding sequence, such as promoters, transcription factors (e.g., enhancers) and termination sequences. Thus, "isolated DNA" only comes about from human intervention.

28. Furthermore, Dr. Mason compares cDNA, which does not naturally exist in the body, with mRNA, which does exist in the body, and implies that they are similar because both

cDNA and mRNA do not contain introns and the letter order of cDNA is just the mirror of mRNA. *See* Mason Decl. ¶ 29. The fact of the matter is, however, that cDNA and mRNA are very different; they are two different chemical entities, with different chemical compositions, and assume different structures because of the inherent differences in helical conformation. Indeed, mRNA can assume different tertiary and quaternary structures, forming structures such as hairpin loops. Also, cDNA is a DNA cognate/derivative, while mRNA is a RNA cognate/derivative. Thus, one cannot compare the cDNA with mRNA and conclude, as Dr. Mason has done, that "even though the structure of cDNA does not exist in precisely the same form in the body, for literally all practical and information-based purposes it is identical to that in the body." Mason Decl. ¶ 32.

29. Also, according to the Mason declaration, patent claims directed to cDNA should be rejected because "cDNA is essentially equivalent to the DNA, and was found using established methods." Mason Decl. ¶33. This, however, is scientifically incorrect. cDNA and DNA differ not only in the absence of introns and the presence of a poly-T tail in the cDNA, but cDNA also is not isolated from the same microenvironment as the native chromosomal sequence, is not subjected to the same modification system (e.g. methylation) and thus cDNA is inherently a different molecular entity then DNA. These differences are not insubstantial.

30. Furthermore, the isolation of the *BRCA1* and *BRCA2* genes and corresponding nucleotide sequences claimed in the Myriad Genetics' patents required skillful and inventive enterprise. When the work was begun, the inventors did not know which of the 3 billion nucleotide sequences in the human genome comprised the *BRCA1* and *BRCA2* genes. As a result of the inventive work of the Myriad inventors, we now know that the longest form of a BRCA gene has about 80,000 nucleotides. A gene comprised of 80,000 nucleotides represents about

0.003% of the human genome, an infinitesimally small portion of the total number of nucleotides in the human genome.

31. The Myriad Genetics' inventors had to use highly sophisticated genetic and molecular techniques to identify and isolate the BRCA genes that pre-dispose women to breast and/or ovarian cancer. The inventors identified populations of women in which pre-disposition for breast and/or ovarian cancer was present. The inventors then identified molecular markers that co-segregated with pre-disposition for breast and/or ovarian cancer. With considerable skill and inventiveness, both the *BRCA1* and *BRCA2* genes were isolated, and mutations in those genes that pre-dispose carriers of those mutations to breast cancer were identified. The Myriad Genetics' patents claim the isolated DNA from the *BRCA1* and *BRCA2* genes and methods of using those genes for diagnosis and treatment of cancer. The claimed methods of diagnosis and treatment would not have become available to women but for the isolation of the claimed non-naturally-occurring DNA.

32. Additionally, the Jackson declaration suggests that isolated and purified genes do not compare to purified adrenaline because "[the genes in the patents] do not have an entirely new function, whereas purified adrenaline's function is enabled by human intervention." Jackson Decl. ¶31. Dr. Jackson's reasoning, however, is incorrect. Although adrenaline could not be taken safely before human intervention, adrenaline still had a function in the body irrespective of human intervention. Similarly, the *BRCA1* and *BRCA2* genes could not have been isolated from the body before human intervention. Moreover, although the *BRCA1* and *BRCA2* genes have use within the body, isolated *BRCA1* and *BRCA2* genes (not found in nature) have entirely new uses (like purified adrenaline, as compared to adrenaline in the body).

III. DNA Is A Chemical Molecule And Like All Chemical Molecules it Contains Information

33. Plaintiffs contend in their SJM that DNA is unique in that the chemical compound conveys information. More specifically, Plaintiffs' contend on page 28 of their SJM that "the gene sequence claims in effect patent any use of the BRCA1/2 genes" and that "[t]he patents cover the genes themselves; because the function of the genes both in the body and in the defendant's lab is to convey information, they cover all of the information for all of its uses." Plaintiffs' SJM, 28. Contrary to the assertion in Plaintiff's SJM, DNA is not unique in this regard. Every chemical compound contains information in the order and arrangement of atoms that comprise it.

34. As with any chemical compound, DNA contains information. One type of information contained in DNA is the order of attachment of bases A, T, G, and C which forms the genetic code. The order of nucleotides may determine the chemical structure of the encoded protein. The order of nucleotides may determine whether a protein binds to DNA and regulates the expression of a gene. The order of nucleotides determines how the DNA works in the nucleus of the cell.

35. But every chemical compound contains information in the order and arrangement of atoms that comprise it. For example, stereoisomers, such as dextrorotatory glucose ("D-glucose") and levorotatory glucose ("L-glucose") contain the same number of atoms and order of atoms (*i.e.*, same molecular formula and sequence of atoms) but they are arranged in a spatially distinct manner. The different three-dimensional spatial orientation of atoms in D- and L-glucose, however, confers distinct properties and uses for each of the two molecules. Indeed, L-glucose cannot be metabolized by cells in the human body while D-glucose can be broken down by a process known as glycolysis. Similarly, D- and L-isomers of a pharmaceutical compound can exhibit differences in ability to treat a disease or disorder. For example, one stereoisomer of

omeprazole is more effective than the other stereoisomer alone for the treatment acid reflux disease. Thus, not only is the "information" that is contained within a chemical molecule important, but other factors ancillary to the biochemical make-up are relevant as well.

IV. Patented Genes Are Not a Disincentive To Further Research

36. I disagree with Dr. Sulston's statement that "[p]atenting a gene or genetic sequence impedes scientific progress . . ." and that "[gene patents] are a disincentive to further research on those genes." Sulston Decl. ¶¶ 28, 37.

37. Several universities and other companies continue to conduct research on and develop assays relating to BRCA genes, despite the Myriad patents. For example, Vanderbilt University and the University of Washington filed patent applications (now US Patent Nos. 6,177,410 and 6,149,903) relating to the BRCA genes after the Myriad patents issued, as well as Baystate Medical Center (now issued US Patent No. 5,965,377). Eli Lily and Company and Dana Farber Cancer Institute also continue to do research in this field, even after the Myriad patents issued. And these entities do not represent an exhaustive list.

38. My personal experiences are also contrary to Dr. Sulston's assertions. I am the founder of at least two companies, including Theranostics Health, a company focused on providing research and development services to pharmaceutical companies and academic institutions, and in developing its own clinical tests. Based on our own innovation, my company continues to make advances in cancer diagnosis and treatment. Funding for Theranostics Health has been predicated in part on the hope investors will obtain a return on their investment through exclusive rights for a limited time period on inventions developed by the company with their financial resources.

39. Furthermore, gene patents or patents on genomic sequences have not obstructed or delayed advances in health care technology in my opinion. Research conducted by all entities,

whether patented or not, has paved the way for future discoveries and in my opinion, has not disincentivized scientific progress.

40. In fact, research is actually impeded by lack of funding and not hindered by the patent landscape with regard to gene patents. Indeed, without research grants or other sources of monies, research on genes and genetic sequences, or any other technology area, cannot continue. To this end, patents provide the financial incentive for innovation, and revenue generated from intellectual property permits research to continue. Thus, contrary to Dr. Sulston's remarks, patenting gene sequences in my opinion do not impede science and future therapeutic developments.

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.

Emanuel Petricoin, Ph.D.

Executed on January 11, 2010