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, 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	Civil Action No. 09-4515 (RWS) ECF Case **DECLARATION OF ROGER D. KLEIN, MD, JD**

I, ROGER D. KLEIN, MD, JD, certify under penalty of perjury that the following is true and correct:

1. I am currently Medical Director of Molecular Oncology at BloodCenter of Wisconsin, and Clinical Assistant Professor in the Department of Pathology at Medical College of Wisconsin. I previously served as Medical Director of Molecular Diagnostics at H. Lee Moffitt Cancer Center, and Assistant Professor

in the Department of Oncologic Sciences at University of South Florida Medical School. The statements herein represent my views as an individual and not those of BloodCenter of Wisconsin or Medical College of Wisconsin.

2. I earned my undergraduate and medical degrees at Case Western Reserve University (OH, USA), and completed an internship in internal medicine at a Case Western Reserve University School of Medicine affiliated hospital. I completed residency training in Laboratory Medicine (Clinical Pathology) and fellowships in Medical Microbiology and Molecular Genetics at Yale University School of Medicine (CT, USA). I then completed a fellowship in Molecular Genetic Pathology at Mayo Clinic (MN, USA). In addition, I earned a law degree (J.D.) from Yale Law School, and am licensed to practice law in the District of Columbia and Ohio.

3. I am board-certified in Clinical Pathology and Molecular Genetic Pathology. I am a member of the Centers for Disease Control (CDC) sponsored Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP), and am a consultant to the U.S. Food and Drug Administration's (FDA) Clinical and Molecular Genetics Advisory Panel. I have served on the College of American Pathologists' 'Biochemical and Molecular Genetics' and 'Point-of-Care Testing' Resource Committees, and am currently a member of the College of American Pathologists' Molecular Oncology Resource Committee. I also serve on the Association for Molecular Pathology's Professional Relations and Economic Affairs and Committees, and am a member of the Clinical Laboratory Standards Institute's (CLSI) Subcommittee on Establishing Molecular Testing in Clinical

Laboratory Environments. In addition, I am a member of the Editorial Advisory Board of the Journal Pharmacogenomics (Future Science).

4. My academic and clinical efforts focus on the translation of genetic knowledge into clinical diagnostic tests for the evaluation and management of hematopoietic and solid tumor malignancies and hereditary cancer syndromes. This work includes the assessment of the clinical validity, clinical utility and the optimal and appropriate use of molecular genetic tests. In addition, I have an active research program involving the ethical, legal and social implications of the Human Genome Project, with particular emphases on the areas of intellectual property and the regulation of *in vitro* diagnostics and clinical laboratories. I have multiple publications in these areas.

5. In my medical practice I oversee the design, validation, and performance of genetic tests for inherited disorders and cancer on patients' blood cells and tissue. I analyze the genetic data that arises from such tests and provide patient-specific reports that interpret this information and place it into clinical context. In addition, I advise ordering physicians on the appropriate use of genetic tests generally and for individual patients, and provide patient-specific consultation about the meaning of the genetic information we provide.

6. Attached as an exhibit is my curriculum vitae.

7. The statements herein describe the molecular structure and biological role of DNA and messenger RNA (mRNA), and specifically address the role and function of DNA and mRNA in genetic testing. These statements also address the mental acts of associating or correlating genetic variation with clinical phenotypes

such as the presence of, predisposition to, and prognosis of human disease. For the purposes of this declaration, I define genetic testing as the interrogation of a patient's cellular DNA to determine its nucleotide sequence followed by comparison of the patient's DNA sequence to that of a reference or "normal" sequence, wherein the presence of a deviation from the reference or normal sequence is associated or correlated with a clinical phenotype as set forth in the preceding sentence.

DNA IS AN INFORMATIONAL MOLECULE

8. DNA contains within its molecular structure the genetic information necessary to specify most if not all aspects of embryogenesis, development, growth, metabolism, and reproduction. DNA provides the blueprint for our highly organized, intricate, complex internal structures, and the template for the complex molecules that allow us to extract, transform, and utilize the energy that is present in our environment. Thus, first and foremost DNA is an informational molecule. DNA has the ability to store and transmit enormous quantities of information. This information is stored in the sequence of adjacent bases within the DNA strand through what is termed the "genetic code." For a DNA molecule that is "N" bases long, there are 4^n possible DNA sequences.

9. DNA is a chemical compound. However, its chief biological role is as an informational molecule. DNA is unique among biological molecules in its ability to store vast quantities of information and to transmit that information to daughter cells through self-replication. The information contained within the DNA sequence is used generate proteins that are assembled from amino acids. The

sequence of amino acids in proteins is integral to their physical structure and biological functions. The genetic code specifies a protein's amino acid sequence. DNA is "transcribed" into mRNA. Messenger RNA carries the information stored in DNA to sites in the cell where the information can be "translated" into proteins on "organelles" called "ribosomes."

10. By comparison, the molecule adrenaline is a signaling chemical that acts on target cells distant from its site of manufacture in the adrenal gland. Whether internally produced or exogenously administered as a drug, adrenaline is carried by the blood to α and β-adrenergic receptors on the surface of its cellular targets, where it non-selectively stimulates these receptors. The stimulated α and β-adrenergic receptors in turn activate "second messengers," leading to a cascade of enzymatic reactions that mediate adrenaline's effects. The adrenal glands release adrenalin in response to danger or stress. Adrenaline provides a *non-specific* fight or flight signal that leads to increases in the rate and strength of heart contractions and the constriction of blood vessels, thereby raising blood pressure. Adrenaline also causes expansion of the diameter of airways within the lungs. Adrenaline causes the mobilization of glucose and free fatty acids. Through these and other effects, adrenaline increases the supply of oxygen and glucose to the brain and muscles, while diverting blood away from less urgent processes like digestion. If DNA is likened to a building's blueprint, adrenaline is analogous to the electric signal that turns on the building's furnace in response to a drop in temperature.

11. Unlike DNA, adrenaline is continually produced and degraded. Adrenaline does not encode for the design of human organs like the brain, heart, lungs, or kidneys.

Adrenalin does not specify the amino acid sequences of the proteins from which the human body is constructed. Adrenaline does not even store information that tells heart cells how to beat faster or blood vessels to narrow. In contrast to individuals' nucleotide sequences, adrenaline's protein sequence does not vary from person-to-person in its essential chemical features. Naturally occurring adrenaline is a general signaling molecule that exerts its effects through chemical action in a manner analogous to that of exogenously administered drugs.

12. A nucleotide sequence is the linear order of the base pairs of the DNA molecule and its embedded genes. Genes are regions of the DNA that encode for a functional product. The nucleotide sequences in the coding regions of genes specify the amino acid sequences of the proteins they generate through the genetic code. The order of the nucleotides is of prime importance, because within this order is contained the genetic code, the information that directs human cells to grow, to differentiate into specialized structures, to divide, and to respond to environmental changes. Nucleotide sequences cannot be equated to chemical formulas that represent chemical compounds (e.g. H_2O, NH_3) because such chemical formulas are merely a shorthand way of listing a molecule's constituent atoms and their respective numbers. All substances, both animate and inanimate, are composed of molecules. Atoms are fundamental units of matter that are the building blocks of molecules. All molecules can theoretically be represented by their chemical symbols. For example, the nucleotide adenylate mono phosphate (AMP) which contains adenine as its base is composed of 10 carbon atoms, 12 hydrogen atoms, 5 nitrogen atoms, 6 oxygen atoms, and 1 phosphorous atom and

can be written as $C_{10}H_{12}N_5O_6P$. Similarly, this shorthand could be used to describe the atomic (elemental) structure of DNA. However, the complexity of the DNA molecule and its constituent bases renders such depictions impractical, particularly in light of the limited utility this information would provide. By contrast, DNA sequences store and convey specific information that serves as the blueprints for all of the proteins, cells, and organs that make up the human body. Molecules represent a higher and a much more complex level of organization than atoms. Moreover, DNA is unique among molecules because the linear arrangement of its component nucleotides stores and transmits the genetic code.

13. Most DNA in non-dividing human cells is packaged within the nucleus in structures called chromosomes. However, during cell division and during the generation of gametes (eggs and sperm), DNA unwinds and is separated into individual strands. The individual DNA strands serve as templates for the synthesis of new complementary strands, resulting in duplication of the DNA content (genetic material) of the nucleus. The duplicated genetic material is passed along to the newly formed daughter cells that arise from the process of cell division. The DNA also unwinds during transcription, the process by which the information contained within the DNA is transferred to mRNA. During transcription, one of the DNA strands serves as a template for the generation of mRNA. Messenger RNA carries this information to structures called ribosomes on which proteins are synthesized.

14. A gene is a hereditary unit. The term gene is commonly used to refer to a segment of DNA that encodes for a functional product, usually a protein. Therefore, genes contain discrete units of genetic information.

15. Each DNA strand contains the full informational content of the DNA molecule and serves as the template for the synthesis of a new complementary strand. One of the 2 complementary DNA strands normally serves as a template for mRNA synthesis. Messenger RNA is translated into proteins. The protein amino acid sequence is directly dependent on the sequences of nucleotide bases in the DNA strand. A protein's amino acid sequence is a key determinant of its structure and function. Thus, mRNA is the essential connecting link between the information contained in the gene, and the specific amino acid sequence of the protein.

16. The language used in the process of translating the information in DNA into protein amino acid sequences is known as the genetic code.

17. Three base pair words (codons) specify the particular amino acid at its specific position in the protein. Because proteins are comprised of 20 amino acids, the codon had to include at least 3 bases (base pairs) to unambiguously specify an amino acid. (There are 4 possible bases at each position in the DNA molecule. If the codon included only 2 base pairs, there would be just 4 x 4, or 16 possible combinations, which would leave too few codons to encode for all 20 amino acids. By contrast, 3 base pair codons have 4 x 4 x 4 = 64 possible combinations, yielding substantially more codons than are necessary to encode for all 20 amino acids.)

18. The excess of codons over the number of amino acids allows for redundancy in the genetic code, which is referred to as degeneracy. This means that some amino acids are encoded for by more than 1 codon (several different codons result in incorporation of the same amino acid in the extending protein chain). Degeneracy may have a biologically protective effect because some of the inevitable mistakes that occur during DNA replication do not alter the amino acid that is incorporated into the protein, and therefore lack functional consequences. The proteins associated with DNA form a type of scaffolding on and around which the DNA is coiled, but do not encode genetic information. A coiling and uncoiling mechanism allows the body to both store and access the vast amount of information contained in DNA within the extremely small physical space of the cell's nucleus. Thus, many of the proteins to which the defendants refer can be viewed as part of DNA's "packaging."

19. DNA provides the blueprint for the cell, the organization of cells, and one could say for human life itself. The information in DNA contains the instructions for the generation of virtually all proteins in the cell. Other protein and nucleic acid elements can influence the expression of the underlying genetic information. For example, epigenetic modification determines whether or to what extent a gene is expressed as protein, and this in turn is governed by the state of the cell and its environment. But the fundamental information needed to produce the protein is contained within the DNA.

20. DNA and its genes are passed from parent to offspring in gamete cells known as eggs and sperm. Essentially one-half of the genes in each individual come from the mother (the egg) and the other half from the father (the sperm).

21. Growth and development of the embryo is produced by cell division. Individual cells copy their essential content and divide into 2 cells, which in turn divide. During embryogenesis, this process of cell replication continues for many cycles. During embryogenesis various genes are turned on and off, causing groups of cells to differentiate into the organs of the body. In many tissues some cells continue to replicate and divide throughout a person's life.

MUTATIONS ARE ERRORS IN THE GENETIC CODE

22. Rarely, cells make copying errors during replication of the DNA molecule, causing permanent heritable changes in the DNA. Such changes are often referred to as mutations. Errors that occur within the coding sequence of a gene change the information it contains, and may change the amino acid sequence of the protein for which the gene encodes, potentially altering its functional properties.

23. Mutations that are present in egg or sperm cells are passed on to offspring. Many such errors will be harmless to the individual and his or her descendents. Others may be lethal to the growing embryo.

24. Some mutations can be responsible for diseases. Diseases that can be passed on to offspring through the germline are known as genetic or heritable (inherited) diseases. Examples of heritable diseases include Huntington disease and Duchenne muscular dystrophy. For these diseases, virtually everybody who has

the associated genetic mutations and has a normal lifespan will eventually suffer from the disorder. People typically have 2 copies of each gene, receiving one copy (termed an allele) from each parent. For some conditions, for example cystic fibrosis, mutations in both alleles are usually necessary to cause the disease. These are termed "recessive" diseases. Other disorders can be caused by only one mutated gene, received from either the mother or the father. These diseases are termed "dominant."

25. Some mutations greatly increase the likelihood that individuals who carry the mutation will eventually get a particular disease. Thus, they confer a heritable predisposition to the disorder. For some of these diseases, many or most individuals who have the disease gene or genes will get the disease. These diseases are said to have high "penetrance." Such is the case with many disease-causing mutations in the BRCA1 and BRCA2 genes. Mutations in these genes greatly increase the probability that individuals unfortunate enough to have them will develop breast and other cancers.

ISOLATION DOES NOT ALTER THE FUNDAMENTAL DNA BLUEPRINT

26. An isolated DNA molecule is not made by the hand of a scientist; it is separated from its natural environment. Moreover, the genes within isolated, purified DNA often retain their arrangement and physical orientation relative to the original surrounding DNA on the chromosome. Most important, the process of isolating DNA does not alter the informational content of DNA or its embedded genes.

27. Individual genes can be isolated and purified through excision from the chromosome. During genetic testing, genes are not typically "excised" from the

chromosome or surrounding DNA. Instead, the gene is left in its native configuration relative to surrounding DNA. However, even a gene that has been isolated through excision is not fundamentally altered because the relevant parts of its sequence, and therefore its informational content, remain unchanged. Isolation does not in any way alter the fundamental DNA blueprint. The informational content of isolated DNA is not different from that of DNA in the body.

28. For the purpose of genetic testing, DNA isolation is a routine preparatory step that removes the DNA from its environment so as to allow us to read gene sequences using current diagnostic methods. Specifically, DNA isolation allows us to make the millions of copies of the coding regions of individual genes that are required by contemporary sequence reading instrumentation. DNA isolation is a routine procedure that is commonly performed using automated instruments or off-the-shelf kits. DNA isolation does not necessarily change the configuration, position, or arrangement of genes relative to surrounding segments of DNA within the native chromosome. Although chromosomal DNA strands may break as a byproduct of the extraction process, less rather than more breakage is generally favored for testing purposes. Most important, DNA isolation does not alter the nucleotide sequence and therefore the informational content of the genes that are embedded within the DNA strands. If DNA isolation changed these fundamental properties, isolated DNA would be of no practical use in genetic testing.

29. Although "isolation" per se does not normally occur in the body, the body unwinds DNA and separates its strands when it replicates the DNA during cell

division and when it transfers the genetic information to mRNA during transcription for use in protein synthesis.

GENETIC TESTING

30. When we perform genetic testing, we extract the DNA and amplify the coding regions and parts of the noncoding regions of particular genes using synthesized primers that hybridize (bind) to the non-coding regions of the genes. When we isolate DNA for genetic testing, we do not "excise" the gene.

31. DNA isolation ("extraction") is a routine procedure that is now performed using kits or automated DNA extraction instruments. In a step termed amplification, we generate large numbers of identical copies of the coding regions and intron-exon boundaries of individual genes contained within the genomic DNA, most often utilizing a process referred to as the polymerase chain reaction ("PCR"). We generate these additional gene copies because current technologies do not allow us to read the DNA at the single molecule level. PCR generates enough copies of the original DNA molecule so that it can be read by contemporary automated sequencers or other gene reading instruments. The patent on PCR, U.S. patent number 4,683,202, is entitled "Process for amplifying nucleic acid sequences," and was issued to Dr. Kary B. Mullis with Cetus Corporation as assignee on July 28, 1987. In 1993, Dr. Mullis was awarded the Nobel Prize in Chemistry for his invention.

32. The claims at issue in this case do not cover diagnostic tools or actual methods used in genetic testing. Nor are they analogous to patents on medical instruments. Rather they claim DNA sequences which are themselves the subject of medical

inquiry. Further, they incorporate generic steps in an effort to describe the biological relationships between mutations in BRCA1 and BRCA2 and the predisposition to cancer in the abstract patent language of a 'process.' However, the key steps in genetic testing, DNA extraction, amplification, and sequencing can now be performed using routine, automated methods. Nevertheless, the defendants claim the exclusive right to read and compare BRCA1 and BRCA2 sequences irrespective of the method used, whether that method is in existence now or will be invented in the future. Correlating a patient's gene sequence with the predisposition to disease is simply another form of medical diagnosis, similar to correlating elevations in blood glucose with diabetes, a heart murmur with mitral stenosis, or the patterns on a pathology slide with a particular type of tumor and its optimal therapy.

33. Automated sequencers reveal the sequence of the nucleotides visually in what is called a chromatogram. That chromatogram is then "read" (by software and visual inspection) to determine a patient's gene sequence.

34. DNA extraction and sequencing are not transformative activities. Rather extraction is a routine, non-substantial preparatory step that allows for PCR amplification and sequencing. Sequencing is an automated procedure. DNA extraction, PCR, and sequencing do not involve transformations that are central to the purpose of the process of reading a patient's gene sequence. Unlike "tanning, dyeing, making waterproof cloth, vulcanizing India rubber, or smelting ores," which are performed for the purpose of physically transforming substances so as to create what are essentially new materials for their own sake, the purpose of

genetic testing is solely to read the sequence of the DNA, not to transform it into something else. Only in this way can the patient and her physician learn whether a medically relevant mutation is present in her body.

35. In genetic testing, we do not ordinarily generate cDNA. We simply amplify and interrogate a gene contained within extracted DNA for medically important mutations. cDNA is not generally used as a probe or primer in genetic testing because it is too big. Moreover, cDNA typically cannot be used as a primer because primers are generally designed to hybridize to noncoding regions of the gene and cDNA does not contain the noncoding gene regions called introns (primers are placed in noncoding regions of the gene to ensure amplification of both the coding regions and the junctions between the coding and noncoding regions).

36. Knowledge of the medical information contained in the BRCA1 and BRCA2 genes can be extremely important for the management of some breast cancer patients and their relatives who carry the same genetic errors.

37. The information contained within the BRCA1 and BRCA2 genes could be routinely accessed by many pathologists and others skilled in the art using routine automated and semi-automated methods, but for the existence of the BRCA1 and BRCA2 patents. An individual patient's gene sequence can be compared in a straightforward manner to reference sequences that are easily accessible through publicly available databases. This mental act of comparing sequences establishes whether or not the patient's gene sequence varies from normal, and whether or not he or she has a medically relevant mutation.

38. Genetic testing can utilize primers and probes. Using probes and primers in genetic testing, including BRCA testing, does not fundamentally change the DNA. Primers and probes do not alter the underlying DNA sequence that is being read. Therefore, they do not alter its functional properties for the purposes of genetic testing. DNA isolated from the body is not typically used as primers or probes. Primers and probes are most often constructed as synthetic DNA. Primers are typically 18-25 nucleotide bases long. For mutation testing "isolated DNA" itself cannot be used as a probe in most circumstances, because the component DNA molecules are too large. Much smaller sequence fragments are ordinarily used as probes.

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.

Roger D. Klein

Executed on January 19th, 2010