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) **DECLARATION OF DEBRA G.B. LEONARD, M.D., Ph.D.**

1. My name is Debra G.B. Leonard, M.D., Ph.D. I am Professor of Pathology and Laboratory Medicine, Vice Chair for Laboratory Medicine and Director of the Clinical Laboratories in the Department of Pathology and Laboratory Medicine at Weill Cornell Medical College and New York-Presbyterian Hospital. I am also Chief Diversity Officer for Weill Cornell Medical College and head of the Office of Faculty Diversity in Medicine and Science.

2. I have been retained by the plaintiffs and their counsel as a consulting expert for this case. I have received no compensation for my services.

3. I received a B.A. in Biology in 1976 from Smith College, a Ph.D. in Biochemistry in 1987 from New York University, and an M.D. in 1988 from New York University School of Medicine. I completed my residency in Anatomic Pathology at New York University Medical Center in 1991. I completed a Surgical Pathology Fellowship at New York University Medical Center in 1992.

4. I have been employed in my current position since 2004. Prior to that, I was Assistant Professor in the Department of Pathology at Case Western Reserve University School of Medicine (1992-1996); and Assistant Professor (1996-2000) and Associate Professor (2000-2004) in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine.

5. I am certified by the American Board of Pathology in Anatomic Pathology, and by the American Boards of Pathology and Medical Genetics in Molecular Genetic Pathology.

6. I am a member of the College of American Pathologists and the Association for Molecular Pathology, two organizational plaintiffs in this case. I served as President of the Association for Molecular Pathology in 2000.

7. I am currently a member of the Institute of Medicine Round Table on Translating Genomic-based Research into Health, and chair of the Stakeholders Group of the CDC Program on Evaluating Genomic Applications in Practice and Prevention. I previously served as a member of the Advisory Committee on Genetics, Health and Society to Secretary of Health and Human Services Michael O. Leavitt.

8. I have spoken widely on various molecular pathology test services, the future of molecular diagnostics and the impact of gene patents on molecular pathology practice.

9. I am Editor of two textbooks of molecular pathology and have published more than 70 peer reviewed articles.

10. A copy of my curriculum vitae is attached hereto as an Exhibit.

IMPACTS OF GENE PATENTS ON MEDICAL PRACTICE

11. Gene patents have prevented me from practicing certain areas of my medical specialty, molecular genetic pathology.

12. I wanted to be a physician since I was 14 years old. My motivation was and remains a simple one: I want to help people who are sick. To achieve this goal, I spent four years in college, seven in graduate school, and another four years in residency and fellowship.

13. Pathologists are the diagnostic detectives for clinicians who directly take care of patients. We are trained in clinical laboratory medicine and understand the appropriate use, performance, and interpretation of the tests that detect disease, predict outcomes, and direct therapies. My medical practice focuses on the appropriate use, performance, and interpretation of the tests that are based on molecular biology methods.

14. Patents on genes are preventing me from including the diagnosis of certain diseases in my medical practice. I can no longer perform testing for Canavan disease, Alzheimer disease, and Charcot-Marie-Tooth Type 1A disease because of patent enforcement. I have received "cease and desist" letters from companies holding patents on genes related to these and other diseases, stating that their patents give them exclusive

rights to diagnostic testing for these diseases. Other physicians are prevented from testing for breast cancer genetic risk (BRCA1 and BRCA2). Studies have demonstrated the negative impact of gene patents for hereditary hemochromatosis mutations on the number of testing laboratories, in that almost 30% of laboratory directors stopped or did not develop hemochromatosis testing due at least in part to the patent on the hemochromatosis genetic sequence. Limiting the practice of physicians by patent law is not in the best interest of the public health.

15. Human genes and genetic sequences are products of nature. Those who patent genetic sequences and the correlation of genetic differences with the incidence or risk of a specific disease claim that they are not patenting part of the genome, since the patents claim only the cloned versions of the human sequence. But when I need to look at the same patented sequence in a patient to provide a diagnosis for her or his genetic disease, I cannot.

16. How do I explain to a patient that someone prevents me from looking at and characterizing a segment of her or his genome? The patient no longer has the ability to control her or his own body and the testing that can be done. How do I explain that I am not allowed by law to provide a test based on a part of her or his genome, a test that both the patient and her or his physician are asking me to perform, and that is necessary for diagnosis? Limiting the broad availability of medical testing is not in the best interest of the public health.

17. It makes perfect sense to me that patents should be granted on genetic diagnostic methods, such as that which was granted on PCR (polymerase chain reaction). But new uses claimed by disease gene patents for old methods of genetic diagnosis do not

make sense. What is claimed when someone patents a gene is any use of any genetic diagnostic method for looking at that gene. This is like allowing the person with a patent on the microscope to claim, through patents, the use of the microscope to view each new small thing – the method of use would be the same, but where one looked and what one saw would vary. This does not make sense. The device was invented to view small items, and new use patents should not be granted on each specific application thereof. Put another way, could the first person to view Pluto through a telescope patent the use of a telescope to view Pluto? Such use of the patent law is misaimed.

18. Anyone skilled in molecular biology has the knowledge and methods to sequence and examine any part of the human genome. Disease gene patents, including the patents on BRCA1 and BRCA2, limit where those skilled in these arts may look, based only on the fact that the patentee has identified an association between different chemical structures and risks of disease occurrence. This association is a natural phenomenon, and these patents essentially claim an observation of nature. Patents that restrict such fundamental knowledge about the human genome and about human disease are too broad.

19. Patents on correlations or associations between a gene sequence and a greater risk of disease allow the patent holder to control the use of that medical fact and information. In many cases, control of specific genetic information limits medical use of the information and impedes or prevents widespread research on the disease, the traditional pathway by which medical knowledge is advanced and shared. Limiting the use of medical information for research or medical practice is not in the best interest of the public health.

20. Gene patents are not necessary to further scientific discovery and the development of diagnostics, and these patents may in fact stifle needed clinical research. In a sense, disease gene patents are an end in themselves: these patents cover genetic diagnostic testing. The underlying knowledge of genetic diversity and the role of genes in causing disease or disease susceptibility can often be put to clinical use immediately by well-known techniques without extensive development such as that necessary for pharmaceuticals. Market exclusivity as allowed by gene patents are not in the best interest of the public health.

21. Physicians in laboratory medicine do not require the incentives of gene patents to develop and provide genetic tests based on the published medical and scientific literature. Laboratories can rapidly translate new genetic knowledge into diagnostic tests for the benefit of patients without the need for the incentives and protection of patents. The driving force for those in the clinical laboratory is the need of the patient, based on calls from clinicians to the laboratory requesting that a test be performed on their patients. We do not check whether a patent has been filed before deciding to develop a diagnostic test based on the published literature, nor do we have the negotiating skills or financial resources for cross-licensing of the patented information required for the diagnostic test. Our motivation is the practice of medicine.

22. Much of the basic research that yields associations between genes and disease has been publicly funded. Most of the disease gene patents issued to date resulted from research performed by university-based clinician-researchers with funding provided at least in part by the federal government. A study I co-authored in 1997, soon after

Myriad Genetics had obtained most of its patents on BRCA1 and BRCA2, showed that 63% of patents on gene sequences resulted from federally supported research.

23. Some companies, including Myriad Genetics, have adopted a business model that aims to become the exclusive provider of a testing service. These companies identify patents needed for specific diagnostic tests before the patent even issues and negotiate an exclusive license for diagnostic testing based on the patent. In the meantime, the gene-disease association is published and clinical laboratories develop tests based on the genetic information. Once the patent issues, the laboratories that have developed the medical need and use for the test and are already performing it, are prevented from continuing to perform the test.

24. When a single provider of a health care service dominates the market, there is no competition for the price of testing, the quality of service, the method used for testing, the further refinement of the test, or access for the uninsured or those with health care coverage requiring that testing be done under contract. A sole provider of a medical service is not in the best interest of the public health.

CLAIM CONSTRUCTION

25. I have reviewed several documents, including: (i) U.S. Patents Nos. 5,747,282 ("the '282 patent"), 5,693,473 ("the '473 patent"), 5,709,999 ("the '999 patent"), 5,710,001 ("the '001 patent"), 5,753,441 ("the '441 patent"), 5,837,492 ("the '492 patent") and 6,033,857 ("the '857 patent") (collectively, "the patents in suit"); and, (ii) the prosecution/file history of each of the patents in suit. After reviewing these documents, I noticed that the '282, '473, '999, '001 and '441 patents all stem from the same patent application family, have substantially identical specifications and relate to

the human gene known as BRCA1. Therefore, I may refer to these five patents as the "BRCA1 patents." I also noticed that the '492 and '857 patents both stem from the same patent application family, have substantially identical specifications and relate to the human gene known as BRCA2. Therefore, I may refer to these two patents as the "BRCA2 patents." Lastly, I also noticed that all seven of the patents in suit have specifications with substantial similarities, including with respect to the definition of certain terms.

26. I have been asked to provide my opinion on the construction of certain terms or phrases contained in certain claims of the patents in suit, including specifically: (i) claims 1, 2, 5, 6, 7 and 20 of the '282 patent; (ii) claim 1 of the '473 patent; (iii) claim 1 of the '999 patent; (iv) claim 1 of the '001 patent; (v) claim 1 of the 441 patent; (vi) claims 1, 6 and 7 of the '492 patent; and, (vii) claims 1 and 2 of the '857 patent. I understand that claims which refer to another claim are called dependent claims and incorporate by reference all of the terms in the claim to which they refer. For example, claim 6 of the '282 patent is dependent upon claim 2 of that patent, which is itself dependent upon claim 1. Thus, claim 6 of the '282 patent is read to include all of the terms of claims 2 and 1.

27. I have been told to provide my opinion as to what a person having ordinary skill in the art would have understood at the time of application for the patents in suit, which I have been told to assume is approximately August 1994 for the five BRCA1 patents and approximately December 1995 for the two BRCA2 patents.

28. Based on the foregoing and my professional experience in the field, I have formed the following opinions.

29. One of ordinary skill in the art at the time of application for the patents in suit would have a doctoral background, either M.D. or Ph.D, a postdoctoral fellowship of 2-5 years and practical experience in the field of genetic testing and analysis of 2-5 years.

"DNA", "DNA molecule", "nucleotide sequence" (claims 1, 2, 5, 6 and 7 of the '282 patent; claim 1 of the '473 patent; and, claims 1, 6 and 7 of the '492 patent)

30. The ordinary or customary meaning of the term "DNA" to one of ordinary skill in the art at the time of application for the patents in suit would have been a sequence of nucleotides (there are only four possible nucleotides, A, C, T and G). Thus, "DNA" is made up of a "nucleotide sequence" and the process of determining the precise nucleotide sequence of DNA (i.e. the precise arrangement of A's, C's, T's and G's) is called "sequencing." All DNA is a molecule, so the term "DNA molecule" is synonymous with just "DNA." While the term "DNA" generally encompasses both double or single stranded DNA, one would understand it means double stranded in the context of BRCA1 because single strands of DNA that are long enough to encode BRCA1 do not exist under most circumstances.

31. I note that the specification of the patents in suit each discuss DNA and nucleotide sequences (sometimes referred to as "polynucleotide sequences") at length. However, I have found nothing in the specifications of the patents in suit that would contradict the ordinary or customary understanding of the terms.

32. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of these terms or that would alter my understanding of what they would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"isolated DNA" (claims 1, 2, 5, 6 and 7 of the '282 patent; claim 1 of the '473 patent; and, claims 1, 6 and 7 of the '492 patent)

33. The ordinary or customary meaning of the term "isolated DNA" to one of ordinary skill in the art at the time of application for the patents in suit would have been a fragment of DNA that is separated from everything else. There would only be that DNA and no other DNA. While the term "isolated" is synonymous with "purified," such separation would not result in DNA that is 100% pure, as there might very well be some other matter, like salts, still in the environment with the DNA. However, such other materials would be relatively minimal in quantity and the vast majority of material in the environment would be the desired DNA fragment. Thus, one of ordinary skill in the art would call the resulting matter "isolated" or "purified" DNA. At the time of application for the patents in suit, there were several well known methods for "isolating" or "purifying" DNA and, thus, the term would not inherently be limited to any particular method or process of doing so.

34. I note that the specification of the patents in suit each contain significant discussion of the term "isolated." For example, the '282 patent states, "An 'isolated' ... nucleic acid (e.g., an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins," and "[t]he terms 'isolated', 'substantially pure', and 'substantially homogeneous' are used interchangeably to describe a protein or polypeptide which has been separated from components which accompany it in its natural state." '282 patent, col. 19, lns. 8-18 and col. 23, lns. 31-34. Identical language is contained in each of the

patents in suit. This comports with the ordinary or customary meaning of the term and I have found nothing in the specifications of the patents in suit that would contradict that understanding.

35. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"coding for" (claims 1, 2, 5 and 6 of the '282 patent; and, claims 1, 6 and 7 of the '492 patent)

36. The ordinary or customary meaning of the term "coding for" with respect to DNA to one of ordinary skill in the art at the time of application for the patents in suit would have been DNA that translates into amino acids according to the well known genetic code established in the 1960's through the work of many investigators. The term is used to refer to DNA that makes a particular protein. "Coding for" is synonymous with "encodes." It is known that any three particular nucleotides (each of the three can be either A, C, T or G) form a codon and that each nucleotide codon translates into one of twenty standard amino acids. Each amino acid is known as a peptide and, as such, a string of two or more amino acids is known as a polypeptide. A polypeptide is a protein. Thus, with respect to claim 1 of the '282 patent, for example, a "DNA coding for a ... polypeptide" means DNA whose nucleotides create codons that translate into (or make) a certain amino acid sequence or protein. It was well known in the art which codons "code for" which amino acids. As such, one of ordinary skill in the art, given a specific DNA, which is just a sequence of nucleotides that could be divided into tri-nucleotide codons,

could determine the sequence of amino acids, or peptides, that such DNA "codes for" or "encodes." It should be noted, though, that it was known that not all portions of DNA necessarily "code for" a polypeptide. Specifically, there are portions of DNA called introns (otherwise referred to as "non-coding regions") that do not translate into amino acids. Also, the terms "amino acid sequence," "polypeptide" and "protein" are all synonymous.

37. I note that the specification of the patents in this suit each contain significant discussion of this term. For example, the '282 patent states, "A polynucleotide is said to 'encode' a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce ... the polypeptide or a fragment thereof." '282 patent, col. 19, lns. 1-5. Identical language is contained in each of the patents in suit. This definition comports with the ordinary or customary meaning of the term and I have found nothing in the specifications of the patents in suit that would contradict that understanding.

38. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"BRCA1", "BRCA1 gene" (claims 1, 2, 5, 6 and 20 of the '282 patent; claim 1 of the '473 patent; claim 1 of the '999 patent; claim 1 of the 001 patent; and, claim 1 of the '441 patent)

39. The term "gene" simply refers to a particular segment of DNA that encodes a protein, in most cases. BRCA1 was known at the time of the application for

the BRCA1 patents to refer to a particular portion of DNA found on chromosome 17 that related to a person's predisposition to develop breast and ovarian cancer. Thus, this particular portion of DNA on chromosome 17 is referred to as "the BRCA1 gene."

40. I note that the specification of the five BRCA1 patents each contain discussion of this term. For example, the '282 patent states, "a human breast and ovarian cancer predisposing gene (BRCA1)," and "'BRCA1 Gene,' 'BRCA1 Nucleic Acids' or 'BRCA1 Polynucleotide' each refer to polynucleotides, all of which are in the BRCA1 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancers." '282 patent, col 1, lns 21-22 and col 19, lns 25-30. Identical language is contained in each of the five BRCA1 patents. This definition comports with the ordinary or customary meaning of the term and I have found nothing in the specifications of the five BRCA1 patents that would contradict that understanding.

41. I did not find anything in the prosecution/file history of any of the five BRCA1 patents relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"*BRCA2*", "*BRCA2* gene" (claims 1, 6 and 7 of the '492 patent; and, claims 1 and 2 of the '857 patent)

42. The term "gene" simply refers to a particular segment of DNA that encodes a protein, in most cases. BRCA2 was known at the time of the application for the BRCA2 patents to refer to a particular portion of DNA found on chromosome 13 that

related to a person's predisposition to develop breast and ovarian cancer. Thus, this particular portion of DNA on chromosome 13 is referred to as "the BRCA2 gene."

43. I note that the specification of the two BRCA2 patents each contain significant discussion of this term. For example, the '492 patent states, "a human breast cancer predisposing gene (BRCA2)," and "'BRCA2 Locus,' 'BRCA2 Gene,' 'BRCA2 Nucleic Acids' or 'BRCA2 Polynucleotide' each refer to polynucleotides, all of which are in the BRCA2 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian and stomach cancers." '492 patent, abstract and col. 18, lns. 12-17. Identical language is contained in both of the BRCA2 patents. This definition comports with the ordinary or customary meaning of the term and I have found nothing in the specifications of the two BRCA2 patents that would contradict that understanding.

44. I did not find anything in the prosecution/file history of either of the two BRCA2 patents relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"polypeptide", "amino acid sequence" (claims 1, 2, 5 and 6 of the '282 patent; and, claims 1, 6 and 7 of the '492 patent)

45. The ordinary or customary meaning of the term "polypeptide" to one of ordinary skill in the art at the time of application for the patents in suit would have meant a string of two or more amino acids, because a peptide is an amino acid and "poly" means "more than one." The terms "polypeptide" and "amino acid sequence" are synonymous with each other and with the term "protein." Thus, with respect to claim 1 of the '282

patent, for example, a "DNA coding for a ... polypeptide" means DNA with at least 6 nucleotides (each nucleotide being either A, C, T or G), because it takes 6 nucleotides to create 2 codons (a codon is a set of three nucleotides), which would each then translate into one of twenty standard amino acids, resulting in two amino acids. Two or more amino acids form a sequence of amino acids, or an "amino acid sequence," "polypeptide" or "protein."

46. I note that the specification of the patents in suit each contain significant discussion of these terms. For example, the '282 patent states, "The term 'polypeptide' refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product." '282 patent, col. 21, lns 3-5. Identical language is contained in each of the patents in suit. This definition comports with the customary and ordinary meaning of these terms and I have found nothing in the specifications of the patents in suit that would contradict that understanding.

47. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of these terms or that would alter my understanding of what they would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"having the [] sequence" (claims 1, 2, 5, 6 and 7 of the '282 patent)

48. The ordinary or customary meaning of the phrase "having the [] sequence" to one of ordinary skill in the art at the time of application for the patents in suit would have inherently meant "having all of but no more than the [] sequence," because construing that phrase any differently would be either over-inclusive (including additional unidentified sequence) or under-inclusive (excluding portions of the identified

sequence). Thus, with respect to claim 1 of the '282 patent, for example, a "polypeptide having the amino acid sequence X" means a polypeptide that has all of but no more than the amino acid sequence X. If the phrase were to be construed to allow for more than just the identified amino acid sequence, then it could encompass a longer series of additional amino acids, which would obviously defeat the purpose of identifying the specific sequence. Similarly, to construe the phrase to include less than the entire identified sequence would potentially leave out important components of the identified sequence, which could have substantial functional effects, as a partial polynucleotide or polypeptide sequence can indeed function much differently or not function at all as compared with the complete sequence from which it derives.

49. I note that the specification of the patents in suit each contain significant discussion relevant to this phrase. For example, the '282 patent states, "The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA1-encoding gene or one having substantial homology with a natural BRCA1-encoding gene or a portion thereof." '282 patent, col. 19, lns. 43-47. Identical language is contained in each of the patents in suit (except that the BRCA2 patents reference BRCA2, not BRCA1). This statement comports with the ordinary or customary understanding of the phrase and I have found nothing in the specifications of the patents in suit that would contradict that understanding.

50. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this phrase or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"SEQ ID NO:[X]" (claims 1, 2, 5, 6 and 7 of the '282 patent; claim 1 of the '473 patent; claim 1 of the '999 patent; and, claims 1, 6 and 7 of the '492 patent)

51. There is no ordinary or customary meaning for the phrase "SEQ ID NO:[X]." This is a generic phrase used to make reference to a specific sequence provided elsewhere within the document making the reference. Without such identification elsewhere in the patents in suit, one of ordinary skill in the art at the time of the application for the patents in suit would not have known what those sequences contained. Thus, the phrase "SEQ ID NO:2," for example, could mean different things depending upon what the supporting document identifies as the sequence with identification number 2.

52. The specifications of the patents in suit each provide a specific sequence for each SEQ ID NO. referenced in the claims. For example, the '282 patent states, "The coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO:1, with the amino acid sequence shown in SEQ ID NO:2," and then continues to specifically set forth those sequences in a "Sequence Listing" section in the back of its specification. '282 patent, col. 19, lns. 47-49 and cols. 67-90. The identical sequences are identified in each of the BRCA1 patents. Similarly, the '492 specifically sets forth the sequences identified in it as "SEQ ID NO:1" and "SEQ ID NO:2" in a "Sequence Listing" section in the back of its specification. '492 patent, cols. 59-100. The identical sequences are identified in both of the BRCA2 patents. Thus, when the claims make references to a "SEQ ID NO:1" or "SEQ ID NO:2", one of ordinary skill in the art at the time of the application for the patents in suit would have known to refer to those sequences set forth in the specifications and identified as such.

53. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"transformed eukaryotic host cell" (claim 20 of the '282 patent)

54. The ordinary or customary meaning of the term "transformed eukaryotic host cell" to one of ordinary skill in the art at the time of application for the patents in suit would have been a cell with a nuclear membrane (that separates DNA replication in the nucleus from translation of proteins in the cytoplasm) that has had something done to it to make the cell malignant or cancerous. Human cells are a type of "eukaryotic" cell and are more advanced evolutionarily than prokaryotic cells, such as bacteria. A cell can be exposed to carcinogenic chemicals or viruses containing specific cancer-causing genes to accomplish the "transformation" from a normal cell to a cancerous or malignant cell, defined by an increased growth pattern of the transformed cell compared to the normal cell. The purpose of such cells is to be used in testing potential treatments for cancer and they are "grown" in an environment with the other things that are needed to keep the cells alive and proliferating.

55. I note that the specifications of the patents in suit each contain a discussion of this term. For example, the '282 patent says, "A further technique for drug screening involves the use of host eukaryotic cell lines or cells (such as described above) which have a nonfunctional BRCA1 gene. These host cell lines or cells are defective at the BRCA1 polypeptide level. The host cell lines or cells are grown in the presence of drug compound. The rate of growth of the host cells is measured to determine if the

compound is capable of regulating the growth of BRCA1 defective cells." '282 patent, col. 31, lns 46-53. Identical language is contained in each of the patents in suit. This description comports with the ordinary or customary meaning of the term and I have found nothing in the specifications of the patents in suit that would contradict that understanding.

56. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"altered", "alterations" (claim 20 of the '282 patent; claim 1 of the '473 patent; claim 1 of the '999 patent; claim 1 of the '001 patent; claim 1 of the '441 patent; and, claim 2 of the '857 patent)

57. The ordinary or customary meaning of the term "altered" or "alteration" to one of ordinary skill in the art at the time of application for the patents in suit would have been being different from the most common typical version. With respect to DNA, an "altered" version is different than what is known as the "wild-type" version that is found most frequently in nature. While alterations can sometimes be made by man, most often, and specifically in the context of the patents in suit, the terms "altered" and "alterations" inherently mean made by nature. Thus, with respect to claim 20 of the '282 patent, for example, the phrase "altered BRCA1 gene" means a BRCA1 gene that is different from the typical BRCA1 gene found in most humans. Such a difference could be as minor as a difference in a single nucleotide, or could be a difference in a larger number of the nucleotides of the gene sequence.

58. I note that the specifications of the patents in suit each contain a discussion of this term. For example, the '282 patent says, "'Alteration of a wild-type gene' encompasses all forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions." '282 patent, col. 12, lns 31-33. Identical language is contained in each of the patents in suit. This definition comports with the ordinary or customary meaning of the term and I have found nothing in the specifications of the patents in suit that would contradict that understanding.

59. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"comparing" (claim 20 of the '282 patent; claim 1 of the '001 patent; claim 1 of the '441 patent; and, claims 1 and 2 of the '857 patent)

60. The ordinary or customary meaning of the term "comparing" to one of ordinary skill in the art at the time of application for the patents in suit would have been looking at two or more things to determine what differences there are between them. In the context of claim 1 of the '001 patent, claim 1 of the '441 patent, and claims 1 and 2 of the '857 patent, the term is used to mean looking at two or more nucleotide sequences to see if they are different in any way. This act of "looking" could be performed by any method and it inherently presumes that such sequences are already provided.

61. I have found nothing in the specifications of the patents in suit that would contradict the ordinary or customary understanding of the term.

62. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"analyzing" (claim 1 of the '999 patent)

63. The ordinary or customary meaning of the term "analyzing" to one of ordinary skill in the art at the time of application for the patents in suit would have been looking at a thing to determine its characteristics. In the context of claim 1 of the '999 patent, the term is used to mean looking at a nucleotide sequence to see if it contains one of a particular known set of alterations. This act of "looking" could be performed by any method, including manually or with instruments or computer software, and inherently presumes that the sequence is already provided.

64. I have found nothing in the specifications of the patents in suit that would contradict the ordinary or customary understanding of the term.

65. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"wild-type", "mutated" (claim 1 of the '441 patent; claims 6 and 7 of the '492 patent; and, claims 1 and 2 of the '857 patent)

66. The ordinary or customary meaning of the phrase "wild-type" to one of ordinary skill in the art at the time of application for the patents in suit would have meant the most common typical version of, for example, a gene across a population of people

without the targeted condition (i.e. cancer). The opposite of a "wild-type" gene is an "altered" gene. "Mutated" means a "harmful alteration," and does not include non-harmful alterations like polymorphisms. So, a "mutated" gene is one that is altered in a way that has some harmful effect. Thus, with respect to claim 1 of the '441 patent, for example, the phrase "wild-type BRCA1 gene" means the normal BRCA1 gene found in the vast majority of human beings and that does not have an "alteration" or "mutation." And, a "mutated BRCA1 gene" or "mutant BRCA1 gene" means an altered BRCA1 gene that results in an increased predisposition to cancer.

67. I note that the specifications of the patents in suit each contain significant discussion of these terms. For example, the '282 patent states, "It has been discovered that individuals with the wild-type BRCA1 gene do not have cancer which results from the BRCA1 allele. However, mutations which interfere with the function of the BRCA1 protein are involved in the pathogenesis of cancer. Thus, the presence of an altered (or a mutant) BRCA1 gene which produces a protein having a loss of function, or altered function, directly correlates to an increased risk of cancer." '282 patent, col. 16, lns. 57-64. Identical language is contained in each of the patents in suit (except that the BRCA2 patents reference BRCA2, not BRCA1). This definition comports with the customary and ordinary meaning of the terms and I have found nothing in the specification that would contradict that understanding.

68. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of these terms or that would alter my understanding of what they would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"germline", "germline alteration", "germline sequence" (claim 1 of the '999 patent; claim 1 of the '441 patent; and, claim 2 of the '857 patent)

69. The ordinary or customary meaning of the term "germline" to one of ordinary skill in the art at the time of application for the patents in suit would have been in the body from birth, meaning that which is passed down to an individual from his or her biological parents and is present in every normal cell of the body. Therefore, a "germline alteration" is an alteration that is inherited by a person from his or her parents and a "germline sequence" is a sequence that in inherited by a person from his or her parents.

70. I note that the specifications of the patents in suit each contain a discussion of this term. For example, the '999 patent says, "Germline mutations can be found in any of a body's tissues and are inherited." '999 patent, col. 12, lns. 40-42. Identical language is contained in each of the patents in suit. This definition comports with the ordinary or customary meaning of the term and I have found nothing in the specifications of the patents in suit that would contradict that understanding.

71. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"RNA" (claim 1 of the '999 patent; claim 1 of the '001 patent; and, claim 1 of the '441 patent)

72. The ordinary or customary meaning of the term "RNA" to one of ordinary skill in the art at the time of application for the patents in suit would have been a

polyribonucleotide molecule, the sequence of which is determined by the DNA nucleotide sequence from which it is made by a process called transcription. RNA, unlike DNA, is single-stranded. The DNA – RNA relationship is determined by the sequence of nucleotides in the DNA, resulting in a corresponding a specific sequence of ribonucleotides in the transcribed RNA, such that an "A" nucleotide in the DNA determines a "U" ribonucleotide in the RNA, a "C" nucleotide in the DNA determines "G" ribonucleotide in the RNA, a "G" in the DNA determines a "C" in the RNA, and finally a "T" in the DNA determines an "A" in the RNA. When DNA and RNA can be completely paired by A to U, C to G, G to C and T to A, then the RNA is said to by "complementary" to the DNA. The production (or transcription) of RNA from DNA is a completely natural process. The first RNA copy of a DNA gene is called the primary transcript and corresponds to both the protein coding and nono-coding (or intron) sequences of the DNA gene. Once the parts of the RNA corresponding to the introns are removed, the RNA is called messenger RNA, or mRNA for short, and is discussed more below.

73. I note that the specification of the patents in suit each discuss RNA at length. However, I have found nothing in the specifications of the patents in suit that would contradict the ordinary or customary understanding of the term.

74. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"cDNA", "mRNA", "cDNA made from mRNA" (claim 1 of the '999 patent; claim 1 of the '001 patent; claim 1 of the '441 patent; and, claim 2 of the '857 patent)

75. The ordinary or customary meaning of the term "cDNA" to one of ordinary skill in the art at the time of application for the patents in suit would have been complimentary DNA, which is synthesized from mRNA. The ordinary or customary meaning of the term "mRNA" to one of ordinary skill in the art at the time of application for the patents in suit would have been messenger RNA, which is RNA that has had all of the sequences that correspond to the gene's introns, or non-coding regions, removed. So, to explain the relationships between DNA, RNA, mRNA and cDNA in a step by step fashion, double-stranded DNA is transcribed to make single-stranded RNA that is complementary to the DNA; the single-stranded RNA is then reduced to mRNA by removing all of the non-coding regions or introns; and then the mRNA is reverse-transcribed into complementary DNA or cDNA. Thus, the coding effect of a cDNA is the same as that of the original DNA from which it was originally derived despite having a shorter sequence (the cDNA will not include the non-coding regions that were part of the DNA). Thus, the phrase "cDNA made from mRNA" means a purely coding polynucleotide sequence that is produced from RNA that has had all of the non-coding regions (called introns) of the gene removed.

76. I note that the specification of the patents in suit each discuss cDNA and mRNA at length. However, I have found nothing in the specifications of the patents in suit that would contradict the ordinary or customary understanding of the term.

77. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of

what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"somatic", "somatic alteration" (claim 1 of the '001 patent)

78. The ordinary or customary meaning of the term "somatic" to one of ordinary skill in the art at the time of application for the patents in suit would have been created within a part of the body, and not inherited from parents. "Somatic" is the opposite of germline. Thus, a "somatic alteration" is one that was developed within a part of a person's body, and not inherited by them from one of their parents. Somatic alterations occur as a result of natural environmental processes. For example, somatic alterations of genes can result from exposure of human cells to viruses or other harmful environmental conditions.

79. I note that the specifications of the patents in suit each contain a discussion of this term. For example, the '001 patent says, "Somatic mutations are those which occur only in certain tissues, e.g., in the tumor tissue, and are not inherited in the germline." '001 patent, col. 12, lns. 40-42. Identical language is contained in each of the patents in suit. This definition comports with the ordinary or customary meaning of the term and I have found nothing in the specifications of the patents in suit that would contradict that understanding.

80. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

"allele", "mutant allele" (claim 1 of the '857 patent)

81. The ordinary or customary meaning of the term "allele" to one of ordinary skill in the art at the time of application for the patents in suit would have been one form of a gene at a specific location on a chromosome, with the understanding that any one gene can be slightly different from one person to another, and each different form of a gene is called an allele of that gene. Every human cell has two copies of each gene, except for the genes on X and Y chromosomes in males, because every cell has two copies of each type of chromosome. Thus, each cell of the body could have a mutated allele and a wild-type allele at the gene location on each of the two chromosomes of the same type.

82. I note that the specification of the patents in suit each use the term "allele" at length. However, I have found nothing in the specifications of the patents in suit that would contradict the ordinary or customary understanding of the term.

83. I did not find anything in the prosecution/file history of any of the patents in suit relevant to the construction of this term or that would alter my understanding of what it would have meant to a person of ordinary skill in the art at the time of application for the patents in suit.

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.

MD, PhD

Debra G.B. Leonard, M.D., Ph.D

Executed on August 24, 2009