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,

-against-

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.

No. 09 Civ. 4515 (RWS)

ECF Case

DECLARATION OF DR. MARK A. KAY

I, Mark Allan Kay, hereby declare that:

I. BACKGROUND AND EXPERIENCE

1. I am currently a tenured professor and Director of the Program in Human Gene Therapy at Stanford University School of Medicine. I am the Dennis Farrey Family Professor in the Departments of Pediatrics and Genetics at Stanford University. I am also the Associate Chair for Basic Research in the Department of Pediatrics at Stanford University

School of Medicine. My qualifications, expertise, and list of publications are set forth in my *curriculum vitae* which is attached as Exhibit 1.

2. I received my Ph.D. in Developmental Genetics and my M.D. from Case Western Reserve University in 1986 and 1987, respectively. I completed my internship and residency in the Department of Pediatrics at the Baylor College of Medicine, Houston, Texas in 1990. Between 1990 and 1993, I was a medical genetics fellow at Baylor College of Medicine where I completed clinical training to be Board eligible in both Clinical Medical Genetics and Biochemical Genetics. During those three years, I also completed my post-doctoral research on gene therapy for hepatic deficiencies at Baylor College of Medicine, Houston, Texas.

3. I was triple-boarded: Pediatrics from 1990 until 1997; Clinical Genetics, and Clinical Biochemical Genetics from 1993 until 2003. In my medical practice, I have seen many patients for diagnosis, recurrence risk, and/or treatment of genetic disorders between 1990 and 1998. Currently, I am involved in Phase I / II clinical trials in gene therapy.

4. My research focuses primarily on developing gene transfer technologies for gene therapy of genetic and acquired diseases of the liver. The second major focus of my research includes the role of small RNAs in mammalian gene regulation.

5. I keep abreast of ongoing research developments in the area of molecular biology and gene therapy by regular perusal of the relevant literature and my service on the editorial boards of several different scientific journals. In particular, I am or have been on the editorial boards of numerous scientific journals, including *Gene Therapy*, *Human Gene Therapy*, and *Molecular Therapy*. I am currently the Associate Editor of *Human Gene Therapy*, *Molecular Therapy*, and *Silence*.

6. In preparing this declaration, I have reviewed the following: (1) Declaration of Sir John E. Sulston, Ph.D. of August 17, 2009 ("Sulston"); (2) Declaration of Christopher E. Mason of August 20, 2009 ("Mason"); (3) Declaration of Wayne W. Grody, M.D., Ph.D. of August 24, 2009 ("Grody"); (4) Declaration of Debra G.B. Leonard, M.D., Ph.D. of August 24, 2009 ("Leonard"); Declaration of Wendy Chung, M.D., Ph.D. of July 30, 2009 ("Chung"); Declaration of Myles W. Jackson of August 18, 2009 ("Jackson"); Declaration of David H. Ledbetter, Ph.D. of August 20, 2009 ("Ledbetter"); and Declaration of Haig H. Kazazian, Jr., M.D. of August 17, 2009 ("Kazazian"). Specifically, I have been asked to comment on the scientific statements contained in these declarations.

7. I have also read the claims, specification, and portions of the prosecution file histories of United States Patent Numbers 5,753,441 (the "'441 patent"); 5,747,282 (the "'282 patent"); 5,710,001 (the "'001 patent"); 5,709,999 (the "'999 patent"); and 5,693,473 (the "'473 patent"), which relate to *BRCA1*, hereinafter referred to as the "*BRCA1* patents," and the claims, specification, and portions of the prosecution file histories of United States Patent Numbers 6,033,857 (the "'857 patent") and 5,837,492 (the "'492 patent"), which relate to the *BRCA2*, hereinafter referred to as the "*BRCA2* patents."

8. I have also reviewed portions of the following textbooks: Bruce Alberts *et al.*, Molecular Biology of the Cell, Third Edition, Garland Publishing, Inc., New York, NY, 1994 ("Alberts") and Lubert Stryer, Biochemistry, Third Edition, W.H. Freeman And Company, New York, NY, 1988 ("Stryer").

9. I have also read the article by Dr. John E. Sulston entitled "Heritage of humanity" published in *Le Monde diplomatique*, English Edition, in 2002 ("Sulston, 2002;" Exhibit 2).

10. I have been asked to provide my opinion from the perspective of one of ordinary skill in the art as of 1994 with respect to the *BRCA1* patents and as of 1995 with respect to the *BRCA2* patents. One of ordinary skill in the art at that time would have been someone with a Ph.D. and several years of postdoctoral experience in the areas of genetics, molecular biology, and/or biochemistry.

II. DEFINITIONS

11. I have been asked to provide my opinion regarding the meaning of certain terms that appear in the claims of the *BRCA1* and the *BRCA2* patents. Such terms are found in, for example, claims 1, 2, 5, 6, 7, and 20 of the '282 patent; claims 1, 6, and 7 of the '492 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 claims 1 and 2 of the '857 patent. I have been advised and understand that certain claims, known as "dependent" claims, can refer to earlier claims, known as "independent" claims, and that the dependent claims are to be interpreted to incorporate all the limitations of the claim to which it refers.

12. I have been advised and understand that claim terms are generally given their ordinary and customary meaning, *i.e.*, the meaning that the terms would have to a person of ordinary skill in the art at the time of filing of the patent application. I also understand that claim terms must be read in the context of the claims, the specification, and the prosecution history, and, when the specification specifically defines a claim term, that definition controls.

13. I have reviewed the '473 Patent, the '282 Patent, and the '492 Patent, each of which has claims reciting the terms **"DNA"** or **"DNA molecule**." Specifically, these terms are recited in claim 1 of the '473 Patent, claims 1, 2, 5, 6, and 7 of the '282 Patent, and claims 1, 6, and 7 of the '492 Patent**.**

14. One of skill in the art as of the time of the filing dates of these patents would understand the term "**DNA**," which stands for **d**eoxyribo**n**ucleic **a**cid, to mean a type of chemical compound called a nucleic acid. At its most basic level, a DNA molecule is composed of several chemical elements, namely Carbon, Hydrogen, Oxygen, Nitrogen, and Phosphorus. These chemical elements make up repeating units that are connected to form a strand or polymer of the DNA molecule. These repeating units of DNA are known as nucleotides. The standard nucleotides in vertebrate DNA contain four different bases: Adenine, Thymine, Cytosine, and Guanine. These bases are linked together by chemical bonds via a sugar-phosphate backbone. As shorthand for convenience, scientists often denote nucleotides by the first letter of the names of their bases: "A" for Adenine; "G" for Guanine; "T" for Thymine; and "C" for Cytosine. DNA can exist as single strand or as double strand molecule. *See*, *e.g.*, Stryer at pages 71-73.

15. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, or the '492 Patent that would contradict or alter this definition. The use of "DNA" and "DNA molecule" in the patents is consistent with the ordinary and customary use of the terms in the field of biotechnology.

16. I have reviewed the '473 Patent, the '282 Patent, and the '492 Patent, each of which has claims reciting the term **"isolated DNA."** Specifically, these terms are recited in

claim 1 of the ‘473 Patent; claims 1, 2, 5, 6, and 7 of the ‘282 Patent; and claims 1, 6, and 7 of the ‘492 Patent.

17. The term “isolated DNA” is defined in the patents as:

> An “isolated” or “substantially pure” 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. The term embraces a nucleic acid sequence or protein 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. ‘473 Patent, col. 19:6-15; ‘282 Patent, col. 19:8-18; and ‘492 Patent, col. 17:62 – col. 18:5.

In other words, someone of ordinary skill in the art would understand that “isolated DNA” has been extracted from the cell and excised from the chromosome, or chemically synthesized. Indeed, an isolated DNA molecule is made by the hand of the scientist, not by nature.

18. I have found nothing in the specification or prosecution history of the ’473 Patent, the ’282 Patent, or the ’492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

19. I have reviewed the ’282 Patent and the ’492 Patent, each of which has claims reciting the terms **“code for,” “coding for,” and “encoding.”** Specifically, these terms are recited in claim 1 of the ’282 Patent and claims 1, 6, and 7 of the ’492 Patent.

20. One of skill in the art at the time of the filing dates of these patents would understand that the term “encode” can be used interchangeably with the terms “code for” and “coding for.” The term “encode” is defined in the patents as:

> 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 mRNA for and/or the polypeptide or a fragment thereof. '282 Patent, col. 19:1-5; and '492 Patent, col. 17:55-59.

21. I have found nothing in the specification or prosecution history of the '282 Patent or the '492 Patent that would contradict or alter this definition. The terms are used according to their specified definition consistently throughout the patents.

22. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent, each of which has claims reciting one or more of the term "**BRCA1.**" Specifically, this term is recited in claim 1 of the '473 Patent; claims 1 and 20 of the '282 Patent**;** claim 1 of the '999 Patent; claim 1 of the '001 Patent, and claim 1 of the '441 Patent.

23. The term "**BRCA1**" means a human breast and ovarian cancer predisposing gene, some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. (*See*, *e.g.*, '282 Patent, col. 1: 20-24; 4:32-36).

24. Dr. Grody and Dr. Leonard state that "**BRCA1**" was known to refer to "a particular portion of DNA found on chromosome 17 that relate[s] to a person's predisposition to develop breast and ovarian cancer." Grody ¶19. Leonard ¶39. I would like to clarify, the *BRCA1* gene is an aggregate of several segments of a chromosome. Some segments regulate the activity of the *BRCA1* gene. From other segments, *BRCA1* pre-mRNA and then mRNA is produced. From the mRNA, BRCA1 protein is typically produced.

25. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent, each of which has claims reciting one or more of the terms **"BRCA1**

Locus," BRCA1 Gene," "BRCA1 Nucleic Acids," and **"BRCA1 Polynucleotide."**

Specifically, these terms are recited in claim 1 of the '473 Patent; claim 20 of the '282 Patent**;** claim 1 of the '999 Patent; claim 1 of the '001 Patent, and claim 1 of the '441 Patent.

26. The meaning of "BRCA1" is further clarified in the Myriad patents:

> As used herein, the terms "BRCA1 locus," "BRCA1 allele" and "BRCA1 region" all refer to the double-stranded DNA comprising the locus, allele, or region, as well as either of the single-stranded DNAs comprising the locus, allele or region. '473 Patent, col. 20:53-57; '282 Patent, col. 20:58-62; '999 Patent, col. 20:61-65; '001 Patent, col. 20:61-65; and '441 Patent col. 20:61-65.

"BRCA1 Locus," BRCA1 Gene," "BRCA1 Nucleic Acids," and "BRCA1 Polynucleotide" are defined in these patents as:

> [P]olynucleotides, 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. Mutations at the BRCA1 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA1 region described *infra*. The BRCA1 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA1 locus is intended to include all allelic variations of the DNA sequence. These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA1 polypeptide, fragment, homolog or variant, including, *e.g.*, protein fusions or deletions. 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. 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. '473 Patent, col. 19:22-45; '282 Patent, col. 19:25-50; '999 Patent, col. 19:27-52; '001 Patent, col. 19:30-44; and the '441 Patent, col. 19:30-54.

27. One of skill in the art would understand that BRCA1/2 are genes, not fragments of DNA. Genes are integrated into the chromosome and not broken or detached from the chromosome, as denoted by the term "fragment."

28. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, or the '441 Patent that would contradict or alter this definition. The terms are used according to their specified definition consistently throughout the patents.

29. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent, each of which has claims reciting one or more of the term "**BRCA2.**" Specifically, this term is recited in claims 1 and 2 of the '857 Patent; and claims 1 and 6 of the '492 patent.

30. The term "**BRCA2**" means a human breast cancer predisposing gene, some alleles of which cause susceptibility to cancer, in particular breast cancer. (*See*, *e.g.*, '492 patent, col. 4: 26-30).

31. Dr. Grody and Dr. Leonard state that "**BRCA2**" was known to refer to "a particular portion of DNA found on chromosome 13 that relate[s] to a person's predisposition to develop breast cancer." Grody Decl. ¶22. Leonard Decl. ¶42. I would like to clarify, the *BRCA2* gene is an aggregate of several segments of a chromosome. Some segments regulate the activity of the *BRCA2* gene. From other segments, *BRCA2* pre-mRNA and then mRNA is produced. From the mRNA, BRCA2 protein is typically produced.

32. I have reviewed the '492 Patent and the '857 Patent, each of which has claims reciting one or more of the terms **"BRCA2 Locus," BRCA2 Gene," "BRCA2 Nucleic Acids,"** and **"BRCA2 Polynucleotide"** Specifically, these terms are recited in claims 1, 6, and 7 of the '492 Patent; and claims 1 and 2 of the '857 Patent.

33. The meaning of "BRCA2" is further clarified in the Myriad patents:

> As used herein, the terms "BRCA2 locus," "BRCA2 allele," and "BRCA2 region" all refer to the double-stranded DNA comprising the locus, allele, or region, as well as either of the single-stranded DNAs comprising the locus, allele or region. '857 Patent, col. 19:45-49; and '492 Patent, col. 19: 43-47.

The terms "BRCA2 Locus," BRCA2 Gene," "BRCA2 Nucleic Acids," and "BRCA1 Polynucleotide" are defined in the patents as:

> [P]olynucleotides, 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. Mutations at the BRCA2 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA2 region described *infra*. The BRCA2 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA2 locus is intended to include all allelic variations of the DNA sequence. These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA2 polypeptide, fragment, homolog or variant, including, *e.g.*, protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA2-encoding gene or one having substantial homology with a natural BRCA2-encoding gene or a portion thereof. The coding sequence for a BRCA2 polypeptide is shown in SEQ ID NO:1 and FIG. 3, with the amino acid sequence shown in SEQ ID NO:2. '857 Patent, col. 18:14-37; and '492 Patent, col. 18:12-35.

34. I have found nothing in the specification or prosecution history of the '492 Patent or the '857 Patent that would contradict or alter this definition. The terms are used according to their specified definition consistently throughout the patents.

35. I have reviewed the '282 Patent and the '492 Patent, each of which has one or more claims reciting the "**polypeptide**." Specifically, this term is recited in claims 1, 2, 5, and 6 of the '282 Patent; and claims 1, 6, and 7 of the '492 Patent.

36. The term "polypeptide" is defined in these patents as

> [A] polymer of amino acids and its equivalent and does not refer to a specific length of the product; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. This term also does not refer to, or exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations, and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. '282 Patent, col. 21:3-14; and '492 Patent, col. 19:55-66.

37. I have found nothing in the specification or prosecution history of the '282 Patent or the '492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

38. I have reviewed the '282 Patent which has one or more claims reciting the **"BRCA1 polypeptide."** Specifically, this term is recited in claims 1, 2, 5, and 6 of the '282 Patent.

39. The term "BRCA1 polypeptide" is defined in the patents as

> [A] protein or polypeptide encoded by the BRCA1 locus, variants or fragments thereof. … Ordinarily, such polypeptides will be at least about

> 50% homologous to the native BRCA1 sequence, preferably in excess of about 90%, and more preferably at least about 95% homologous. Also included are proteins encoded by DNA which hybridize under high or low stringency conditions, to BRCAl-encoding nucleic acids and closely related polypeptides or proteins retrieved by antisera to the BRCAI protein(s). The length of polypeptide sequences compared for homology will generally be at least about 16 amino acids, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. '282 Patent, col. 21:1-27.
>
> The sequence of the BRCA1 protein is disclosed (SEQ ID NO:2). *Id.* at col. 34: 41-43.

40. I have found nothing in the specification or prosecution history of the '282 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

41. I have reviewed the '492 Patent which has one or more claims reciting the **"BRCA2 polypeptide."** Specifically, this term is recited in claims 1, 6, and 7 of the '492 Patent.

42. The term "BRCA2 polypeptide" is defined in the patents as

> "BRCA2 protein" or "BRCA2 polypeptide" refer to a protein or polypeptide encoded by the BRCA2 locus, variants or fragments thereof. The term "polypeptide" refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. This term also does not refer to, or exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations, and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. Ordinarily, such polypeptides will be at least about 50% homologous to the native BRCA2sequence, preferably in excess of about 90%, and more preferably at least about 95% homologous. Also included are proteins encoded by DNA which hybridize under high or low stringency conditions, to BRCA2-encoding nucleic

> acids and closely related polypeptides or proteins retrieved by antisera to the BRCA2 protein(s). '492 col. 19:53-20:7.
>
> The sequence of the BRCA2 protein is disclosed (SEQ ID NO:2). *See id.* at col. 18:33-35.

43. I have found nothing in the specification or prosecution history of the '492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

44. I have reviewed the '282 Patent and the '492 Patent, each of which has claims reciting the term **"amino acid sequence."** Specifically, this term is recited in claims 1, 2, 5, and 6 of the '282 Patent, and claim 1 of the '492 Patent.

45. One of skill in the art as of the time of the filing dates of these patents would understand the term "amino acid sequence" as a description of the linear order of the amino acid subunits in a polypeptide or protein. *See* Stryer, at 16-17. The amino acid sequence of a protein is also called the primary structure of that protein. *See id.* at 31.

46. In the context of the patents, "amino acid sequence" was used to describe polypeptides or proteins, or their encoding polynucleotides via the arrangement of the amino acids. The specific amino acid sequences for particular polypeptides or proteins are generally identified as "SEQ ID NO:X." For example, as described in the patents:

> The coding sequence for a BRCA[1/2] polypeptide is shown in SEQ ID NO:l. with the amino acid sequence shown in SEQ ID NO:2. '282 Patent, col. 19:48-50; '492 Patent, col. 18:33-35.

47. I have found nothing in the specification or prosecution history of the '282 Patent or the '492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

48. I have reviewed the '473 Patent, '282 Patent, '999 Patent, and the '492 Patent, each of which has claims reciting the term **"SEQ ID NO:1."** Specifically, this is recited in claim 1 of the '473 Patent, claims 2, 6, and 7 of the '282 Patent, claim 1 of the '999 Patent, and claim 7 of the '492 Patent.

49. In the context of the BRCA1 patents, the term "SEQ ID NO:1" refers to the nucleotide sequence of the BRCA1 cDNA as depicted in the Sequence Listing of the '473 Patent, the '282 Patent, and the '999 Patent. As described in Example 8 of the '473 Patent, the '282 Patent, and the '999 Patent:

> Combination of sequences obtained from cDNA clones, hybrid selection sequences, and amplified PCR products allowed construction of a composite full length BRCA1 cDNA (SEQ ID NO: 1). The sequence of the BRCA1 cDNA (up through the stop codon) has also been deposited with GenBank and assigned accession number U-14680. This deposited sequence is incorporated herein by reference. '473 Patent, col. 52:50-56; '282 Patent, col. 53:4-9; and '999 Patent, col. 53:16-22.

50. In the context of the BRCA2 patents, the term "SEQ ID NO:1" refers to the nucleotide sequence of the BRCA1 cDNA as depicted in the Sequence Listing of the '492 Patent. As described in Example 4 of the '492 Patent:

> The full-length sequence of the BRCA2 was assembled by combination of several smaller sequences obtained from hybrid selection, exon trapping, cDNA library screening, genomic sequencing, and PCR experiments using cDNA as template for amplification (*i.e.*, island hopping"). … This cDNA sequence is set forth in SEQ ID NO:1 and FIG.3. '492 Patent, col. 44:53-col. 45:10.

51. I have found nothing in the specification or prosecution history of the ‘473 Patent, the ‘282 Patent, the ‘999 Patent, and the ‘492 Patent that would contradict or alter this definition. The term is used according to their specified definition consistently throughout the patents.

52. I have reviewed the ‘282 Patent and the ‘492 Patent, each of which has claims reciting the term **“SEQ ID NO:2.”** Specifically, this is recited in claims 1, 2, 5, 6 of the ‘282 Patent and claims 1, 6, and 7 of the ‘492 Patent.

53. In the context of the BRCA1 patents, “SEQ ID NO:2” refers to the amino acid sequence of the BRCA1 polypeptide as depicted in the Sequence Listing of the ‘282 Patent. In the ‘282 Patent, the BRCA1 polypeptide is defined as having “[t]he coding sequence … shown in SEQ ID NO:l with the amino acid sequence shown in SEQ ID NO:2.” ‘282 patent, col. 19:48-50.

54. In the context of the BRCA2 patents, “SEQ ID NO:2” refers to the amino acid sequence of the BRCA2 polypeptide as depicted in the Sequence Listing of the ‘492 Patent. In the ‘492 patent, the BRCA2 polypeptide is defined as having “[t]he coding sequence … shown in SEQ ID NO:l and FIG. 3, with the amino acid sequence shown in SEQ ID NO:2.” ‘492 patent, col. 18:33-35.

55. I have found nothing in the specification or prosecution history of the ‘282 Patent and the ‘492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

56. I have reviewed the '282 Patent which has a claim reciting the term **"transformed eukaryotic host cell."** Specifically, this is recited in claim 20 of the '282 Patent.

57. The '282 patent defines "transformation" as "[t]he introduction of the polynucleotides into the host cell by any method known in the art." '282 Patent, col. 27:28-30. In addition, the '282 patent refers to "host cells which are stably transformed with recombinant polynucleotides." '282 patent, col. 30:67 to col. 31:1. Thus, in the context of claim 20 of the '282 Patent, the term "transformed eukaryotic host cell" refers to a eukaryotic cell where polynucleotides have been introduced into the host cell by any method known in the art.

58. I have found nothing in the specification or prosecution history of the '282 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

59. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent each of which has a claim reciting the term **"altered"** and **"alteration."** Specifically, this is recited in claim 1 of the '473 Patent, claim 20 of the '282 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.

60. The terms "altered" and "alterations" are defined in these patents as

> [A]ll forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions. Deletions may be of the entire gene or of only a portion of the gene. Point mutations may result in stop codons, frameshift mutations or amino acid substitutions. Somatic mutations are those which occur only in certain tissues, *e.g.*, in the tumor tissue, and are not inherited in the germline. Germline mutations can be found in any of a body's tissues and are inherited. If only a single allele is somatically mutated, an early neoplastic state is indicated. However, if

> both alleles are somatically mutated, then a late neoplastic state is indicated. The finding of BRCA1 mutations thus provides both diagnostic and prognostic information. A BRCA1 allele which is not deleted (*e.g.*, found on the sister chromosome to a chromosome carrying a BRCA1 deletion) can be screened for other mutations, such as insertions, small deletions, and point mutations. It is believed that many mutations found in tumor tissues will be those leading to decreased expression of the BRCA1 gene product. However, mutations leading to non-functional gene products would also lead to a cancerous state. Point mutational events may occur in regulatory regions, such as in the promoter of the gene, leading to loss or diminution of expression of the mRNA. Point mutations may also abolish proper RNA processing, leading to loss of expression of the BRCA1 gene product, or to a decrease in mRNA stability or translation efficiency. '473 Patent, col. 12:32-58; '282 Patent, col. 12:31-57; '999 Patent, col. 12:33-59; '001 Patent, col. 12:35-61; and '441 Patent, col. 12:39-65.

61. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent that would contradict or alter this definition. These terms are used according to their specified definition consistently throughout the patents.

62. I have reviewed the '282 Patent, the '001 Patent, the '441 Patent, and the '857 Patent each of which has a claim reciting the term **"comparing."** Specifically, this is recited in 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.

63. In the context of the method of claim 20 of the '282 Patent, the term "comparing the growth rate of said host cells" and wherein one host cell is a "transformed eukaryotic host cell" necessarily involves first transforming the cells, *i.e.*, introducing a polynucleotide into the cell.

64. In the context of the method of claim 1 of the '001 Patent, the term "comparing a first sequence selected form the group consisting of a BRCA1 gene from said

tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample" necessarily involves first isolating nucleic acids from the tumor sample and nontumor sample from the same human subject and determining the sequence of the BRCA1 gene or portions thereof from both samples. *See* '001 Patent, col. 13:49-59. Once the sequences have been determined, they are examined to identify any somatic changes in the gene.

65. In the context of the method of claim 1 of the '441 Patent, the term "comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA" necessarily involves first isolating nucleic acids from the tissue sample of said subject and from a wild-type sample from a different human subject and determining the sequence of the BRCA1 gene or portions thereof from both samples. *See* '441 Patent, col. 13:53-63. Once the sequences have been determined, they are examined to identify any germline alterations in the gene of said subject.

66. In the context of the method of claim 1 of the '857 Patent, the term "comparing the nucleotide sequence of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence" necessarily involves first isolating the suspected BRCA2 allele from the chromosome and a wild-type allele sample, then determining the sequence of the BRCA2 gene or portions thereof from both samples. *See* '857 Patent, col. 26:66 – col. 27:20.

Once the sequences have been determined, they are examined to identify any alterations in the suspected BRCA2 allele.

67. In the context of the method of claim 2 of the '857 Patent, the term "comparing the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA" necessarily involves first isolating nucleic acids from the tissue sample of said subject and from a wild-type sample from a different human subject and determining the sequence of the BRCA2 gene or portions thereof from both samples. *See* '857 Patent, col. 12:34-44. Once the sequences have been determined, they are examined to identify any germline alterations in the gene of said subject.

68. I have found nothing in the specification or prosecution history of the '001 Patent, the '441 Patent, and the '857 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

69. I have reviewed the '999 Patent which has a claim reciting the term **"analyzing."** Specifically, this is recited in claim 1 of the '999 Patent.

70. In the context of the method of claim 1 of the '999 Patent, the term "analyzing a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or analyzing a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1" necessarily involves first isolating nucleic acids from a human and determining the sequence of the BRCA1 gene or portions thereof. *See* '999 Patent, col. 64:35-46. Once the sequence has been determined, it is examined to identify where any one of the alterations set

forth in Tables 12A, 14, 18 or 19 is present. Accordingly, analyzing *BRCA1* requires a probe or primer specific to the *BRCA1* gene, RNA, or cDNA to obtain the sequence from the human tissue sample. One of skill in the art would further understand that the step requires using an isolated DNA molecule specific to *BRCA1*, such as a sequencing probe or primer specific to the *BRCA1* gene, *BRCA1* mRNA or *BRCA1* cDNA, to analyze the sequence from the human sample. Without this isolated DNA molecule, the sequence cannot be analyzed. The DNA or RNA of the tissue sample is changed when the isolated *BRCA1* DNA molecule is used to bind to and "hybridize" the DNA or RNA in the human sample. A new "hybrid" DNA/DNA or DNA/RNA compound is formed, allowing its sequence to be analyzed. As a result, the original human sample is no longer the same human sample, and the DNA and mRNA obtained from the human sample are no longer the same DNA and mRNA molecules that were present in the original human sample.

71. I have found nothing in the specification or prosecution history of the '999 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

72. I have reviewed '441 Patent and the '857 Patent which has a claim reciting the term **"wild type."** Specifically, this term is recited in claim 1 of the '441 Patent and claims 1 and 2 of the '857 Patent.

73. The terms "wild type" in the context of a *BRCA1* or *BRCA2* sequence refers to the *BRCA1* or *BRCA2* of the non-mutant *BRCA1*- or *BRCA2*-encoding gene. 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. *See* '441 Patent, col. 19:48-54; and '857 Patent, col. 18:31-37.

74. I have found nothing in the specification or prosecution history of the '441 Patent and the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

75. I have reviewed the '492 Patent and the '857 Patent each of which has a claim reciting the terms **"mutated," "mutant,"** and **"mutation."** Specifically, this is recited in claims 6 and 7 of the '492 Patent and claim 1 of the '857 Patent.

76. The terms "mutated," "mutant," and "mutation" in the context of these patents refer to a change in the sequence of nucleotides found in the DNA molecule relative to the "wild type" sequence. Contrary to Dr. Leonard's statement (Leonard, ¶66), not all mutations result in disease as the term is used in the '492 patent:

> Silent mutations or those resulting in conservative amino acid substitutions would not generally be expected to disrupt protein function. '492 Patent, col. 11:8-10; and '857 Patent, col. 11:11-14.

> "Alteration of wild type gene" encompasses all forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions. Deletions may be of the entire gene or of only a portion of the gene. Point mutations may result in stop codons, frameshift mutations or amino acid substitutions. Somatic mutations are those which occur only in certain tissues, *e.g.*, in the tumor tissue, and are not inherited in the germline. Germline mutations can be found in any of a body's tissues and are inherited. If only a single allele is somatically mutated, an early neoplastic state is indicated. However, if both alleles are somatically mutated, then a late neoplastic state is indicated. The finding of BRCA2 mutations thus provides both diagnostic and prognostic information. A BRCA2 allele which is not deleted (*e.g.*, found on the sister chromosome to a chromosome carrying a BRCA2 deletion) can be screened for other mutations, such as insertions, small deletions, and point mutations. It is believed that many mutations found in tumor tissues will be those leading to decreased expression of the BRCA2 gene product. However, mutations leading to non-functional gene products would also lead to a cancerous state. Point mutational events may occur in regulatory regions, such as in the promoter of the gene, leading to loss or diminution of expression of the mRNA. Point mutations may also abolish proper RNA processing,

> leading to loss of expression of the BRCA2 gene product, or to a decrease in mRNA stability or translation efficiency. '492 Patent, col. 11:16-42; and '857 Patent, col. 11:20-46.

77. I have found nothing in the specification or prosecution history of the '492 Patent and the '857 Patent that would contradict or alter this definition. These terms are used according to their specified definition consistently throughout the patents.

78. I have reviewed the '441 Patent, the '999 Patent, and the '857 Patent each of which has a claim reciting the term **"germline."** Specifically, this is recited in claim 1 of the '441 Patent, claim 1 of the '999 Patent, and claim 2 of the '857 Patent.

79. One of skill in the art as of the time of the filing dates of these patents would understand the term "germline" refers to the lineages of cells that give rise to germ cells, *i.e.*, eggs and sperm cells. *See* Alberts, at G-10. Thus, a mutation in the DNA of a germline cell may be transmitted in the next generation.

80. In the context of the patents, "germline" is used to describe mutations that can be found in any of the body's tissues, *i.e.*, not just the tissue from the tumor, and are inherited. *See* '441 Patent, col. 12:46-47; '999 Patent, col. 12:40-41; and '857 Patent, col. 11:27-28.

81. I have found nothing in the specification or prosecution history of the '441 Patent, the '999 Patent, and the '857 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

82. I have reviewed the '441 Patent and the '857 Patent each of which has a claim reciting the term **"germline sequence."** Specifically, this is recited in claim 1 of the '441 Patent and claim 2 of the '857 Patent.

83. One of skill in the art as of the time of the filing dates of these patents would understand the term "germline sequence" refers to a sequence that is inherited. An alteration in a germline sequence can occur in the germ cells anytime in life.

84. According to the '441 patent:

> Germline mutations can be found in any of a body's tissues and are inherited. *See* '441 Patent, col. 12:46-47; and '857 Patent, col. 11:27-28.

85. I have found nothing in the specification or prosecution history of the '441 Patent and the '857 that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

86. I have reviewed the '001 Patent which has a claim reciting the term **"somatic."** Specifically, this is recited in claim 1 of the '001 Patent.

87. One of skill in the art as of the time of the filing dates of these patents would understand the term "somatic" refers to non-germline cells of the body. *See* Alberts, at 1012.

88. In the context of the patents, "somatic" is used to describe mutations that "occur only in certain tissues, *e.g.*, in tumor tissue, and are not inherited in the germline." '001 Patent, col. 12:40-42.

89. I have found nothing in the specification or prosecution history of the '001 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

90. I have reviewed the '999 Patent, the '001 Patent, and the '441 Patent each of which have a claim reciting the term **"RNA."** Specifically, this is recited in claim 1 of the '999 Patent, claim 1 of the '001 Patent, and claim 1 of the '441 Patent.

91. One of skill in the art as of the time of the filing dates of these patents would understand the term "RNA" stands for ribonucleic acid. RNA, like DNA, is a chemical compound called a nucleic acid and is formed by a strand of bases that are linked together via a sugar-phosphate backbone. Unlike DNA, however, the four different bases in RNA uracil, adenine, cytosine, and guanine. Common abbreviations for these chemical compounds are "U" for uracil, "A" for adenine, "C" for cytosine, "G" for guanine. Each base together with one sugar and one phosphate molecule makes up a nucleotide. The structures of the sugar-phosphate backbone of RNA and DNA are also different from each other—while RNA contains a ribose sugar, the sugar component of DNA is a deoxyribose. The different chemical components of RNA and DNA affect their functions and properties. For example, unlike DNA, which forms a double helix, RNA usually exists as a single strand. *See* Alberts, at 4-7, 46-47, 60.

92. In the context of the patents, "RNA" is a subgroup of "the polynucleotide compositions of this invention" (*see* '999 Patent, col. 19:53-54; '001 Patent, col. 19:55-56; and '441 Patent, col. 19:55-56).

93. I have found nothing in the specification or prosecution history of the '999 Patent, the '001 Patent, and the '441 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

94. I have reviewed the '999 Patent, the '001 Patent, and the '441 Patent each of which has a claim reciting the term **"cDNA."** Specifically, this is recited in claim 1 of the '999 Patent, claim 1 of the '001 Patent, and claim 1 of the '441 Patent.

95. One of skill in the art as of the time of the filing dates of these patents would understand the term "cDNA" to mean a DNA molecule that is commonly synthesized from a mature mRNA in a reaction catalyzed by a protein known as reverse transcriptase. cDNA received its name because each base in the cDNA can bind to a base in the mRNA from which the DNA is synthesized. In other words, it is "complementary" to the mRNA from which it is synthesized.

96. I have reviewed the '001 Patent, and the '852 Patent each of which has a claim reciting the term **"mRNA."** Specifically, this is recited in claim 1 of the '001 Patent, in claim 1 of the '999 Patent, in claim 1 of the '441 Patent, and claim 2 of the '857 Patent.

97. One of skill in the art as of the time of the filing dates of these patents would understand the term "mRNA" to mean messenger RNA that functions during the production of protein, *i.e.*, translation, to specify the sequence of amino acids in a polypeptide. In eukaryotes, mRNA is formed in the nucleus from pre-messenger RNA. The pre-messenger RNA molecule is initially transcribed and than processed into mRNA by removing the introns and splicing together some or all of the exons. *See* Alberts at p. 368. Pre-messenger RNA is commonly many times larger than the resulting mRNA. Splicing of a pre-messenger RNA typically occurs concurrently with transcription of the pre-messenger RNA.

98. I have reviewed the '001 Patent which has a claim reciting the term **"cDNA made from mRNA."** Specifically, this is recited in claim 1 of the '001 Patent, in claim 1 of the '999 Patent, and in claim 1 of the '441 Patent.

99. One of skill in the art as of the time of the filing dates of these patents would understand the term "cDNA made from mRNA" to mean a cDNA that is artificially created via the reverse transcription of an mRNA. A cDNA made from an mRNA is structurally and functionally different from the mRNA. While the four bases in cDNA are adenine, cytosine, guanine, and thymine, the four bases in mRNA are uracil, adenine, cytosine, and guanine. Second, the sugar-phosphate backbone in cDNA is chemically different from the sugar-phosphate backbone of mRNA. This difference in structure allows cDNA to form the famous double helix. Around 1994, for genes as large as *BRCA1* or *BRCA2*, the synthesis of cDNA from an mRNA molecule did typically not result in a DNA strand that is as long as the mature RNA chain. Instead, several DNA fragments had to be ligated together to form a full length cDNA. Initially, the cDNA is single stranded but the second strand can be synthesized to form a double stranded cDNA molecule. *See* '999 Patent, col. 52:39-53:19; '001 Patent, col. 52:39-53:19; and '441 Patent, col. 53:1-49.

100. Moreover, cDNA is a much more stable molecule than mRNA. The stable nature of cDNA molecules or fragments of cDNA molecules make them suitable as primers and probes for, *e.g.*, biotechnological and diagnostic applications. Protein can be translated directly from mRNA whereas protein cannot be directly translated from cDNA but requires the additional step of RNA transcription. In the body, tens of thousands different mRNA molecules are present. Synthesized cDNA, on the other hand, is generated in the laboratory commonly as a homogenous population of molecules of the same kind to study a specific gene of interest.

101. I have found nothing in the specification or prosecution history of the '999 Patent, the '001 Patent, the '441 Patent and the '857 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

102. I have reviewed '857 Patent which has a claim reciting the term **"allele."** Specifically, this is recited in claim 1 of the '857 Patent.

103. One of skill in the art as of the time of the filing dates of these patents would understand the term "allele" refers to alternative forms of a gene located at a specific chromosomal location (locus). The alleles of the same gene in the human body differ in their DNA sequence from each other because one is inherited from the mother and one is inherited from the father.

104. In the context of the patents,

> "BRCA2 allele" refers to normal alleles of the BRCA2 locus as well as alleles carrying variations that predispose individuals to develop cancer of many sites including, for example, breast, ovarian and stomach cancer. Such predisposing alleles are also called "BRCA2 susceptibility alleles. '857 Patent, col. 18:8-13.

"BRCA1 allele" refers

> [T]o the double-stranded DNA comprising the locus, allele, or region, as well as either of the single-stranded DNAs comprising the locus, allele or region. '857 Patent, col. 19:46-49.

105. I have found nothing in the specification or prosecution history of the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

106. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '492 Patent, and the '857 Patent each of which has a claim reciting the term **"nucleotide."** Specifically, this term is recited in claim 1 of the '473 Patent, claims 2, 5-7 of the '282 Patent, claim 1 of the '999 Patent, claim 7 of the '492 Patent, and claim 1 of the '857 Patent.

107. One of skill in the art as of the time of the filing dates of these patents would understand the term "nucleotide" refers to a chemical compound. A nucleotide molecule contains one base together with one sugar and one phosphate. Connecting multiple nucleotides through their phosphate backbone results in a nucleic acid or polynucleotide molecule. *See* Alberts, at 46-47, 60.

108. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, the '999 Patent, the '492 Patent, and the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

109. I have reviewed the '282 Patent, the '492 Patent, and the '857 Patent each of which has a claim reciting the term **"nucleotide/nucleic acid sequence."** Specifically, this is recited in claim 2, 6 and 7 of the '282 Patent, claim 7 of the '492 Patent, and claim 1 of the '857 Patent.

110. One of skill in the art as of the time of the filing dates of these patents would understand the term "nucleotide/nucleic acid sequence" to refer to the order of nucleotides in a nucleic acid molecule. *See* Alberts, at 60. A "nucleotide/nucleic acid sequence" is a convenient abstract representation of the linear structural arrangement of nucleotides in a nucleic acid molecule.

111. In the context of the patents, "nucleotide/nucleic acid sequence" is the specific order in which the nucleotides are arranged in a particular nucleic acid.

> The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA[1/2]-encoding gene or one having substantial homology with a natural BRCA[1/2] encoding gene or a portion thereof. '282 Patent, col. 19:44-48; '492 Patent, col. 18:29-33; and '857 Patent, col. 18:31-35.

112. I have found nothing in the specification or prosecution history of the '282 Patent, the '492 Patent, and the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

113. I have reviewed the '282 Patent, the '001 Patent, and the '441 Patent each of which has a claim reciting the term **"method of screening," "method of identifying,"** and **"method of detecting."** Specifically, this is recited in claim 20 of the '282 Patent, claim 1 of the '999 Patent, claim 1 of the '001 Patent, claim 1 of the '441 Patent and claim 1 of the '857 Patent.

114. One of skill in the art as of the time of the filing dates of these patents would use the terms "method for screening," "method of identifying," and "method of detecting" interchangeably, and would understand that they mean any method to survey a large number of subjects to rapidly narrow or pinpoint or identify a specific phenotype or mutation.

115. In the context of the patents:

> The present invention further provides methods of screening the BRCA1 gene to identify mutations. Such methods may further comprise the step of amplifying a portion of the BRCA1 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA1 locus. The method is useful for identifying mutations for use in either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer. The present invention further provides methods of screening suspected BRCA1 mutant alleles to identify

> mutations in the BRCA1 gene. In addition, the present invention provides methods of screening drugs for cancer therapy to identify suitable drugs for restoring BRCA1 gene product function. '282 Patent, col. 6:59 – col. 7:6; '001 Patent, col. 6:62 – col. 7:9; and '441 Patent, col. 6:64 – col. 7:11.

116. I have found nothing in the specification or prosecution history of the '282 Patent, the '001 Patent, and the '441 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

117. I have reviewed the '857 Patent which has a claim reciting the term **"method of diagnosing."** Specifically, this is recited in claim 2 of the '857 Patent.

118. In the field of Human Genetics, one of skill in the art as of the time of the filing dates of these patents would understand that the term "method for diagnosing" commonly included determining whether or not the patient has a genetic alteration.

119. In the context of the patents, "methods for diagnosing"

> [A]re applicable to any tumor in which BRCA2 has a role in tumorigenesis. The diagnostic method of the present invention is useful for clinicians, so they can decide upon an appropriate course of treatment. '857 Patent, col. 15:9-13.
>
> The probes and primers based on the BRCA2 gene sequences disclosed herein are used to identify homologous BRCA2 gene sequences and proteins in other species. These BRCA2 gene sequences and proteins are used in the diagnostic/prognostic, therapeutic and drug screening methods described herein for the species from which they have been isolated." '857 Patent, col. 26:57-63.

120. I have found nothing in the specification or prosecution history of the '857 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

121. I have reviewed the ‘282 Patent , the ‘999 Patent , the ‘001 Patent , the ‘441 Patent and the ‘857 Patent each of which has a claim reciting the term **“gene.”** Specifically, this is recited in claim 20 of the ‘282 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.

122. One of skill in the art as of the time of the filing dates of these patents would define “gene” as aggregates of segments of the chromosome. This individual would also understand that a “gene” did not necessarily encode a single protein, but may encode multiple isoforms due to alternative splicing, or does not encode a protein at all.

123. In the context of the patents, the

> “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. Mutations at the BRCA2 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA2 region described *infra*. The BRCA2 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA2 locus is intended to include all allelic variations of the DNA sequence. These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA2 polypeptide, fragment, homolog or variant, including, *e.g.*, protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA2-encoding gene or one having substantial homology with a natural BRCA2 encoding gene or a portion thereof. The coding sequence for a BRCA2 polypeptide is shown in SEQ ID NO:l and FIG. 3, with the amino acid sequence shown in SEQ ID NO:2.” ‘857 Patent, col. 18:8-37.

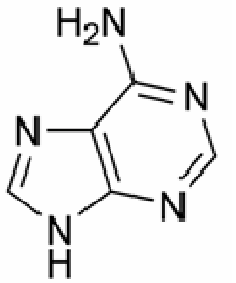
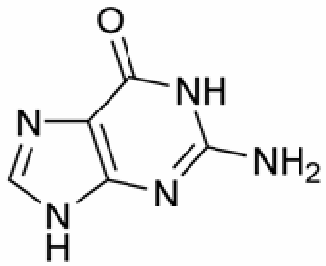
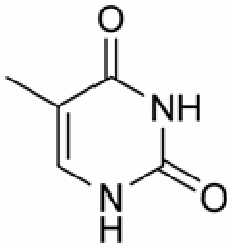
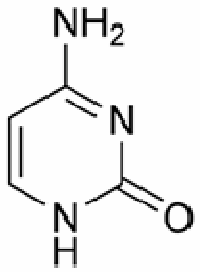
124. I have found nothing in the specification or prosecution history of the ‘282 Patent, the ‘999 Patent , the ‘001 Patent , the ‘441 Patent and the ‘857 Patent that would

contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

III. DNA IS A CHEMICAL COMPOUND

125. DNA, which stands for **d**eoxyribo**n**ucleic **a**cid, is a type of chemical compound called a nucleic acid. At its most basic level, a DNA molecule is composed of several chemical elements, namely Carbon, Hydrogen, Oxygen, Nitrogen, and Phosphorus. These chemical elements make up repeating units that are connected to form a strand or polymer of the DNA molecule. These repeating units of DNA are known as nucleotides. The standard nucleotides in vertebrate DNA contain four different bases: Adenine, Thymine, Cytosine, and Guanine. These bases are linked together by chemical bonds via a sugar-phosphate backbone. As shorthand for convenience, scientists often denote nucleotides by the first letter of the names of their bases: "A" for Adenine; "G" for Guanine; "T" for Thymine; and "C" for Cytosine. Presented below in Figure 1[1] are depictions of the chemical structures of the four nucleotides Adenine, Guanine, Thymine, and Cytosine.

Fig. 1

			
Adenine	Guanine	Thymine	Cytosine

[1] Figure 1 is modified from the online source Wikipedia.com.

126. A molecule of DNA is typically represented by the linear order of its nucleotides, *i.e.*, its "nucleotide sequence" or simply – its "sequence." A nucleotide sequence is not merely information or letters of the English alphabet – the nucleotide sequence defines the structure and chemical properties of a particular DNA molecule based on the linear order of nucleotides in that particular DNA molecule. The structure and chemical properties of a particular DNA molecule can thus determine its function.

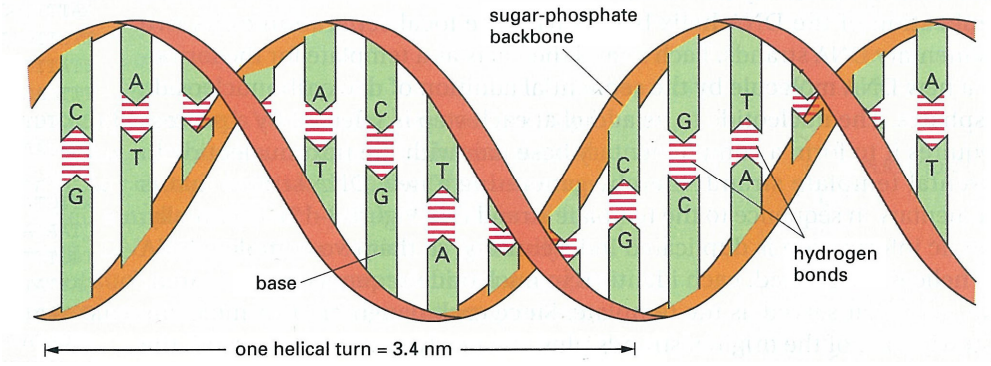
127. Indeed, the letters of the alphabet are often used to name most chemical compounds, not just DNA. For example, the substance commonly known as water is often represented by its chemical formula, H_2O. This chemical formula not only tells a scientist that the chemical substance in question is water, but it also provides other important information about its chemical, structural, physical, and thus, its functional properties. The scientist could readily deduce, for example, that one molecule of water is made up of two atoms of Hydrogen and one atom of Oxygen that are bonded together, and that the structure of an individual water molecule tells a chemist how many water molecules interact with each other and thereby form, *e.g.*, an ice crystal. Accordingly, the scientific notation of any chemical compound provides information about that chemical compound, such as its chemical, structural, and physical properties. These very properties can thus determine the compound's function. Likewise, the physical, structural, and chemical properties of a DNA molecule determine its function. Treating DNA as purely informational is inaccurate.

128. Various molecules can, through chemical reactions and physical interactions, transmit information. Adrenaline (also known as Epinephrine), for example, is secreted by the adrenal gland of the body in response to a stressful situation. Once secreted, adrenaline increases the strength and rate of the heartbeat and raises the blood pressure to prepare the body to react to

the stressful situation. This cascade of events is a transmission of information—from one part of the body to another. On a molecular level, however, this cascade is caused by adrenaline's chemical composition and structure, which allow adrenaline to bind to certain cells throughout the body thereby conveying the message that certain metabolic effects are desired. Thus, adrenaline is an information carrier whose information is conveyed through its chemical structure.

129. Generally, DNA exists as a double helix, which consists of two intertwined strands of DNA. This structure is made possible because each base in one strand is paired via hydrogen bonds with another base in the other, complementary strand (Adenine pairs with Thymine and Cytosine pairs with Guanine). Figure 2[2] depicts the structure of the double-helix and the complementary pairing of the four bases, represented by A, T, C, and G.

Fig. 2

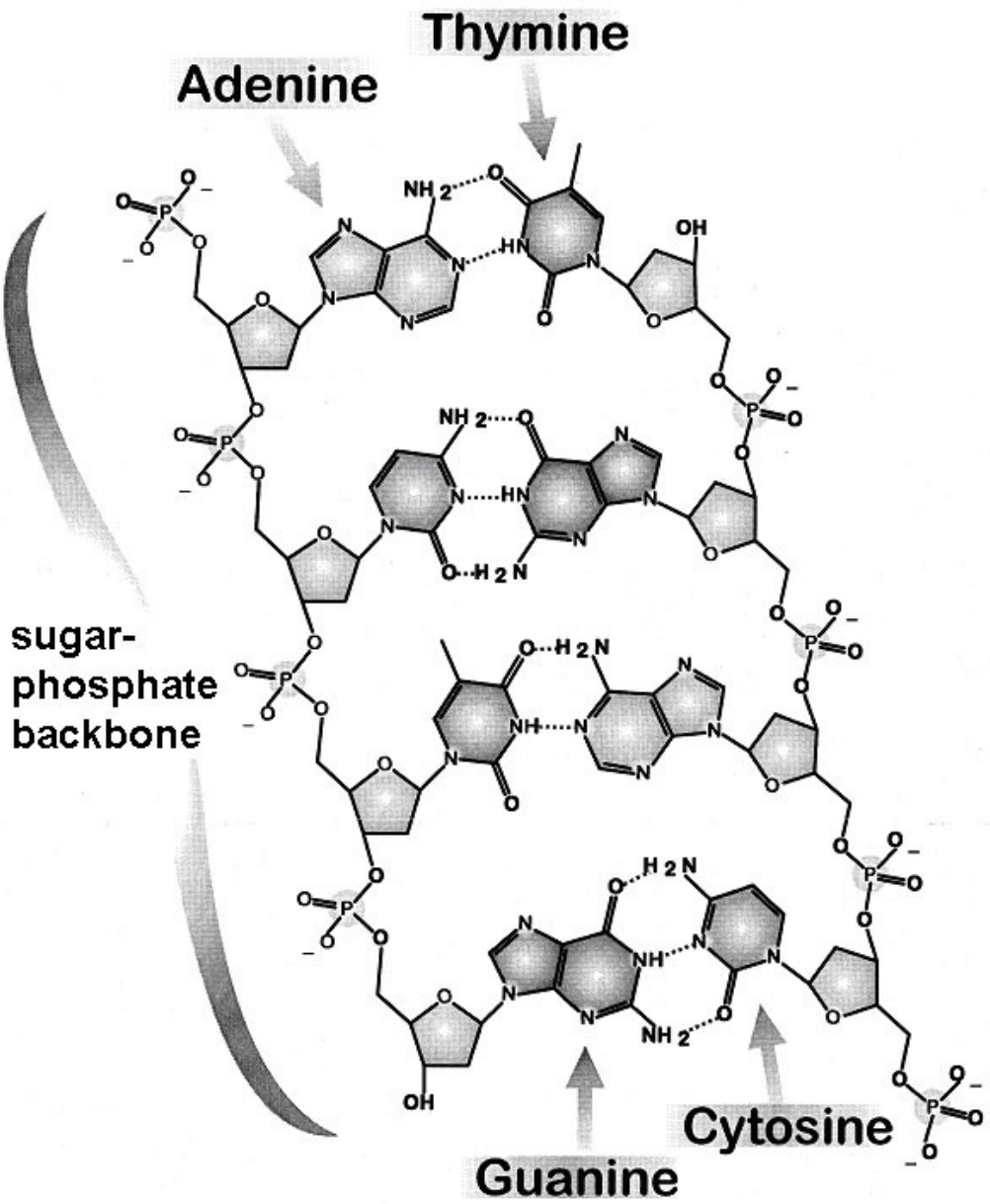


130. Figure 3[3] illustrates the chemical bonding between the bases and the sugar-phosphate backbone of the double helix structure.

[2] Figure 2 is modified from a figure at page 101 of Alberts.

[3] Figure 3 is modified from the entry for "DNA" at the online source Wikipedia.com.

Fig. 3

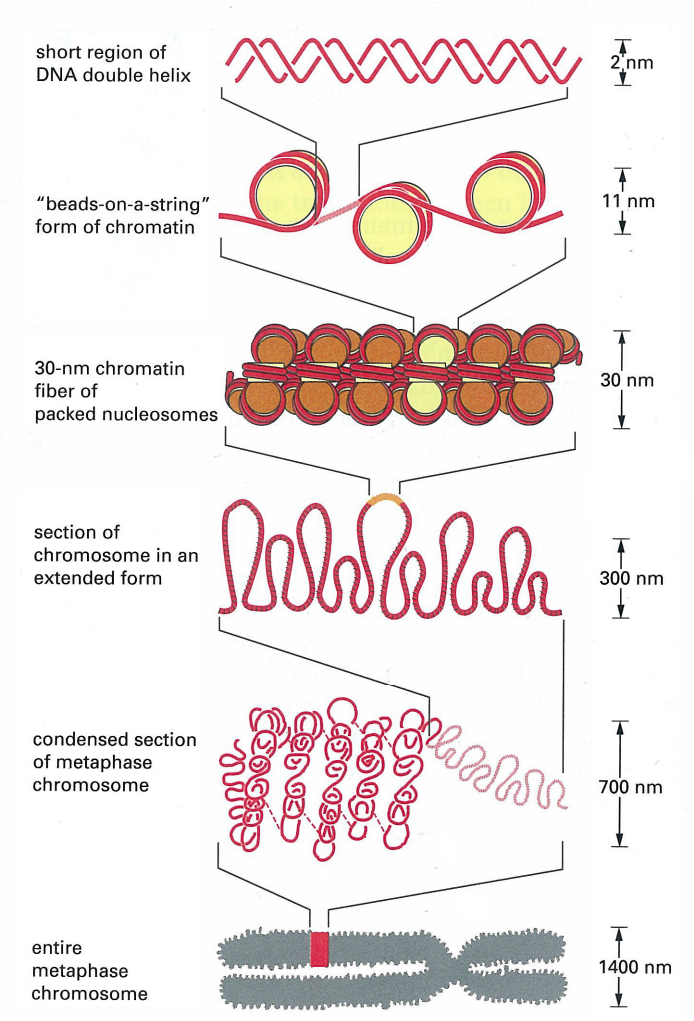


IV. NATIVE DNA HAS DIFFERENT PROPERTIES AND FUNCTIONS FROM ISOLATED DNA

131. DNA as it is found in the human body, *i.e.*, native DNA, is one integral component of chromosomes. Chromosomes are complex structures that carry genes and which are located in most cells of the human body. Proteins represent another integral component of chromosomes. These proteins are bound to the DNA molecules in the chromosomes and

modulate the structure and function of the DNA molecules to which they are bound. Thus, native DNA is never found floating freely in cells of the body, but is packaged along with proteins to form chromosomes. Figure 4[4] below is a schematic drawing of the many levels of packaging of DNA and proteins in a chromosome structure.

Fig. 4



132. The dynamic interaction between chromosomal proteins and native DNA in the body has a major role in establishing which genes are active and which are inactive and the

[4] Figure 4 is modified from Figure 8-30 of Alberts.

level of their activity. In addition, the chromosomal proteins mediate the interplay between the native DNA and the rest of the cell. Moreover, chemical modifications of the DNA molecule, *e.g.*, methylation, can have a major impact on the function of the DNA molecule in the body. Accordingly, there are many factors in the cell, so-called epigenetic factors, which can influence native DNA and consequently the presentation of a trait.

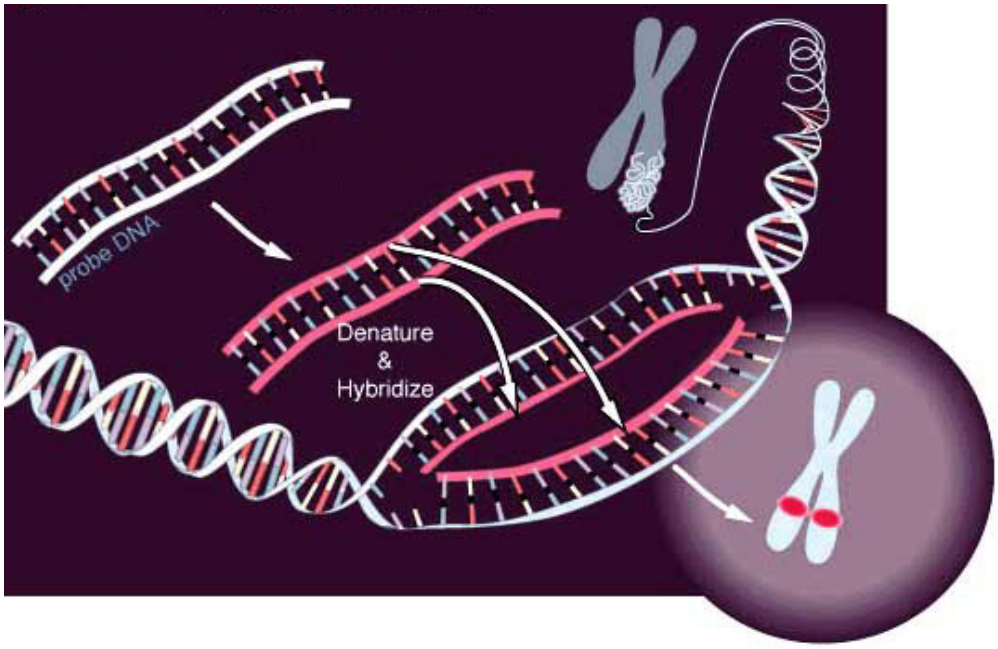
133. To isolate DNA molecules from the body, the entire genome must be extracted from tissues or cells of the body and the chromosomal proteins must be removed. To isolate a specific gene of interest, the relevant DNA fragment must be excised from the genome. The dynamic chemical, physical, and functional interaction between DNA and chromosomal proteins is therefore eliminated from an isolated DNA molecule.

134. Once a DNA molecule is isolated, it gains new properties which, in its native state, it did not possess. These functions make isolated DNA molecules useful as tools for many biotechnological applications such as, for example, diagnostic assays to identify and detect potentially lethal human genetic alterations, and to identify drugs that might be able to cure cancer.

135. One example is the use of isolated DNA molecules as probes. A probe can be a fragment of a DNA molecule of variable length (usually 100-1000 bases long), which is used to detect the presence of a specific target DNA molecule in a sample. The probe is designed to bind specifically to the target DNA molecule of interest based on the nucleotide sequence of the target DNA. The sequence of bases in the probe determines the sequence of bases in the target to which the probe can bind because Adenine always binds to Thymine and Guanine to Cytosine. This pairing between the probe and its complementary target DNA is called hybridization. To

detect hybridization of the probe to its target sequence, the probe is labeled with a detectable, *e.g.*, fluorescent or radioactive, marker. Figure 5[5] below illustrates how an isolated DNA molecule can serve as a probe to target a specific region in the native DNA located within a chromosome.

Fig. 5



136. Isolated DNA molecules can also be used as primers for sequencing reactions. As with probes, primers that are complementary to an exact location of a much larger target DNA molecule can be designed to initiate a sequencing reaction at that location. A scientist can use the probe to analyze the native DNA molecule. Native DNA, in contrast, cannot be used as a primer or a probe.

[5] Figure 5 is modified from a figure at the website of the Mount Sinai Hospital (http://www.mountsinai.on.ca/care/pdmg/genetics/chromosomes).