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.

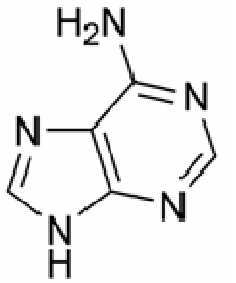
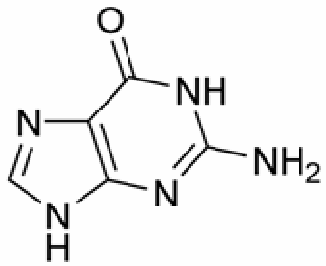
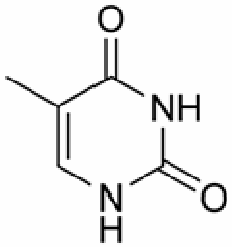
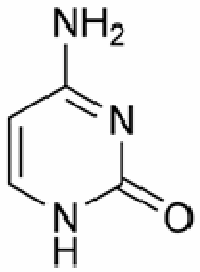
124. I have found nothing in the specification or prosecution history of the '282 Patent, the '999 Patent , the '001 Patent , the '441 Patent and the '857 Patent that would

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.

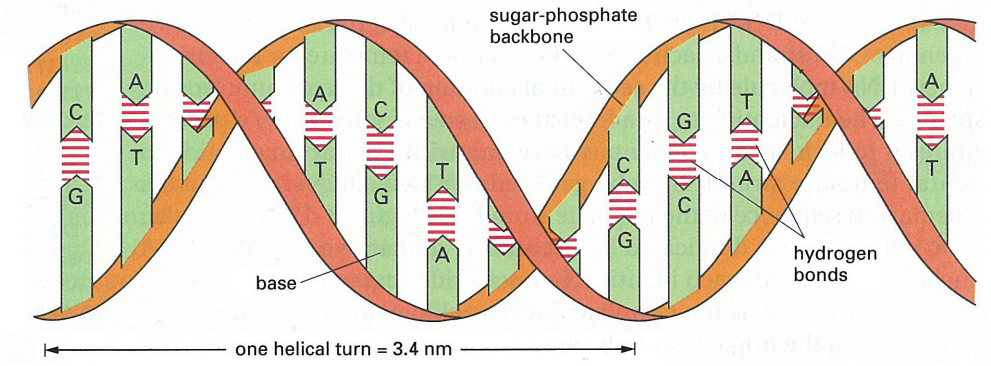
127. Indeed, the letters of the alphabet are often used to name most chemical compounds, not just DNA. For example, the substance commonly known as water is often represented by its chemical formula, H_2O. This chemical formula not only tells a scientist that the chemical substance in question is water, 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

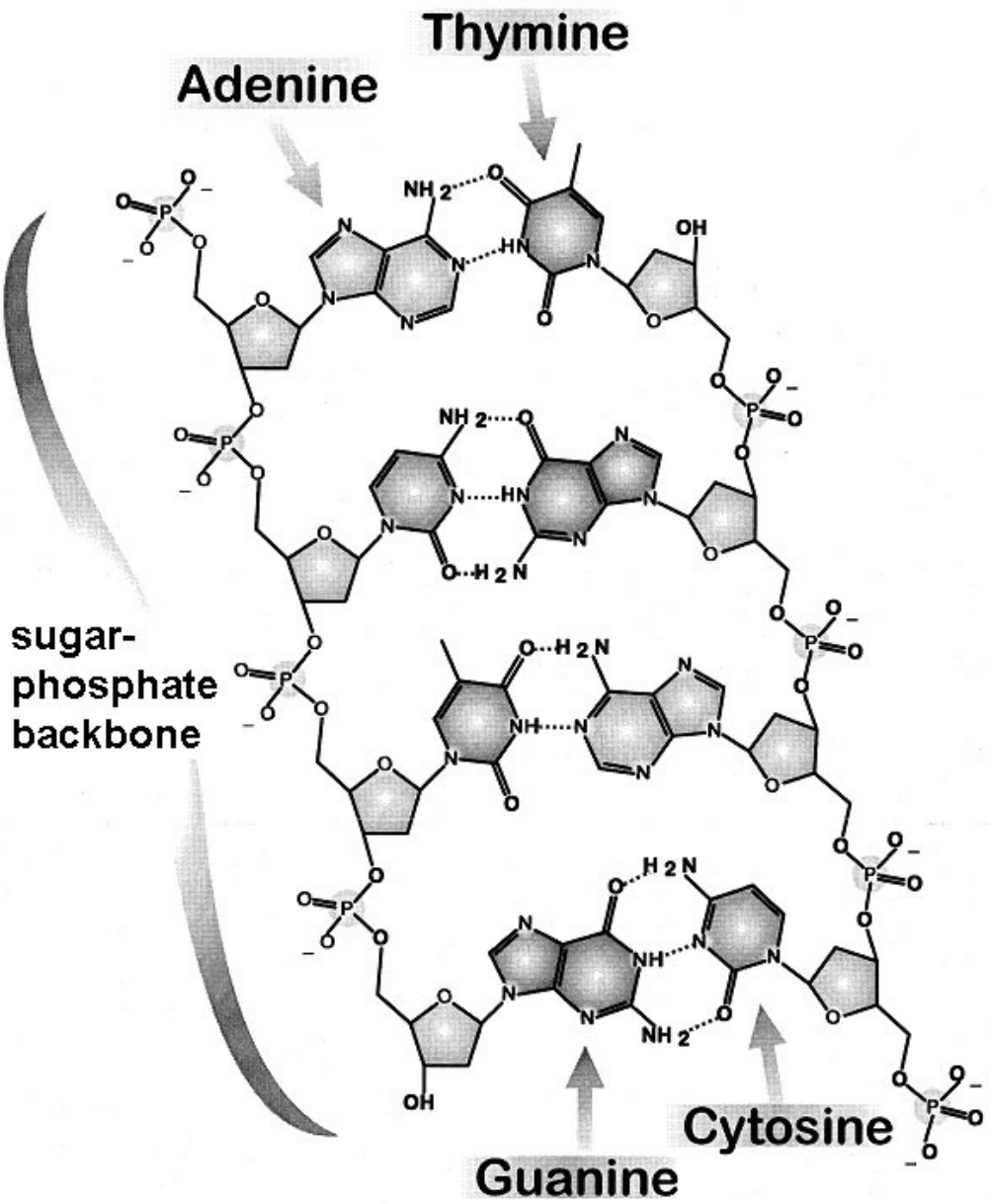


130. Figure 3[3] illustrates the chemical bonding between the bases and the sugar-phosphate backbone of the double helix structure.

[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

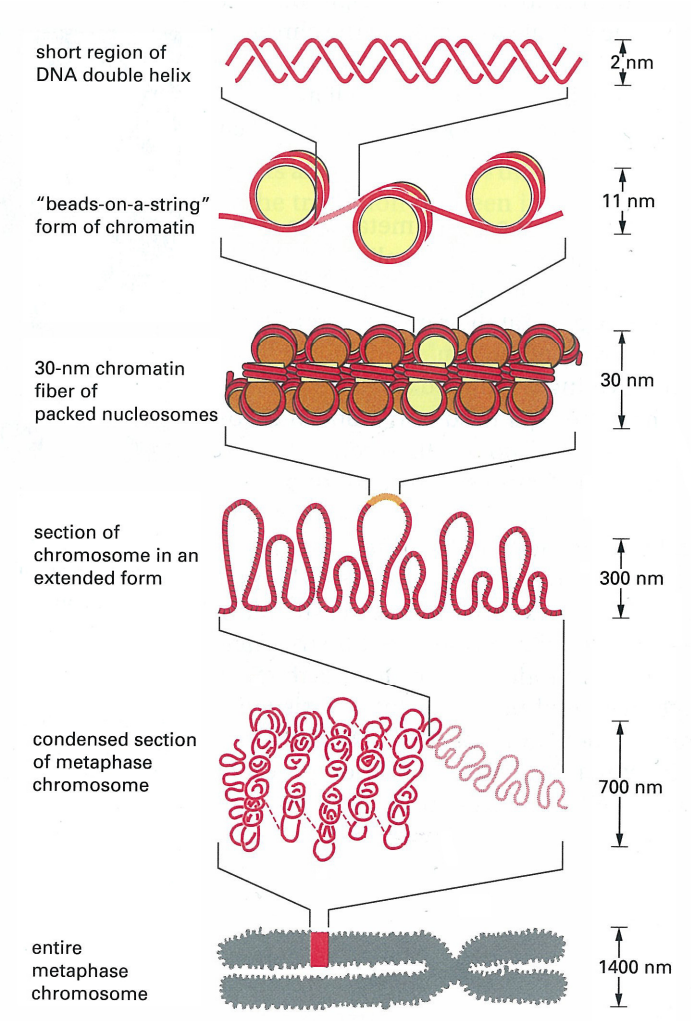


IV. NATIVE DNA HAS DIFFERENT PROPERTIES AND FUNCTIONS FROM ISOLATED DNA

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.

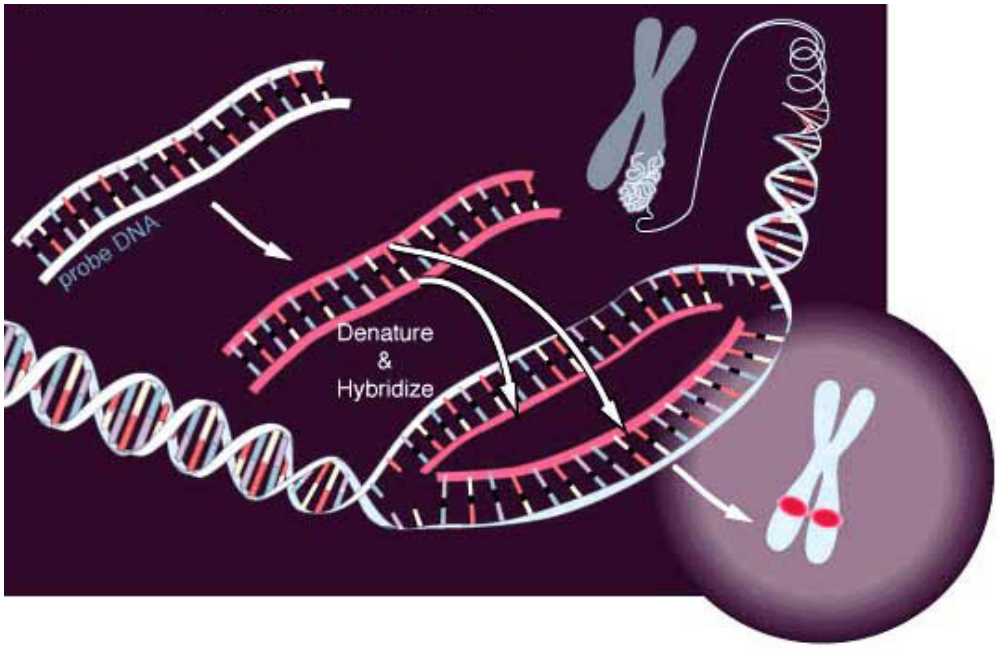
133. To isolate DNA molecules from the body, the entire genome must be extracted from tissues or cells of the body and the chromosomal proteins must be removed. To isolate a specific gene of interest, the relevant DNA fragment must be excised from the genome. The dynamic chemical, physical, and functional 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).

137. The isolated DNAs are excised, extracted or synthetic chemical compounds made by the hands of molecular biologist, not by nature. They are structurally distinct from any substance found in the human body—indeed, in all of nature.

138. Isolated DNA is different in kind, not merely different in degree of purity, from any composition found in nature. Isolated DNA acquires new properties not shared by its native counterpart. These new properties impart the isolated DNA molecules with new characteristics and new utilities. Unlike native DNA, the isolated form can be used as a probe, a diagnostic tool that a molecular biologist uses to target and bind to a particular portion of DNA, allowing it to be detectable using laboratory machinery. Native DNA cannot be used this way. Isolated DNA can also be used as another diagnostic tool, a "primer," which is used in "sequencing" DNA, a method used by a molecular biologist to determine the primary structure of a DNA molecule. In sequencing, a primer binds to, or "hybridizes" with, a DNA target, such as a BRCA1/2 gene, DNA, or a synthetic DNA complementary to mRNA ("cDNA") to form a hybridization product that acts as a substrate for the enzymes used in the sequencing reaction.

139. Native DNA does not have the chemical, structural, functional properties that make isolated DNA so useful to the molecular biologist. Native DNA cannot be used as molecular tools, such as probes and primers, and cannot be used to detect mutations. Nor can it be used in sequencing reactions to determine the structure of a DNA molecule. Excision, extraction, and purification from cellular components, or synthesizing DNA directly from its nucleotide components, is essential to be able to use the isolated DNA molecules as primers or probes. Thus, only isolated DNA molecules have the required chemical, structural and functional properties important for use as diagnostic tools and in the claimed diagnostic methods.

140. RNA cannot be used as a sequencing primer, because its chemistry is incompatible with performing as a sequencing primer.

141. Dr. Sulston's statement that "[t]he physical form in which [genetic sequences] occur is unimportant; what matters is the *informational content*" is thus inaccurate (*see* D. Sulston, ¶15). To the contrary, the physical form of a DNA molecule can significantly impact its function and the information it can yield.

V. GENES ARE INEXTRICABLY LINKED TO OTHER COMPONENTS IN THE HUMAN BODY

142. In the human body, genes are located on chromosomes. Historically, the term "gene" has been used to describe the unit that is responsible for the inheritance of a discrete trait, such as the color of peas in a peapod. In molecular terms, a gene is an aggregate of several segments of a chromosome. Some segments regulate the activity of the gene. From other segments, various types of RNA are produced. Types of RNA include tRNA, rRNA, and mRNA. From an mRNA template, protein is typically produced. In addition, the segments that make up one gene can be physically located adjacent to each other or apart on the chromosome.

143. The body does not have a mechanism "for isolating" genes, contrary what Dr. Jackson contends (*see* Jackson, ¶29). In the body, native DNA remains associated with chromosomes. Moreover, genes are also not like "mathematical algorithms" as Dr. Jackson proclaims (*see* D. Jackson, ¶47). This is because genes are *physical* entities, the functions of which are inextricably linked to their chemical composition and their interaction with other cellular components. Besides, the patents at issue in this case define an "isolated" nucleic acid as "substantially separated from other cellular components." '473 Patent, col. 19:8-9.

144. In the human body, the 23 pairs of chromosomes are located in a cellular structure called the nucleus. Mitochondria, other cellular structures that convert food into energy, also contain a chromosome. A small fraction of human genes are carried by this mitochondrial chromosome. In humans, mitochondrial genes are maternally inherited because the mitochondria of an embryo are supplied by the egg but not by the sperm cell.

145. Cells divide throughout a person's life. The chromosomes, and with them genes and the DNA of which they are comprised, are also duplicated. The process of cell division takes place in the germline to generate egg and sperm cells. Cell division also takes place in the remaining, so-called somatic, cells of the body.

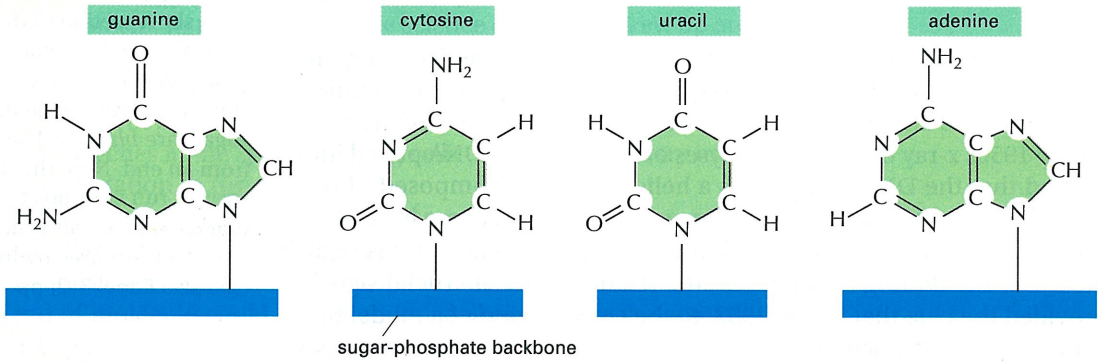
VI. RNA IS STRUCTURALLY AND FUNCTIONALLY DISTINCT FROM DNA

146. Like DNA, RNA – which stands for **r**ibo**n**ucleic **a**cid – is a chemical compound. Unlike DNA, however, the four bases that make up RNA are Guanine, Cytosine, *Uracil*, and Adenine. Thus, instead of the base Thymine, RNA contains Uracil. Common abbreviations of the bases of RNA are: "G" for guanine; "C" for Cytosine, "U" for Uracil, and "A" for Adenine. Each base together with one sugar and one phosphate molecule makes up one repeating unit known as a nucleotide of the RNA. Figure 6[6] below provides an illustration of the chemical structures of the four chemical bases of RNA.

[6] Figure 6 is modified from a figure at page 100 of Alberts.

Fig. 6

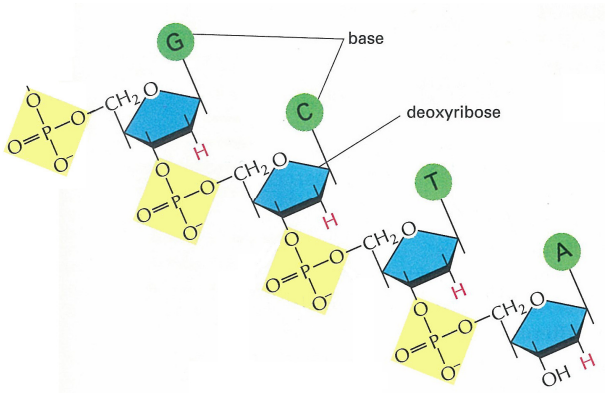
FOUR BASES OF RNA



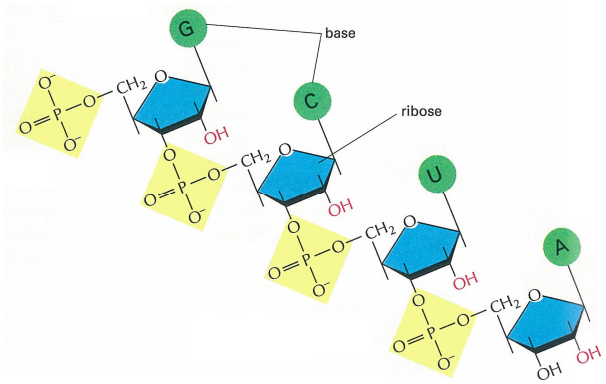
147. Also like DNA, RNA is formed by a strand of bases that are linked together via a sugar-phosphate backbone. The structures of the sugar-phosphate backbone of RNA and DNA, however, are different from each other—while RNA contains a ribose sugar, the sugar component of DNA is a deoxyribose. Figure 7[7] below is a depiction of the four bases of DNA and RNA, respectively, linked by a sugar-phosphate backbone.

Fig. 7

SUGAR-PHOSPHATE BACKBONE OF DNA



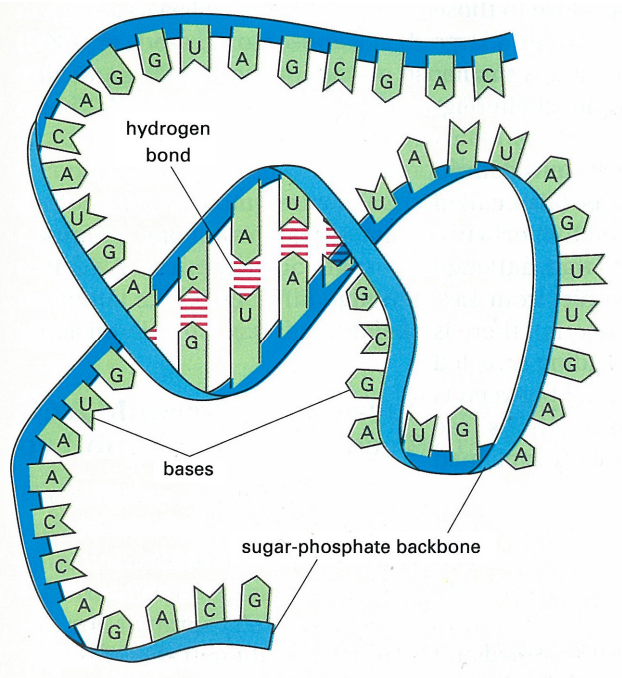
SUGAR-PHOSPHATE BACKBONE OF RNA



[7] Figure 7 is modified from a figure at pages 100 and 101 of Alberts.

148. The different structures of RNA and DNA affect their respective properties and functions. For example, unlike native DNA, which forms a double helix, RNA usually exists as a single strand. Like DNA in a cell, RNA is typically not found floating freely in solution. Cellular RNA is always bound to proteins. Further, DNA is a very stable molecule—DNA has been recovered from millennia-old fossils—whereas RNA, on the other hand, is much less stable. Even in the cell, RNA is sometimes degraded within hours of its generation. This difference in stability is one reason why isolated DNA molecules are more suitable for many biotechnology and diagnostic applications. Figure 8[8] below is an illustration of a single-stranded molecule of RNA.

Fig. 8



149. The process of RNA generation is called "transcription." Many different RNA molecules are transcribed and processed from the native DNA of a chromosome. The

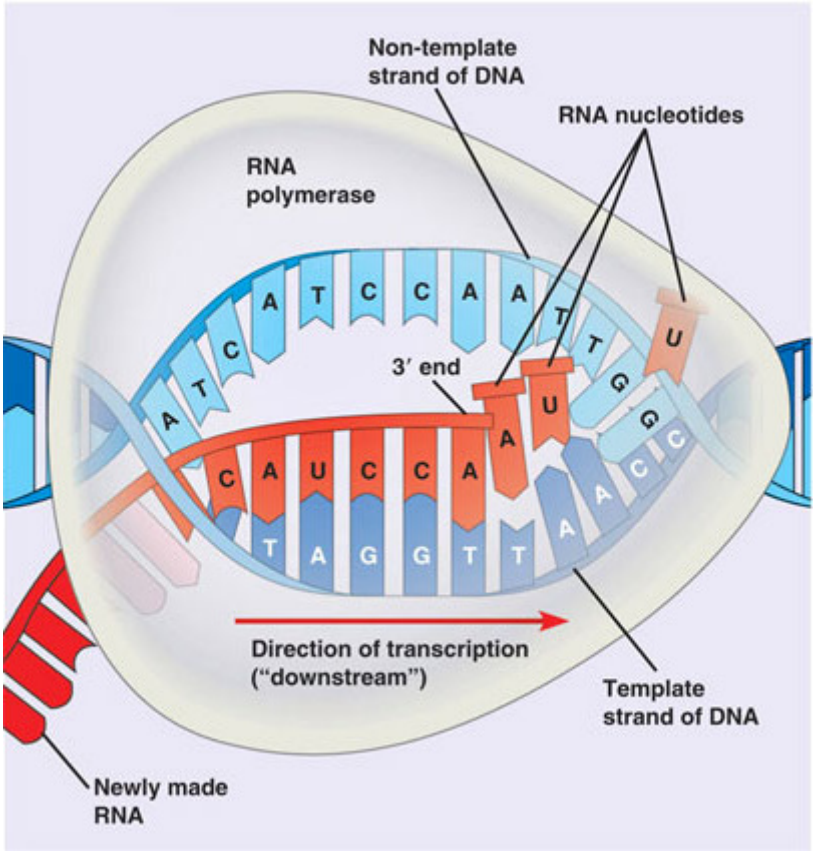
[8] Figure 8 is modified from a figure at page 100 of Alberts.

regulation of RNA transcription involves chromosomal segments that are usually not themselves transcribed into RNA. In fact, regulatory sequences can be at a very different location on the chromosome. These regulatory regions together with the region that is transcribed into RNA form a gene.

150. During transcription of RNA from DNA, a discrete segment of the DNA unwinds and the bases of the DNA molecule act as "clamps" that hold the bases of the newly forming RNA in place while the chemical bonds of the sugar-phosphate backbone are formed. This process is mediated by a structure in the cell known as the RNA polymerase. Adenine binds to Uracil, Thymine to Adenine, Guanine to Cytosine, and Cytosine to Guanine. Figure 9[9] below is an illustration of the process of RNA transcription from a DNA template strand.

[9] Figure 9 is modified from a figure at the website of the Department of Biology of the University of Miama (http://www.bio.miami.edu/~cmallery/150/gene/c7.17.7b.transcription.jpg).

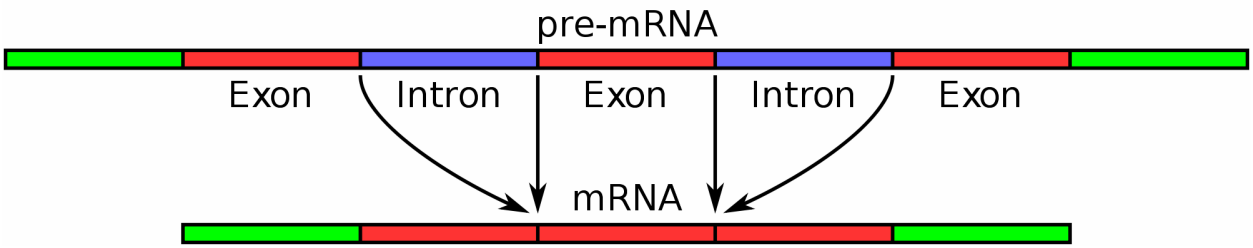
Fig. 9



151. A single gene may give rise to various different RNA molecules, which in turn may give rise to various different proteins. A newly transcribed RNA molecule (a "transcript"), or precursor messenger RNA ("pre-mRNA"), is processed to result in a mature messenger RNA ("mRNA"). Pre-mRNA contains nucleotides that are eliminated during a process called "splicing." The segments of the pre-mRNA that spliced out are called introns (which can contain regulatory sequences), while the remaining segments, called exons, are ligated together. In addition, a chemical "cap" is added to one end of the RNA. A "tail" of nucleotides that contain the base adenine is added to the other end. The final mRNA molecule

contains only exons, a cap, and a poly-adenine tail. Figure 10[10] below is a simplified illustration of the process of pre-mRNA splicing to form mature mRNA.

Fig. 10

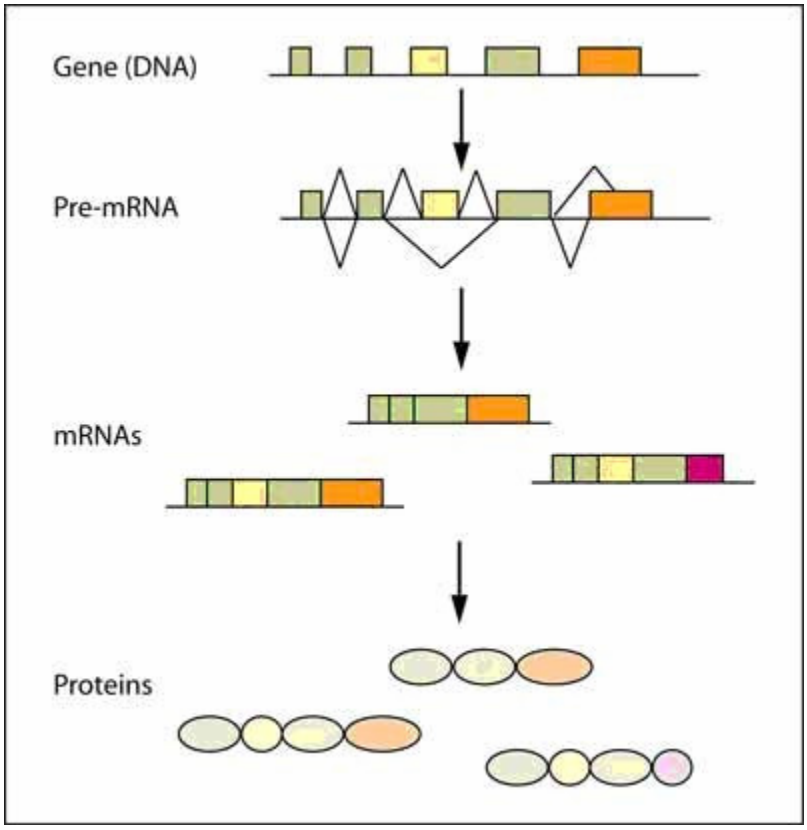


152. In addition, during a process called "alternative splicing," different combinations of exons from the same pre-mRNA molecule can be spliced together yielding alternative mRNA products. Figure 11[11] is an schematic drawing of the process of alternative splicing.

[10] Figure 10 is modified from the entry for "intron" at the online source Wikipedia.com.

[11] Figure 11 is modified from a figure at the website of the Scottish Crop Research Institute (http://www.scri.ac.uk/scri/image/Research/genetics/genesanddevelopment/RNA_fig1.jpg).

Fig. 11



153. Moreover, Dr. Grody's statement that "RNA will have the same (*i.e.*, complementary) nucleotide sequence as the DNA from which it is transcribed," is simply inaccurate because: (i) RNA is composed of different bases; (ii) the nucleotides in the RNA bind to the nucleotides in the DNA—they are not the same; and (iii) the RNA nucleotide sequence is modified by splicing, and adding of a cap and a tail of adenine. *See* D. Grody, ¶52.

154. Thus, contrary to Dr. Leonard's statement that "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," alternative splicing can give rise to many different mRNAs from the same native DNA molecule (*see* Leonard, ¶75). cDNAs can be prepared from mRNAs as discussed

below. However, the cDNA captures that one mRNA from which it was synthesized and not all other splice variants that result from that one gene.

VII. PROTEINS ARE TRANSLATED FROM RNA

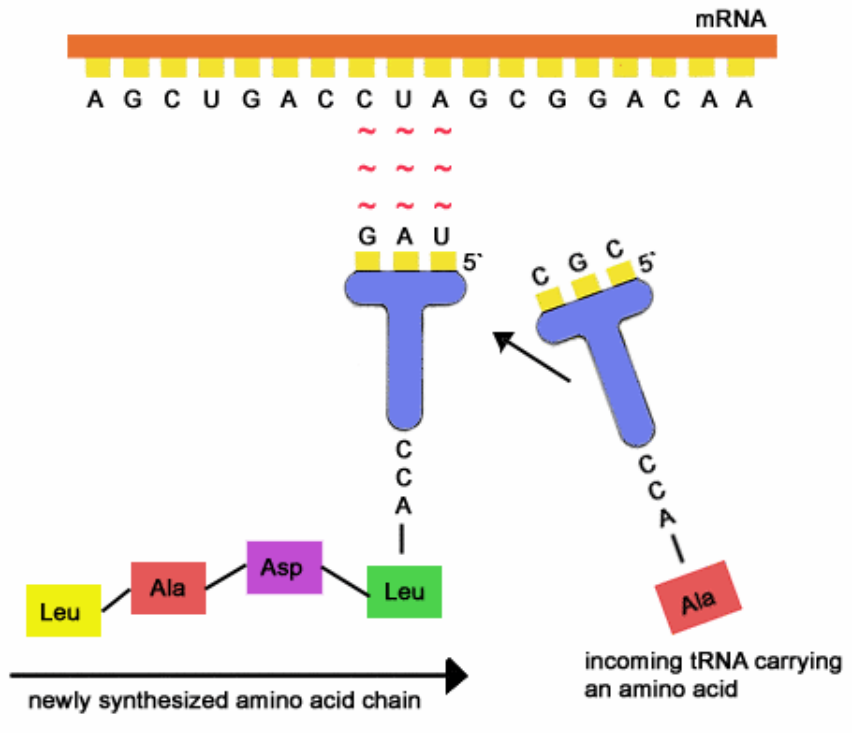
155. Proteins are generally large, complex molecules that play many critical roles in the body. They do most of the "work" in the body and are required for the structure, function, and regulation of the body's tissues and organs.

156. Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains. There are 20 different types of amino acids that can be combined to make a protein. The sequence of amino acids determines each protein's unique 3-dimensional structure and its specific function.

157. Proteins are translated from mRNA through a process called "translation." During translation, mRNA serves as a template to assemble a protein. Three consecutive bases in an mRNA molecule constitute a "codon," which codes for one of the 20 amino acids. Pairing interactions take place between an mRNA molecule and another RNA molecule known as tRNA, which serves as an adaptor during protein translation. Specifically, sets of three nucleotides in the coding region of an mRNA, react with three nucleotides in a tRNA in such a way as to cause the amino acid linked to the tRNA molecule to be chemically transferred to the growing polypeptide chain destined to become a protein. The bases of the mRNA serve as "clamps" to hold the amino acids in place while the chemical bonds between the individual amino acids are formed. During translation, the mRNA template, the tRNA, the newly forming polypeptide chain, and the next amino acid reside in a multi-protein complex named ribosome. Once a protein is translated in typically undergoes post-translational modifications that are important for

the protein's function. Figure 12[12] below provides an illustration of the process of protein translation.

Fig. 12



158. The genetic code describes which codons code for which amino acids. For example, the codon Adenine-Thymine-Guanine encodes the amino acid Methionine. Thus, the chemical composition of an mRNA molecule determines the amino acid composition of a protein.

159. The genetic code is very much dependent on the cellular environment. For example, the three nucleotides Uracil-Guanine-Adenine do not encode an amino acid in the cytoplasm of a typical cell but it stops the process of translation so that the polypeptide is no

[12] Figure 12 is modified from a figure at the website of the Genome Engineering Laboratory of the Institute for Bioinformatics at the National Yang Ming University, Taiwan (http://gel.ym.edu.tw/~ycl6/sc2005/images/translation.gif).

further extended. In mitochondria, however, the same codon encodes the amino acid Tryptophane.

160. I note that in his declaration, Dr. Sulston states that "it wasn't until 1953—the year of the discovery of the structure of DNA—that we came to understand how DNA played its role." D. Sulston, ¶13. I disagree. While the DNA double helix was originally suggested in 1953 by James D. Watson and Francis Crick, the genetic code was not elucidated until the early 1960's. The physical structure of the DNA molecule by itself does not reveal how the DNA molecule functions. In fact, even knowing the nucleotide sequence by itself does not tell function.

VIII. cDNA, RNA, AND NATIVE DNA ARE STRUCTURALLY AND FUNCTIONALLY DIFFERENT FROM EACH OTHER

161. Complementary DNA, or "cDNA," 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 cDNA is synthesized. In other words, it is "complementary" to the mRNA from which it is synthesized.

162. cDNA, as other isolated DNA molecules that are extracted, excised or synthesized, can be a useful tool for researchers as primers and probes in biotechnological and diagnostic applications. In the real world, virtually only synthetic DNA is used as primers and probes.

163. Moreover, when a scientist wants to express a specific protein in a cell that does not normally express that protein to learn more about the protein, the scientist can transfer the cDNA that codes for the protein to a recipient cell. If the cDNA is operatively linked to a

promoter that initiates transcription from the cDNA, the recipient cell will then express the protein of interest.

164. An isolated cDNA molecule is an artificial construct that does not exist in the body and hence is structurally and functionally different from both native DNA and RNA.

165. The method of cDNA construction helps to understand its multiple structural and functional differences from both native DNA and RNA. Several steps are required to construct a cDNA, involving many elegant molecular biology techniques. First, mature RNA is isolated from the tissues or cells of an organism. cDNA is then synthesized from the mature RNA using reverse transcriptase. In this process, the bases of the RNA serve as clamps while the chemical bonds between the nucleotides of the newly forming cDNA strand are formed. Uracil binds to and thereby acts as a clamp for Adenine, Thymine for Adenine, Guanine for Cytosine, and Cytosine for Guanine.

166. The synthesis of cDNA from very long mRNA molecules, such as *BRCA1* and *BRCA2*, often does not result in a cDNA strand that is as long as the mRNA chain. Instead, not unlike a puzzle, several cDNA fragments have to be pieced together to arrive at a composite full length cDNA. Initially, the cDNA is single stranded but the second strand can be synthesized to form a double stranded cDNA molecule.

167. Contrary to Dr. Mason's statement that "cDNA is simply a mirror of the RNA" and that "the functional sequence of the cDNA is identical to the functional sequence of the DNA," cDNA is both structurally and functionally different from RNA and from native DNA. cDNA is not mirror of mRNA nor is it identical to native DNA found in the body. *See* Mason, ¶29.

168. cDNA is *structurally* different from native DNA. First, cDNA made from an mRNA does not contain introns in contrast to native DNA, which contains many intronic sequences. Second, cDNA can contain sequences that correspond to the poly-adenine tail of mRNA, which does not exist in native DNA. Third, because it is not associated with proteins as with native DNA and because it lacks a 5' cap, no protein can be produced from an isolated cDNA molecule without introduction of regulatory sequences. Fourth, the sugar-phosphate backbone of native DNA is usually chemically modified, *e.g.*, by methylation. In contrast, the sugar-phosphate backbone of cDNA is not modified. Finally, as discussed above, isolated cDNA can serve as a probe, as a target for a probe, and as a template for a polymerase chain reaction ("PCR"), all of which native mRNA cannot do.

169. cDNA is also *functionally* different from native DNA. First, native DNA contains regulatory sequences. These regulatory sequences are not present in cDNA because they are not present in the mRNA from which the cDNA was synthesized. Second, because cDNA does not contain intronic sequences, mRNA can be transcribed from cDNA without the need for splicing. Third, introducing a cDNA alone into a cell does not give rise to protein production from that cDNA. Fourth, native DNA and chromosomal proteins form a functional unit; isolated or synthetic cDNA, however, is not associated with chromosomal protein and can thus be used as a molecular tool in various biotechnological applications.

170. As with native DNA, cDNA is *structurally* different from RNA, both pre-mRNA and mature mRNA. First, the set of bases in DNA is different from the set of bases in RNA. While the four bases in DNA are Adenine, Cytosine, Guanine, and Thymine, the four bases in RNA are Uracil, Adenine, Cytosine, and Guanine. Second, the sugar-phosphate

backbone in DNA is chemically different from the sugar-phosphate backbone of RNA. This difference in structure allows DNA to form the famous double helix.

171. cDNA is also *functionally* different from mRNA. First, cDNA is a much more stable molecule than mRNA. Second, protein can be translated directly from mRNA whereas protein cannot be directly translated from cDNA but requires the additional step of RNA transcription. Third, 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 the properties and functions of a specific gene of interest.

172. In addition to being structurally and functionally different from each other, native DNA and mRNA convey less information to researchers, as opposed to isolated DNA molecule such as cDNA. In its native state, the sequence of DNA or RNA molecule is almost like a mystery – they convey little or no information regarding their biological or clinical significance. Only upon isolation, synthesis, and complex analysis can this information become available to researchers and clinicians. Thus, isolated DNA is very much *informationally* different in kind.

IX. ISOLATED *BRCA1* AND *BRACA2* cDNAS ARE SYNTHETIC, MAN-MADE COMPOSITIONS THAT ARE STRUCTURALLY AND FUNCTIONALLY DIFFERENT FROM NATIVE *BRCA1* AND *BRACA2* RNA AND DNA

173. Isolated DNAs are structurally and functionally distinct from any DNA found in nature. The isolated *BRCA1* and *BRCA2* DNA molecules claimed in the *BRCA1* and *BRCA2* patents are likewise extracted, purified, or synthetic, and are structurally distinct from any substance found in the human body, or elsewhere in nature. For example, native DNAs are

physically connected to DNA regulatory sequences and proteins that determine which DNA sequences are expressed, how and where they expressed, and their level of expression. In contrast, the claimed isolated *BRCA1* and *BRCA2* DNAs are not associated with these regulators and do not contain this information.

174. As with isolated cDNA molecules described above, isolated *BRCA1* and *BRCA2* DNA molecules are typically man-made, synthetic molecules. They are structurally distinct from any substance found in the human body, or anywhere else in nature. Based on these structural differences, isolated *BRCA1* and *BRCA2* DNA molecules have very different functions and uses than native *BRCA1* and *BRCA2* RNA and DNA molecules. For example, isolated *BRCA1* and *BRCA2* DNA molecules can function as diagnostic probes and primers for detecting mutations, whereas native *BRCA1* and *BRCA2* RNA and DNA molecules cannot. Likewise, native *BRCA1* and *BRCA2* DNA molecules can pass genes from generation to generation, whereas isolated *BRCA1* and *BRCA2* DNA molecules cannot.

175. With regard to real world practical functions, isolated *BRCA1* and *BRCA2* DNA molecules can be used as primers for DNA sequencing to determine the chemical structure of a patient's *BRCA1* and *BRCA2* DNA sequence, respectively—native genes or DNA in a chromosome cannot be used for these functions.

176. Dr. Sulston states in his declaration that "[g]enetic sequencing is the process by which one 'reads,' or determines, the ordering of the 4 letters (A, T, C, and G) within a specified part of the genome." D. Sulston, ¶ 20. However, sequencing is not simply "reading" a series of letters through a microscope. A DNA sequence cannot be determined by mere inspection. Instead, a series of extractions and chemical reactions must be performed.

177. In order to initiate a DNA sequencing reaction, at least part of the sequence of the target DNA molecule must be known. Plaintiffs fail to appreciate that sequencing of the *BRCA1* and *BRCA2* genes today is based on the breakthrough inventions that led to the patents at issue in this case, *i.e.*, the elucidation of the chemical structure of the genes and their association with an increased risk in breast and ovarian cancer.

178. To determine a DNA sequence of a patient for diagnostic purposes, a biological sample, such as a blood sample, from the patient must be processed. Native DNA or mRNA must be purified from the patient sample. The purification of native DNA of the entire genome, however, does not result in the purification of a single gene. Given that the DNA sequence of the human genome is over three billion nucleotides long, this initial purification step is still a long way from obtaining the sequence of a specific gene. To put things in perspective, the size of the *BRCA1* cDNA relates to the size of the entire genome approximately as a grain of sand to the height of the observation floor of the Empire State Building.[13]

179. Similarly, purification of mRNA from a patient sample yields a mixture of thousands or tens of thousands of different mRNA molecules. Even if cDNA is synthesized from this pool of mRNA molecules, the resulting cDNA molecules are similarly a mixture of thousands or tens of thousands of different cDNAs.

180. The standard method for sequencing DNA commonly used at the filing date of the patents was called the dideoxy sequencing method. Site-specific sequencing, as opposed to full length sequencing, is often used to identify an alteration at a specific nucleotide position.

[13] For this analogy, I have used the following numbers: diameter of a grain of sand—0.6mm; height of the observation floor of the Empire State Building—320m; length of the cDNA of BRCA1 in the '473 patent (SEQ ID NO:1)—5914 nucleotides; and size of the human genome—3,000,000,000 nucleotides.

181. To put things into perspective, one dideoxy sequencing reaction can provide the sequence of a DNA fragment that is about 300 nucleotides long. This is only 1/100,000 of one percent of the human genome! Thus, the sequencing reaction has to be initiated precisely at the target DNA sequence.

182. In his declaration, Dr. Jackson compares the process of extracting genes with the process of extracting paper pulp from wood. *See* Jackson, ¶19. *See also* Jackson ¶22. This analogy fails, however, because at least part of the sequence of the gene of interest must be known to allow the researcher or clinician to isolate and sequence the specific gene of interest.

183. To sequence a particular target, at least part of the target sequence must be known to design a suitable primer. The initial sequencing of a target sequence requires ingenuity far beyond the mere application of routine laboratory techniques and usually involves a significant amount of trial and error. A primer is used to initiate the sequencing reaction at the desired location of a target sequence. A primer is an artificial DNA fragment, usually between 15 and 30 nucleotides long, that binds specifically to the target nucleotide sequence. The nucleotide sequence of the primer is complementary to the target sequence such that the bases of the primer and the bases of the target sequence bind to each other. *See* Figure 5 above.

184. Target-sequence specific primers can also be used to initiate polymerase chain reaction ("PCR"), a technique that can be employed to isolate specific target DNA fragments for sequencing. For example, PCR can be used to synthesize a fragment of genomic DNA. The resulting fragment can then be sequenced. However, to do so, at least part of the sequence of the target DNA molecule must be known so that the target specific primer can be designed. Thus, the use of PCR requires knowledge of at least part of the target DNA sequence to design these

specific primers. In the case of *BRCA1* and *BRCA2*, for example, this knowledge has been provided by the inventors of the patents at issue in this case.

185. After diagnostic sequencing, the patient's sample, such as blood or tissue, is no longer blood or tissue but is has been processed to obtain DNA. The DNA has then been subjected to a sequencing reaction. At the end, instead of blood or tissue, the clinician has the chemical structure of a small portion of the patient's DNA.

186. The gene, mRNA and allele are in the body and must be obtained from a patient's tissue sample in order to be sequenced. The cells of the tissue sample must be broken open and a sample of DNA or RNA or allele extracted from the cells. cDNA can be synthesized using mRNA obtained from the patient sample. Various types of patient sample can be used, for example, a blood, tumor tissue, or non-tumor tissue. The DNA has to be isolated from these samples and put through sequencing reactions in order to obtain the sequence. This is transformative—the blood sample no longer resembles blood, and the patient's tissue no longer resembles the tissue.

187. The claimed diagnostic methods transform a deleterious gene buried among the over 25,000 other known genes in the human genome and make it detectable in the clinic. None of the method claims involve "looking" at genes. One cannot detect or determine a human subject's genes by mere inspection. Detection of a gene marker requires breaking open the cells of a tissue sample, and extracting and excising the native DNA. Using a set of molecular tools, such as a diagnostic probe or a primer that can specifically bind to a BRCA1/2 DNA molecule in a tissue sample, the native DNA is analyzed to determine if the structural composition is the same or different from the normal native gene. These molecular diagnostic tools were designed

based on their ability to bind to and form a stable chemical structure with a target gene sequence. Thus, the claimed diagnostic methods are not mere abstract ideas, and cannot be performed by simply looking at a gene.

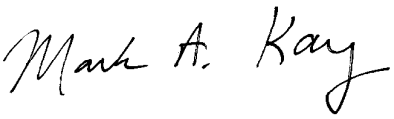
188. The nucleotide sequence of the human native DNA differs from person to person. Some alterations of the native DNA sequence have no known effects, while others may affect a particular trait, such as eye color. Other alterations may cause disease. Determining a DNA sequence and correlating it with pathological phenotypes can result in such life-saving diagnostics as Myriad's BRAC*Analysis*® test.

189. Alterations of genomic DNA sequences are inherited to the next generation if they occur in the germline. Alterations may also be caused by artificial environmental factors in somatic tissues. Such somatic alterations are normally not passed on to the next generation.

190. Without knowing the correlation between DNA sequence and a disease state, the nucleotide sequence of DNA by itself in a chromosome of a person does not say anything about the disease susceptibility of that person. Dr. Sulston himself has stated that: "The genome by itself does not provide answers to any of these questions." Sulston, 2002. Rather, extensive statistical analysis is required to identify those alterations in a nucleotide sequence that correlate with a particular medical condition. Nucleotide sequences of a large group of people have to be painstakingly sequenced, analyzed, and correlated with the presence or absence of disease in the carrier of the sequence. This process can take many years.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on: 12/21/09



Mark Allan Kay

LIST OF EXHIBITS

1	*Curriculum vitae*
2	Dr. John E. Sulston, 2002, "Heritage of humanity," *Le Monde diplomatique*, English Edition

CERTIFICATE OF SERVICE

This is to certify that on December 23, 2009, a true and correct copy of the foregoing document has been served on all counsel of record via the court's ECF system.

/s/ Brian M. Poissant
Brian M. Poissant

EXHIBIT 1

A. Identifying Data:

Name: Mark Allan Kay
Nationality: U.S.A.
Born: January 9th, 1958

B. Academic History:

Education

1976-1980 B.S. Michigan State University
Physical Sciences

1980-1986 Ph.D. Case Western Reserve University
Developmental Genetics

1980-1987 M.D. Case Western Reserve University

Postgraduate Training

1987-1990 Internship and Residency, Baylor College of Medicine,
Houston, TX - Department of Pediatrics

1990-1993 Medical Genetics Clinical Fellowship, Baylor College of Medicine.
Post-doctoral research - Laboratory director, Savio Woo, Ph.D.
Project - Gene Therapy for Hepatic Deficiencies

Educational Scholarships and Honors

Phi Kappa Phi Honorary Society - 1980

Arthur F. Hughes Memorial Award for Outstanding Research in Developmental Biology - 1986

The Upjohn Achievement Award - Excellence in Clinical Pharmacology – 1987

Henry Christian Award for Excellence in Research - American Federation for Clinical Research – 1992,

American Society of Human Genetics - student award for best paper in category of post-doctoral, basic sciences - 1992

Board Certification

Diplomate of the American Board of Pediatrics - 1990-1997
Diplomate of the American Board of Medical Genetics in:
1) Clinical Biochemical Genetics -1993-2003
2) Clinical Genetics - 1993-2003

Clinical Trials
Phase I/II AAV-human factor IX mediated gene transfer into skeletal muscle 1998-1999 Co-PI; 1999-2001 Scientific Advisor
Phase I/II AAV-human factor IX mediated gene transfer into liver IND BB-9398 Holder 1/2001-1/2002; Scientific advisor 2002-2005

C. Employment History:
Faculty Appointments

03/01/93- 06/30/93	Acting Assistant Professor, Department of Medicine University of Washington
06/01/93 - 1994	Assistant Professor, Department of Medicine Investigator, Markey Molecular Medicine Center University of Washington
1994	Adjunct Assistant Professor, Department of Pediatrics University of Washington
1995	Adjunct Assistant Professor, Department of Biochemistry University of Washington
1995	Adjunct Assistant Professor, Department of Pathology University of Washington
1997 - 07/31/98	Associate Professor of Medicine with adjuncts in Pediatrics, Biochemistry and Pathology, University of Washington
8/01/98 (with tenure)	Associate Professor, Departments of Pediatrics and Genetics, Stanford University School of Medicine
8/01/98 - present	Director, Program in Human Gene Therapy, Stanford University School of Medicine
5/01/01 - present	Professor, Departments of Pediatrics and Genetics, Stanford University
2/01/03 - 2004	Co-Founder and Chief Scientific Advisor of Avocel
10/01/05 - present	Dennis Farrey Family Professor
4/2009 – present	Associate Chair for Basic Research- Dept of Pediatrics

D. Public and Professional Service:
University Committees

University of Washington

1994-1998	Medical Scientist Training Program Steering Committee
1995-1997	Medical School Admissions

Stanford University

1998-1999	Children's Health Initiative - Genetics Subcommittee
1998-present	Medical Scientist Training Program Steering Committee
1998-present	Search Committees for 4 separate faculty positions
1999-9/2004	Dean's Fellowship Committee
1999-present	Administrative Panel on Biosafety Committee
2000-present	Children's Health Initiative Grant Review Committee

2001-9/2003	Dean's Committee on Post-doctoral Affairs
2003-present	Department of Genetics Graduate School Admissions
2001-present	Berry Foundation Committee
2002-9/2005	Stanford University Faculty Senate
2002-9/2005	Faculty Senate Executive Committee
2006-present	Chairman, Berry Fellowship Committee

E. Honors and Awards:
Memberships in Professional Associations and Learned Societies

American Society of Human Genetics
American Academy of Pediatrics
American Association for the Advancement of Science
Western Society for Clinical Investigation
American Society of Gene Therapy
American Society of Microbiology
Japanese Society of Inherited Metabolic Disease- honorary member

Editorial Boards/Editorships

1. Editorial Board, Gene Therapy, March 1995-2007
2. Editorial Board, Human Gene Therapy, September 1995-present
3. Editorial Board, Molecular Therapy, August 1999-2003
4. Associate Editor, Human Gene Therapy, 2000-present
5. Associate Editor, Molecular Therapy, 2006-present
6. Associate Editor, Silence 2009-present

Other Scientific Leadership Roles

1. National Gene Vector Laboratory Scientific Review Board, March 1996-2002
2. Advisory Board for the Max Delbruck Center Sixth International Symposia of Gene Therapy, 1997-1998
3. Scientific planning board of the German-American Frontiers of Science sponsored by the National Academy of Science, 1997-1998
4. American Society of Gene Therapy - Board of Directors, 1997-2000
5. Ad hoc reviewer for the NIH, 1997-2000
6. Founding Board of Directors, American Society for Gene Therapy, 1997-2000
7. Co-organizer, 1999 Keystone Symposium on Gene Therapy
8. FDA-AAV working group related to planning platform studies and a shared drug master file for rare diseases, 1999-2000

9. European Society for Gene Therapy, Committee on Gene Therapy for Genetic Diseases, November 2000-November 2001
10. NIH Study Section Member - Medical Biochemistry, February 2000-January 2004
11. Co-organizer of 2001 Keystone meeting on Gene Therapy
12. IND Holder BB-9398 Intrahepatic AAV Gene Transfer for Hemophilia B, January-December 2001
13. Co-Organizer American Society of Microbiology Meeting on Viral Vectors, April 2001
14. Gene Therapy Working Group-National Hemophilia Foundation, June 2001-2003
15. Chair, Committee on Genetic Diseases-American Society for Gene Therapy, 2001-2003
16. Co-Organizer American Society of Microbiology Meeting on Viral Vectors, February 2002
17. Chair, Organizing Committee of the Gordon Conference on Viral Vectors for Gene Therapy, 2003-2004
18. Vice President of the American Society of Gene Therapy, 2003-2004.
19. President Elect of the American Society of Gene Therapy, 2004-2005.
20. President of the American Society of Gene Therapy, 2005-2006.
21. Vice President of Oligonucleotide Therapeutic Society 2009-2011.

Academic Honors and Awards

Western Society for Clinical Investigation, Young Investigator Award - February 1996
Arosenius Swedish Honorary Lectureship - 1997
American Society for Clinical Investigation-elected member - 1997
E. Mead Johnson Award for Pediatric Researcher of the Year - 2000
National Hemophilia Foundation Researcher of the Year - 2000
Named Professorship-Dennis Farrey Family Professor -2005

Invited Addresses
(Selected-excluding seminars at academic/industrial institutions – over 300 total)

1. Cold Spring Harbor Human Gene Therapy, Cold Spring Harbor, NY, October 1992.
2. Human Gene Therapy and Mutant Annual Models, Max-Delbruck Center for Molecular Medicine Berlin-Buch, Berlin, Germany, March 1993.
3. American Society of Human Genetics - Workshop on Human Gene Therapy, New Orleans, LA, October 1993.
4. International Conference on Coagulation Inhibitors, Chapel Hill, NC, November 1993.
5. Hemophilia Today, Poitiers, France, March 1994.
6. Immuno Hemophilia Update, St. Thomas, VI, March 1994.
7. American Pediatric Society and Society of Pediatric Research, National Pediatric Blood Club Symposium, Seattle, WA, May 1994

8. International Conference of the American Thoracic Society, Boston, MA, May 1994.
9. Advances in the Treatment of Hemophilia and von Willebrand's Disease, Oakland, CA, June 1994.
10. International Symposium on Gene Therapy, Valencia, Spain, November 1994.
11. Science in Medicine Lecture, University of Washington, WA, February 1995.
12. American Association for the Advancement of Science (AAAS) plenary session of Gene Therapy, Atlanta, GA, February 1995.
13. Third Annual Conference on Gene Therapy, Berlin, Germany, April 1995.
14. NIH Panel to Assess the NIH Investment in Research on Gene Therapy, San Francisco, CA, August 1995.
15. National Hemophilia Foundation Meeting, Philadelphia, PA, October 1995.
16. Tenth Anniversary: Vascular Gene Transfer: Models of Disease and Therapy, Bethesda, MD, March 1996.
17. Region IX Hemophilia Foundation Meeting, Napa Valley, CA, March 1996.
18. Organizer and Chair of session on Gene Therapy and Animal Models for the XXII International Congress of the World Federation of Hemophilia, Dublin, Ireland, June 1996.
19. Eighth Japanese-American Conference of Pharmacokinetics and Biopharmaceutics, Seattle, WA, July 1996.
20. National Hemophilia Meeting, San Diego, CA, September 1996.
21. Organizing committee of the 10th Annual Cystic Fibrosis Conference, Orlando, FL, October 1996.
22. 39th Meeting of the Japanese Society of Inherited Metabolic Disease, Tokyo, Japan, November, 1996.
23. Third Japanese Workshop on Gene Therapy, Tokyo, Japan, November, 1996.
24. American Association for the Advancement of Science (AAAS) plenary session on Human Genetics, Seattle, WA February, 1997.
25. Keystone Meeting, Cellular and Molecular Basis for Gene Therapy, Snowbird, UT, April 1997.
26. Muscular Dystrophy Association DMD Gene Therapy Workshop, Tucson, AZ, May 1997.
27. Williamsburg Cystic Fibrosis Meeting on Recent Advances in Gene Therapy, Williamsburg, VA, June 1997.
28. 3rd Annual Symposium on German-American Frontiers of Science, Munich, Germany, June 1997.
29. International Conference on Gene Therapy for Hemophilia, Chapel Hill, NC, September 1997.
30. The 11th Annual Cystic Fibrosis Conference, speaker and session chair Nashville, TN, October 1997.
31. International Society for Liver Transplantation, Seattle, WA, October 1997.
32. American Society for Human Genetics-Educational Session speaker, Baltimore, MD, October 1997.
33. European Workshop on Gene Therapy, Milan, Italy, November 1997.
34. Arosenius Honorary Lecture on Gene Therapy for Hemophilia, Stockholm, Sweden, November 1997.
35. Keystone Symposium on the Molecular and Cellular Biology of Gene Therapy, Keystone, CO, January 1998.

36. Society for Pediatric Research, State-of-the-Art Lecture on Gene Therapy for Genetic Diseases, New Orleans, LA, May 1998.
37. XXIII International Congress of the World Federation of Hemophilia-State-of-the-Art Plenary Session and Chair of Plenary distinguished lecture, The Hague, Netherlands, May 1998.
38. FASEB meeting on Mechanisms of Liver Growth and Differentiation in Health and Disease - Chair and speaker on Liver Gene Therapy and Cellular Transplantation, Snowmass, CO, July 1998.
39. NHF Workshop on Gene Therapy for Hemophilia, San Diego, CA, November 1998.
40. International Conference on Gene Therapy and Molecular Biology, Redwood City, CA, April 1999.
41. NIH/FDA Workshop on Non-Clinical Toxicology Study, Design Issues for Development of AAV-Based Gene Therapeutics, Bethesda, MD, May 1999.
42. 8th Biennial International Congress on Liver Development, Gene Regulation and Disease, Orvieto, Italy, June 1999
43. Williamsburg CF Meeting on Recent Progress in Gene Therapy, Williamsburg, VA, June 1999.
44. American Heart Failure Society, San Francisco, CA, September 1999.
45. American Society of Human Genetics: Symposia on Gene Therapy, San Francisco, CA, October 1999.
46. National Hemophilia Foundation, Presymposia on Gene Therapy for Hemophilia, Dallas, TX, November 1999.
47. Gene Therapy Approaches for Diabetes and Its Complications, Rockville, MD, November 1999.
48. Keystone Symposium on Gene Therapy 2000, Keystone, CO, January 2000.
49. FASEB Liver Regeneration, Snowmass, CO, July 2000.
50. National Hemophilia Foundation, Workshop on Gene Therapy for Hemophilia, San Diego, CA, April 2001.
51. American Academy of Pediatrics-Educational Session-Gene Therapy: Pitfalls and Promises, San Francisco, CA, October 2001.
52. American Society of Hematology, Symposia on Gene Therapy for Hemophilia, A phase 1 liver-based clinical trial for hemophilia B, Orlando, FL, December 2001.
55. Gordon Conference on Hemostasis and Thrombosis, Colby, ME, July 2002.
56. World Congress of International Society of Hematology - Plenary Speaker, Seoul, Korea, August 2002.
57. 10th Annual European Society for Gene Therapy - Plenary Speaker, Niece, France, October 2002.
58. American Society for Microbiology - Speaker, Banff, Alberta, Canada, March 2003
59. American Society for Human Gene Therapy - Speaker, Workshop on RNAi, Washington DC, June 2003.
60. 1st Annual International Conference on Transposition and Animal Biotechnology - Speaker, Minneapolis, MN, July 2003.
61. Falk Symposium - Speaker, Germany, October, 2003.
62. Gordon Conference on Viral Vectors for Gene Therapy - Speaker, Santa Barbara, CA, February 2004.
63. American Chemical Society Annual Meeting - Speaker, Anaheim, CA, March 2004.

64. Keystone Symposium on siRNAs and miRNAs - Speaker, Keystone, CO, April 2004.
65. RNAi Conference - Speaker, Boston, MA, May 2004.
66. American Society for Gene Therapy - Education Session, Gene Transfer in Liver, Minneapolis, MN, June 2004.
67. CHI RNAi Conference - Speaker, San Francisco, CA June 2004.
68. FASEB Meeting on Liver Biology - Speaker, Snowmass, CO, August 2004.
69. European Society of Gene Therapy Annual Meeting - Speaker, Edinburgh, Scotland, November 2004.
70. European Society for Gene Therapy - Speaker, Finland, November 2004.
71. Spanish Society for Gene Therapy - Keynote Speaker, Pamplona, Spain, January 2005.
72. Bari International Hemophilia Conference - Pizzomunno, Italy, May 2005.
73. American Society of Gene Therapy Symposia - Speaker, St. Louis, MO, June 2005.
74. Japanese Society of Gene Therapy Plenary Session - Speaker, Tokyo, Japan, July 2005.
75. Rennebohm Symposium, University of Wisconsin, Milwaukee, WI, September 2005.
76. Memorial Sloan Kettering Harold Varmus Presidential Symposium - Speaker, September 2005.
77. Conference on Cell and Gene Therapy - Speaker, Barcelona, Spain, October 2005.
78. University of Toronto Langdon Hall Conference-Gene Therapy - Speaker, Toronto, Canada, May 2006.
79. Mary Crowley Gene Therapy for Cancer - Speaker, Dallas, TX, September 2006.
80. Keystone meeting on RNAi/microRNA - Speaker, Keystone, CO, January 2007.
81. International Society for Heart and Lung Transplantation Plenary overview on RNAi, San Francisco, CA, March 2007.
82. Gordon Conference on Human Genomics and Genetics - Speaker, Newport, RI, July 2007.
83. Oligotherapeutics Society 13th annual meeting - Speaker, Berlin, Germany, October 2007.
84. 50th Anniversary Reunion for University of Washington Medical Genetics, October 2007.
85. American Society of Hematology, Educational Session on Micro RNA/RNAi, December 2007.
86. Gordon Research Conference, Science of Viral Vectors, Ventura, California, March, 2008.
87. Keystone meeting on RNAi/microRNA - Speaker, Keystone, CO, March, 2008.
88. Gene Therapy & Vaccines - Student invitee, University of Pennsylvania, May 2008.
89. Drug Delivery and Translational Research Conference, New York City, May 2008
90. American Society of Gene Therapy, 11th annual meeting, two plenary talks - Speaker, May 2008.
91. FASEB Liver meeting, Snowmass, Colorado, August 2008.
92. Keystone Meeting on RNA therapeutics Lake Louise, CA Feb. 2009. Session Chair and Plenary speaker
93. Keystone Meeting MicroRNAs in Cancer Keystone, CO June 2009. Plenary speaker
94. Oligonucleotide Therapeutic Society and Nucleic Acid Society of Japan. Speaker and Chair Nov, 2009. Fukuoka , Japan

95. RNAi: Therapeutics and Mechanism University of Hong Kong. Plenary Speaker Nov 2009. Hong Kong,

F. Bibliography:
Peer-reviewed articles

1. Kay, M.A., M. Jacobs-Lorena. 1985, Selective translational regulation of ribosomal protein gene expression during early development of Drosophila Melanogaster. Mol Cell Biology, 5:3583-3592.
2. Qian, S., J.-Y. Zhang, M.A. Kay, M. Jacobs-Lorena. 1987, Structure analysis of the Drosophila rpA1 gene, a member of the eucaryotic 'A' type ribosomal protein family. Nucleic Acids Res, 15:987-1003.
3. Kay, M.A., M. Jacobs-Lorena. 1987, Developmental genetics of ribosome synthesis in Drosophila. Trends Genet, 3:347-351.
4. Kay, M.A., J.-Y. Zhang, M. Jacobs-Lorena. 1988, Identification and germ line transformation of the ribosomal protein rp21 gene of Drosophila: Complementation analysis with the Minute QIII locus reveals nonidentity. Mol Gen Genet, 213:354-358.
5. Kay, M.A., W. O'Brien, B. Kessler, R. McVie, S. Ursin, K. Dietrich, E.R.B. McCabe. 1990, Transient organic aciduria and methemoglobinemia with acute gastroenteritis. Pediatrics, 85:589-592.
6. Kay, M.A., E.R.B. McCabe. 1990, E. coli Sepsis and Prolonged Hypophosphatemia Following Exertional Heat Stroke. Pediatrics, 86:307-309.
7. Kay, M.A., P. Baley, S. Rothenberg, F. Leland, L. Fleming, K. Ponder, T.J. Liu, M. Finegold, G. Darlington, W. Pokorny, S.L.C. Woo. 1992, Expression of human alpha-1-antitrypsin in dogs after autologous transplantation of retroviral transduced hepatocytes. Proc Natl Acad Sci USA, 89:89-93.
8. Liu, T.J., M.A. Kay, G. Darlington, S.L.C. Woo. 1992, Reconstitution of Enzymatic Activity in Hepatocytes of Phenylalanine Hydroxylase-Deficient Mice. Somat Cell Mol Genet, 18:89-96.
9. Kay, M.A., Q.T. Li, T.J. Liu, F. Leland, M. Finegold, S.L.C. Woo. 1992, Hepatic Gene Therapy: Persistent Expression of Human ά1-Antitrypsin in Mice after Direct Gene Delivery In Vivo. Hum Gene Ther, 3:641-647.
10. Li, Q.T., M.A. Kay, L. S. Perricaudet, M. Finegold, S.L.C. Woo. 1993, Assessment of Recombinant Adenoviral Vectors for Hepatic Gene Therapy. Hum Gene Ther, 4:403-409.
11. Kolodka, T.M., M. Finegold, M.A. Kay, S.L.C. Woo. 1993, Hepatic Gene Therapy: Efficient Retroviral-Mediated Gene Transfer into Rat Hepatocytes In Vivo. Somati Cell Mol Genet, 19:491-497 erratum appears in vol 20:3 (1994).
12. Kay, M.A., S. Rothenberg, C. Landon, D. Bellinger, F. Leland, C. Toman, A. Thompson, M. Read, K. Brinkhous, S.L.C. Woo. 1993, In Vivo Gene Therapy of Hemophilia B: Sustained Partial Correction in Factor IX-Deficient Dogs. Science, 262:117-119.
13. Cristiano, R.J., L.C. Smith, M.A. Kay, B. Brinkley, S.L.C. Woo. 1993, Hepatic gene therapy: Efficient gene delivery expression in primary hepatocytes utilizing a conjugated adenovirus-DNA complex. Proc Natl Acad Sci USA, 90:11548-11552.
14. Kay, M.A., C.N. Lander, S.R. Rothenberg, L.A. Taylor, F. Leland, S. Wiehle, B. Fang, D. Bellenger, M. Finegold, A.R. Thompson, M.S. Read, K.M. Brinkhous, S.L.C. Woo. 1994, In vivo hepatic gene therapy: Complete albeit transient correction of factor IX deficiency in hemophilia B dogs. Proc Natl Acad Sci USA, 91:2353-2357.

15. Jones, D., M.A. Kay, W. Craigen, E. McCabe, H. Hawkins, A. Dominey. 1995, Coal-black hyperpigmentation at birth in a child with congenital adrenal hypoplasia. J Am Acad Dermatol, 33:323-326.

16. Kay, M.A., F. Graham, F. Leland, S.L.C. Woo. 1995, Therapeutic serum concentrations of human alpha 1-antitrypsin after adenoviral-mediated gene transfer into mouse hepatocytes. Hepatology, 21:515-519.

17. Barr, D., J. Tubb, D. Ferguson, A. Scaria, A. Lieber, C. Wilson, J. Perkins, M.A. Kay. 1995, Strain related variations in adenoviral-mediated transgene expression from mouse hepatocytes in vivo: Comparisons between immunocompetent and immunodeficient inbred strains. Gene Ther, 2:151-156.

18. Lieber, A., M.J. Vrancken-Peeters, M.A. Kay. 1995, Adenovirus-Mediated Transfer of the Rat Retrovirus Amphotropic Receptor cDNA Increases Retrovirus Transduction in Cultured Cells. Hum Gene Ther, 6:5-11.

19. Scaria, A, D.T. Curiel, M.A. Kay. 1995, Complementation of a human adenovirus early region 4 deletion mutant in 293 cells using adenovirus-polylysine-DNA complexes. Gene Ther, 2:295-298.

20. Lieber, A., M.J. Vrancken Peeters, L. Meuse, N. Fausto, J. Perkins, M.A. Kay. 1995, Adenovirus mediated urokinase gene transfer induces liver regeneration and allows for efficient retrovirus transduction of hepatocytes in vivo. Proc Natl Acad Sci USA, 92:6210-6214.

21. Lieber, A., M.J. Vrancken Peeters, A. Gown, J. Perkins, M.A. Kay. 1995, A Modified Urokinase Plasminogen Activator Induces Liver Regeneration without Bleeding. Hum Gene Ther, 6:1029-1037.

22. Fang, B., R.C. Eisensmith, H. Wang, M.A. Kay, G. Zhao, R.E. Cross, C.N. Landen, G. Gavin, D.A. Bellinger, M.S. Read, P.C. Hu, K.M. Brinkhous, S.L.C. Woo. 1995, Gene Therapy for Hemophilia B: Host Immunosuppression Prolongs the Therapeutic Effect of Adenovirus-Mediated Gene Transfer. Hum Gene Ther, 6:1039-1044.

23. Kay, M.A., A.X. Holterman, L. Meuse, A. Gown, H. Ochs, P.S. Linsley, C.B. Wilson. 1995, Long-term hepatic adenovirus-mediated gene expression in mice following CTLA4Ig administration. Nat Genet, 11:191-197.

24. Vrancken-Peeters, M.J., A. Lieber, J. Perkins, M.A. Kay. 1996, Method for Multiple Portal Vein Infusions in Mice: Quantitation of Adenovirus-Mediated Hepatic Gene Transfer. BioTechniques, 20:278-285.

25. Liu, M.L., B. Winther, M.A. Kay. 1996, Pseudotransduction of Hepatocytes by Using Concentrated Pseudotyped Vesicular Stomatitis Virus G Glycoprotein (VSV-G)-Moloney Murine Leukemia Virus-Derived Retrovirus Vectors: Comparison of VSV-G and Amphotropic Vectors for Hepatic Gene Transfer. J Virol, 70:2497-2502.

26. Lieber, A., M.A. Kay. 1996, Adenovirus-Mediated Expression of Ribozymes in Mice. J Virol, 70:3153-3158.

27. Deshane, J., G.P. Siegal, R.D. Alvarez, M. Wang, M. Feng, G. Cabrera, T. Liu, M.A. Kay, D.T. Curiel. 1995, A strategy to accomplish gene therapy for ovarian carcinoma based upon targeted tumor killing via an intracellular antibody directed against the erbB-2 oncoprotein. J Clin Invest, 96:2980-2989.

28. Grim, J., J. Deshane, M. Feng, A. Lieber, M.A. Kay, D.T. Curiel. 1996, ErbB-2 knockout employing an intracellular single chain antibody (sFv) accomplishes specific toxicity in erbB-2 expressing lung cancer cells. Am J Respir Cell Mol Biol, 15:348-354.

29. Lieber, A., C.Y. He, S. Polyack, D. Gretch, D. Barr, M.A. Kay. 1996, Elimination of Hepatitis C Virus RNA in Infected Human Hepatocytes by Adenovirus-Mediated Expression of Ribozymes. J Virol, 70:8782-8791.

30. Brand, K., W. Arnold, T. Bartels, A. Lieber, M.A. Kay, M. Strauss, B. Dorken. 1997, Toxicity associated with the treatment of liver tumors using the HSV-tk/GCV system and adenoviruses as vectors. Cancer Gene Ther, 4:9-16.

31. Sandig, V., P. Liser, A. Lieber, M.A. Kay, M. Strauss. 1996, HBV-derived promoters direct liver-specific expression of an adenovirus transduced LDL receptor gene. Gene Ther, 3:1002-1009.

32. Kay, M.A., N. Fausto. 1997, Liver regeneration: prospects for therapy based on new technologies. Mol Med Today, 3:108-115.

33. Vrancken Peeters, M.J., G. Patijin, A. Lieber, L. Meuse, M.A. Kay. 1996, Adenovirus-Mediated Hepatic Gene Transfer in Mice: Comparison of Intravascular and Biliary Administration. Hum Gene Ther, 7:1693-1699.

34. Murry, C.E., M.A. Kay, S.D. Hauschka, S.M. Schwartz. 1996, Muscle differentiation during repair of myocardial necrosis via gene transfer with MyoD. J Clin Invest, 98:2209-2217.

35. Schowalter, D.B., J.C. Tubb, M. Liu, C.B. Wilson, M.A. Kay. 1997, Heterologous expression of adenovirus E3-gp19K in an E1a deleted adenovirus vector inhibits MHC I expression in vitro but does not prolong transgene expression in vivo. Gene Ther, 4:351-360.

36. Lieber, A. C.Y. He, I. Kirillova, M.A. Kay. 1996, Recombinant Adenoviruses with Large Deletions Generated by Cre-Mediated Excision Exhibit Different Biological Properties Compared with First generation vectors in vitro and in vivo. J Virol, 70:8944-8960.

37. Vrancken Peeters, M.J., G.A. Patijn, A. Lieber, J. Perkins, M.A. Kay. 1997, Expansion of donor Hepatocytes after Recombinant Adenovirus-Induced Liver Regeneration in Mice. Hepatology, 25:884-888.

38. Bethune, C., T. Bui, M.L. Liu, M.A. Kay, R.J.Y. Ho. 1997, Development of a High-Performance Liquid Chromatographic Assay for G418 Sulfate (Geneticin). Antimicrob Agents and Chemother, 41:661-664.

39. Overturf, K., M. Al-Dhalimy, C.N. Ou, M. Finegold, R. Tanguay, A. Lieber, M.A. Kay, M. Grompe. 1997, Adenovirus-Mediated Gene Therapy in a Mouse Model of Hereditary Tyrosinemia Type 1. Hum Gene Ther, 8:513-521.

40. Kay, M.A., L. Meuse, A.M. Gown, P. Linsley, D. Hollenbaugh, A. Aruffo, H. Ochs, C.B. Wilson. 1997, Transient immunomodulation with anti-CD40 ligand and CTLA4Ig enhances persistence and secondary adenovirus-mediated gene transfer into mouse liver. Proc Natl Acad Sci USA, 94:4686-4691.

41. Snyder, R.O., C.H. Miao, G.J. Patijn, S.K. Pratt, O. Danos, A.M. Gown, B. Winther, L. Meuse, L.K. Cohen, A.R. Thompson, M.A. Kay. 1997, Persistent and therapeutic concentrations of human factor IX in mice after hepatic gene transfer of recombinant AAV vectors. Nat Genet, 16:270-276.

42. Schowalter, D.B., L. Meuse, C.B. Wilson, P. Linsley, M.A. Kay. 1997, Constitutive expression of murine CTLA4Ig from a recombinant adenovirus vector results in prolonged transgene expression. Gene Ther, 4:853-860.

43. Bennett, R.L., M. Karayiorgou, C.A. Sobin, T.H. Norwood, M.A. Kay. 1997, Identification of an interstitial deletion in an adult female with schizophrenia, mental retardation, and dysmorphic features: Further support for a putative schizophrenia susceptibility locus at 5q21-23.1. Am J Hum Genet, 61:1450-1454.

44. Nelson, J.E., M.A. Kay. 1997, Persistence of recombinant adenovirus in vivo is not dependent on vector DNA replication. J Virol, 71:8902-8907.

45. Lieber, A., C.Y. He, L. Meuse, D. Schowalter, I. Krillova, B. Winther, M.A. Kay. 1997, The role of Kupffer cell activation and viral gene expression in early liver toxicity following infusion of recombinant adenoviral vectors. J Virol, 71:8798-8807.

46. Lieber, A., C.Y. He, M.A. Kay. 1997, Adenoviral preterminal protein stabilizes mini-adenoviral genomes in vitro and in vivo. Nat Biotechnol, 15:1383-1387.

47. Patijn, G.A., A. Lieber, D.B. Schowalter, R. Schwall, M.A. Kay. 1998, Hepatocyte Growth Factor (HGF) induces hepatocyte proliferation in vivo and allows for efficient retroviral-mediated gene transfer in mice. Hepatology, 28:707-716.

48. Patijn, G.A., A. Lieber, L. Meuse, B. Winther, M.A. Kay. 1998, High-efficiency retrovirus-mediated gene transfer into the livers of mice. Hum Gene Ther, 9:1449-1456.

49. Patijn, G.A., O. Terpstra, M.A. Kay. 1998, Method for continuous perfusion into the livers of mice. Lab Anim Sci, 48:379-383.

50. Wilson, C.B., L.J. Embree, D. Schowalter, R. Albert, A. Aruffo, D. Hollenbaugh, P. Linsley, M.A. Kay. 1998, Transient inhibition of CD28 and CD40 ligand interactions prolongs adenoviral mediated transgene expression in the lung and facilitates expression after secondary vector administration. J Virol, 72:7542-7550.

51. Miao, C.H., R. Snyder, D.B. Schowalter, G.A. Patijn, B. Donahue, B. Winther, M.A. Kay. 1998, The kinetics of rAAV integration in the liver. Nat Genet, 19:13-15.

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EXHIBIT 2

NOBEL PRIZE FOR DISCOVERIES IN GENETICS

Heritage of humanity

The 2002 Nobel Prize in physiology or medicine was presented this month to John Sulston, Sydney Brenner and H Robert Horvitz for discoveries about the genetic regulation of organ development and programmed cell death. John Sulston is also a principal player in another remarkable scientific endeavour, the human genome project. The entire sequence of the genome will be made public next year, despite many obstructions because of greed over lucrative genetic patents.

by John Sulston

ALTHOUGH the genome is the starting point for human life, we should view it as a source of possibility rather than as a constraint. Many fear that individuals' genetic information will be used against them, and these concerns should be taken seriously. Insurers are pushing for the right to use genetic test results in deciding whether or not to issue policies. If permitted by law, insurers and employers could make genetic testing a prerequisite for issuing policies or offering jobs. We should oppose such discrimination.

And since people continue to suffer from cancer, heart disease, senile dementia and other diseases, newspaper headlines such as "Miraculous gene code could eradicate all disease" will only lead to disappointment.

Still, our recently acquired genetic knowledge is enormously valuable to the twin fields of biology and medical research. That is why it is so important to complete a definitive version of the preliminary human genome sequence – the draft version's release was celebrated worldwide on 26 June 2000 – and to give researchers access to the data without delay. The sequence will be completed sometime next year and should become a permanent scientific archive and reference tool.

The genome will undoubtedly have a huge impact on people's choice of diet and lifestyle. In Western societies this will be a major marketing opportunity: I fear that people will begin choosing restaurants according to their genotype.

In all likelihood we will develop new drug treatments for hard-to-treat diseases over the next decade. For example, Mike Stratton's cancer team at the Sanger Centre is currently screening tumours to see how they differ genetically from normal tissues. In many cases it is still easier to kill a cell than to cure it. Genome information may help drugs find targets on cancer cells and destroy

cells selectively, leading to fewer side-effects and better remission rates.

Genome sequencing is a major step forward for our knowledge of the human body at the molecular level. Yet we are only in the early stages. We still do not know what most of the genes look like, nor do we know when or where they are expressed as proteins. The genome by itself does not provide answers to any of these questions. Nevertheless, the information is available to everyone as a resource tool. The next step is to track down all the genes, determining their significance, their location and how their control signals work.

In November 1995 Stratton's team at the United Kingdom-based Institute of Cancer Research (ICR) found a mutation in one of their breast-cancer gene "families", apparently connected with the BRCA2 gene. The region containing that gene had just been sequenced at the Sanger Institute, and within two weeks the ICR team had not only confirmed the discovery but found five more mutations. Stratton moved fast to publish the findings in the international weekly scientific journal Nature, keeping them secret from his colleagues until the last minute. But despite his efforts, some information reached Utah-based Myriad Genetics Inc in the United States, which then located the gene. Myriad's chief scientific officer, Mark Skolnick, then filed a patent application - on the day before the ICR paper was published.

With the threat of commercialisation looming, the ICR moved to patent the mutations it had discovered. At the same time, Myriad used its own patent applications to claim rights to the BRCA2 gene as well as to the entire BRCA1 gene, which Myriad's scientists were the first to clone. Myriad set up a commercial diagnostic laboratory, and once its patents were granted, the company threatened legal action against any other United States laboratory using either gene for breast cancer screening. This meant that Myriad had the only lab that could perform such screening, at a cost of nearly $2,500 per patient. The company also had the right to grant licences to other labs to carry out simpler procedures at a cost of $200 per test.

One of Myriad's tests focused on a mutation discovered by the ICR affecting the BRCA2 gene, commonly found among Ashkenazi Jews from central and eastern Europe. "The Ashkenazi A mutation was the framework for our original paper," says Professor Stratton. "Myriad is claiming a fee for a mutation that we discovered." As an Ashkenazi Jew, Stratton found this especially galling.

By claiming proprietary rights to the diagnostic tests for the two BRCA genes and

charging for the tests, Myriad is adding to total health-care costs. Even worse, once scientists really understand how the BRCA1 and 2 mutations cause tumours to grow, they might be able to devise new therapies. But because of its patents, Myriad has exclusive marketing rights.

Throughout the formidable task of sequencing the human genome, we were faced with the question of research-related proprietary rights. Although the full impact of Myriad's aggressive approach was unclear in 1995, it was clear where a focus on commercial profit and patents would lead. What was needed was a commitment from the international sequencing community to make all genome information publicly available and not to parcel it out via individual deals between companies and researchers.

How to manage the data?

We decided to hold an international meeting to hammer out a strategy deciding who would do what, and how to manage the data. The UK selected Bermuda, close to the US, as the site of the meeting. This was our introduction to the world of international politics. The meeting was extremely constructive, since it was the first opportunity for researchers to compare notes freely. We were forced to work together because nobody at that time could complete the sequencing alone. Everyone arrived with pieces of paper stating their intentions to sequence a particular region of the genome, and during the meeting we resolved the overlapping claims.

At that time there was no mechanism for loading preliminary data into public databases, which were set up for finished data only. Even in raw form, the human genome sequence data obtained from our machines might prove useful to other researchers seeking to localise genes or to check hypotheses. As we had done with the nematode (1), we made all of our data available electronically from our own sites at the Sanger Institute, so that people could download information and do with it as they saw fit (2). We merely asked them to recognise that the data was preliminary and to acknowledge us as the source in any publications.

The principle of data availability had to be endorsed at the Bermuda meeting or else mutual trust would have been impossible. At first I thought it unlikely that everyone would come to an agreement. Several of those present, including Craig Venter of the Institute for Genomic Research (TIGR) (3), already had links to commercial organisations and might oppose the idea of giving everything away

to the public, with nothing in return. But as I stood at the white board, scribbling away, erasing and rewriting, we eventually came up with a statement. The Wellcome Trust – a medical research charity and the Sanger Institute's main financial backer – still has a photo of that handwritten statement with its three bullet points:

- Automatic release of sequence assemblies larger than 1 kb (preferably within 24 hours).
- Immediate publication of finished annotated sequences.
- Aim to make the entire sequence freely available in the public domain for both research and development in order to maximise benefits to society.

While Bob Waterston of St Louis's Washington University and I were drafting the statement together with our colleagues, another colleague, Michael Morgan, was meeting with representatives from the funding agencies to secure support for our initiative. What I had written on the board, with minor modifications, became known as the Bermuda principles, and these have since served as the benchmark for publicly funded large-scale sequencing projects.

The principles of accessibility and on-the-spot release mean that anyone in the international biological community can use the data and ultimately turn them into new inventions that are eligible for patents. But when the raw sequence is released publicly, it will be unpatentable. It promised well that so many people came to share a vision of the genome sequence as the heritage of humanity, as stated in Article 1 of the universal declaration on the human genome and human rights, which emerged from Unesco's general conference in 1997.

The 20th century saw a split between the sciences and the humanities. Many no longer perceive science as a manifestation of culture. One reason is that science has become increasingly equated with technology; in many quarters technological development represents science's sole purpose. Scientists are encouraged to capitalise on their discoveries commercially, regardless of the social consequences.

A discovery, not an invention

The genome sequence is a discovery, not an invention. Like a mountain or a

river, the genome is a natural phenomenon that existed, if not before us, then at least before we became aware of it. I believe that the Earth is part of the common good; it is better off not owned by anyone, even though we may fence off small parts of it. But if an area proves important because it is especially scenic or is home to some rare species, then it should be protected in the public interest.

To be sure, there will always be arguments concerning the balance between private and public lands and how they should be used. The human genome is an extreme example. We all carry our personal copies of the genome, and each portion of it is unique. You cannot say that you own a gene because you would then own one of my genes as well. And you cannot say that we can share our individual genes because we need every single one of our genes. A patent may not grant literal ownership of a gene but it does specifically bestow the right to prevent others from using that gene for commercial purposes.

Placing legal or proprietary restrictions on genes should be confined strictly to current applications or to inventive steps. Someone else may choose to work on another application and may thus need to have access to the same gene. Inventing human genes is impossible. So every discovery relating to genes – their sequence, functions and everything else – should be placed in the pre-competitive arena. After all, one goal of the patent process is to stimulate competition. The most valuable gene-related applications are often far removed from the first easy steps. So this is a matter of science, not just a matter of principle.

In March 2000 Maryland-based Human Genome Sciences Inc (HGSI), a company set up alongside TIGR in 1992, announced that it had been granted a patent on the CCR5 gene, which encodes a receptor on the surface of cells. When HGSI initially applied for its patent it did not know how this receptor functioned. While the patent was pending, a group of publicly funded researchers at the US National Institutes of Health (NIH) discovered that some people with CCR5 gene defects were resistant to infection with the AIDS virus (HIV). CCR5 appeared to be one of the gateways the virus uses to invade cells. As soon as they found out about the NIH discovery, HGSI confirmed the role of CCR5 through experiments and obtained the patent. HGSI asserted its proprietary rights to use the CCR5 gene for any purpose and then sold licences to several pharmaceutical companies to develop drugs and vaccines.

But who took the inventive step? Was it the company that made a lucky match

with the right gene? Or was it the researchers who determined that HIV-resistant individuals had a defective gene?

William Haseltine, HGSI's chief executive officer, argues that patents stimulate progress in medical research, and that the CCR5 patent may well lead to a new drug or vaccine for HIV. But a survey of researchers at US university labs found that many of them have been deterred from working on particular gene targets, fearing that they might have to pay hefty licence fees (or royalties) to companies or risk lawsuits (4).

The patent question

The US recently clarified its guidelines on granting gene patents to provide a somewhat tighter definition of utility – use must now be "substantial, specific and credible". But the guidelines still allow sequences to be patented since they can be used as probes to detect genes responsible for various diseases. The European patent directive, approved by the European parliament in 1998, states that a sequence or partial sequence of a gene is only eligible for a "composition of matter" patent when it can be replicated outside the human body (in vitro), for example copied in bacteria, as we do for human genome sequencing.

This argument has always seemed absurd to me. The essence of a gene is the information it provides – the sequence. Copying it into another format makes no difference. It is like taking a hardback book written by someone else, publishing it in paperback and then claiming authorship because the binding is different.

The number of applications for gene patents on humans and other organisms has now passed the half-million mark, and several thousand such patents have been granted. Nevertheless, the issue of gene patents remains complex and confused. The US Patent and Trademark Office (USPTO) still maintains that a gene discovery is patentable. Until the recent changes, the USPTO granted patents even for partial gene fragments whose only claimed utility was as gene probes. The European Patent Office remained unconvinced about gene patents until the European Union issued its 1998 biotechnology patent directive, which explicitly permitted the patenting of gene sequences. Several EU member states, including France, are opposed to the EU directive, while other EU members, such as the UK, maintain a more neo-liberal line on patenting so that their biotechnology industries remain competitive with those in the US.

I realised long ago that trying to reach an equitable solution using moral or even legal arguments was doomed to failure. The best way to prevent the sequence being carved up by private interests was to place it within the public domain so that, in patent office jargon, as much as possible became "prior art" and thus unpatentable by others. The international sequencing consortium, while working on the human genome project, succeeded in doing just that with respect to the raw sequence data. Now we are raising the bar by placing as much information as possible about the annotated gene sequence and gene function in the public domain.

Some have proposed drawing a patent line between life and non-life. While agreeing with the concerns, and with the urgent need for a value other than a commercial one to be placed on living things, I think there is no case for this particular line. Because the chasm that previously existed between the biological and the chemical is closing, such a distinction will not be sustainable. We should not be patenting whole life forms, such as transgenic mice or cotton plants – and not just because they are living organisms. A sounder reason is this: we did not invent these organisms, only the specific modification that made the mice susceptible to cancer or the cotton resistant to pests.

The future of biology is strongly tied to that of bioinformatics, a field of research that collects all sorts of biological data, tries to make sense of living organisms in their entirety and then makes predictions. If this data is freely accessible, bioinformatics will allow experimental biologists to complement the work of other researchers and to connect with them. If we wish to move forward with this fascinating endeavour, which will undoubtedly translate into medical advances, the basic data must be freely available for everyone to interpret, change and share, as in the open-source software movement. The situation is too complex for a piecemeal approach, with limited amounts of data released at a time and with a single entity holding the access keys.

The saga of the human genome project proves that publicly financed science is extremely effective because it is so intensely competitive. The project's success also refutes the widespread notion that only private industry is capable of carrying out large-scale research.