

DAVID G. MANGUM (4085)
C. KEVIN SPEIRS (5350)
KRISTINE EDDE JOHNSON (7190)
MICHAEL R. MCCARTHY (8850)
PARSONS BEHLE & LATIMER
One Utah Center
201 South Main Street, Suite 1800
Salt Lake City, UT 84111
Telephone: (801) 532-1234
Facsimile: (801) 536-6111
ecf@parsonsbehle.com

BENJAMIN G. JACKSON (admitted *pro hac vice*)
MATHEW GORDON (12526)
MYRIAD GENETICS, INC.
320 Wakara Way
Salt Lake City, UT 84108
bjackson@myriad.com
mgordon@myriad.com
Attorneys for Plaintiffs

**IN THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF UTAH, CENTRAL DIVISION**

UNIVERSITY OF UTAH RESEARCH
FOUNDATION, et. al.,

Plaintiffs,

vs.

AMBRY GENETICS CORPORATION,

Defendant.

UNIVERSITY OF UTAH RESEARCH
FOUNDATION, et. al.,

Plaintiffs,

vs.

GENE BY GENE, LTD.,

Defendant.

**DECLARATION OF MARK
ALLAN KAY, M.D., PH.D.**

Case No. 2:13-cv-00640-RJS

Judge Robert J. Shelby

I, Mark Allan Kay, hereby declare that:

I. QUALIFICATIONS AND BACKGROUND

1. I am currently a tenured professor and Head of the Division of 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 A.

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 joined the Department of Molecular and Human Genetics at Baylor College of Medicine as a medical genetics fellow 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. I have been and continue to be 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 and continue to be on the editorial boards of other scientific journals. Based on this work, I am familiar with the review process associated with publishing scientific articles. That process can involve multiple rounds of edits, including requests for authors to run additional experiments to generate more data to include in the manuscript before publication. In my experience, it is common for the content of manuscripts to change considerably between when an article is first submitted and when it is published.

6. I have been retained by attorneys for Plaintiffs to provide consultation and expert opinions regarding United States Patent Nos. 5,747,282 (the “’282 patent”); 5,837,492 (the “’492 patent”); 5,753,441 (the “’441 patent”); 6,033,857 (the “’857 patent”); 6,951,721 (the “’721 patent”); and 5,654,155 (the “’155 patent”) (collectively, the “patents-in-suit”) in support of Plaintiffs’ Motion for a Preliminary Injunction. I have been asked to provide opinions in response to the declarations of Dr. Anne Bowcock (“Bowcock Declaration”) and Dr. Simon Gregory (“Gregory Declaration”), both dated August 14, 2013.

7. This declaration and the opinions set forth herein are based on Defendants’ Opposition to Plaintiffs’ Motion for Preliminary Injunction, the Bowcock Declaration, the Gregory Declaration, along with the references and other documents cited therein, documents cited herein, and my personal education, professional experience and general knowledge of the

field as of the early-to-mid-1990s and thereafter. A full list of the materials I considered in preparing this declaration is attached as Exhibit B.

8. In the past four years, I have testified at trial or by deposition in the following matter: Tekmira Pharmaceuticals Corp. and Protiva Biotherapeutics, Inc. v. Alnylam Pharmaceuticals, Inc. and Alkana Technologies, Inc., Civil Action No. 11-10-10-BLS2 (Mass. Super. Ct.).

9. I am being compensated at my normal consulting rate of \$650 per hour for non-testimonial work, and \$850 per hour for testimony at depositions, hearing and trial. My compensation is no way dependent on the outcome of this litigation.

10. I continue my investigation and study. I may review additional documents and information the parties provide or rely on after the submission of my declaration. If Defendants' experts provide additional opinions not expressed in their reports, I may supplement my report to respond to them. Therefore, I may expand or modify my opinions as my investigation and study continues, and supplement my opinions in light of any additional information I review, any matters Defendants raise, or any opinions Defendants' experts may provide.

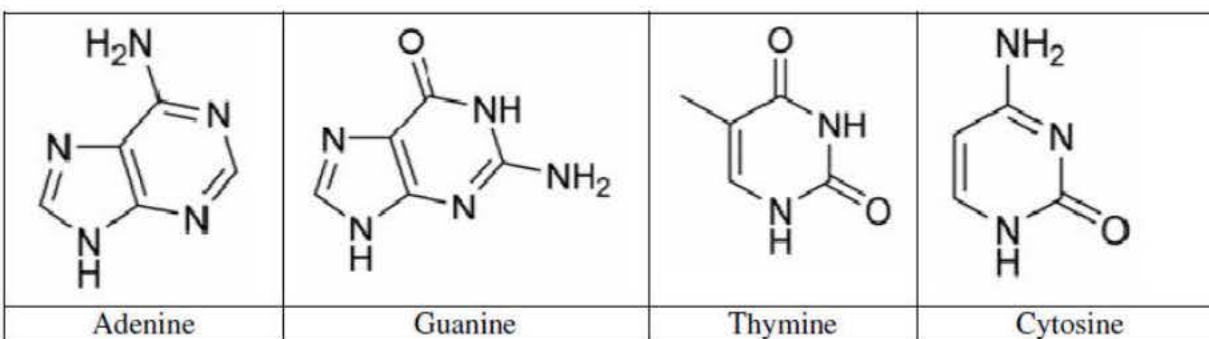
11. I reserve the right to make demonstratives for use at trial or hearings that include figures or text from any of the materials I have considered, as well as any other information that I believe may assist me in explaining issues relevant to this case.

II. TECHNOLOGY BACKGROUND

A. DNA

12. DNA, which stands for deoxyribonucleic acid, 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 are depictions of the chemical structures of the four nucleotides:



13. A molecule of DNA is typically represented by the linear order of its nucleotides, i.e., its “nucleotide sequence” or simply – its “sequence.” The nucleotide sequence defines important 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 help establish its function.

14. 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).

15. 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. 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 includes the aggregate of several segments of a chromosome.

16. Generally speaking, a gene is a segment of DNA that codes for a protein, as described more fully below.

17. A single-stranded DNA molecule has “directionality,” i.e., the two ends of the molecule are chemically different. The “beginning” of a DNA molecule is called the 5’ (“5 prime”)-end and the “end” of the molecule is called the 3’ (“3 prime”)-end.

18. Typically, the sequences at the 5’- and sometimes the 3’- ends of the strand of native DNA coding for a protein correspond to regulatory elements that control when a cell activates a gene. For example, a regulatory element can determine in which tissue types or under what conditions a gene may be turned on (“expressed”). The native DNA of a gene also contains regions that can, as described in more detail below, code for protein molecules. Protein-coding segments of native DNA are contained in “exons.” In humans and other higher organisms, protein-coding exonic DNA sequences are typically interrupted by intervening DNA sequences known as “introns” that do not code for proteins, but may contain regulatory elements.

19. Native DNA sequence alterations that cause disease conditions (often termed “mutations”) can be found in exons, introns, or regulatory elements, although it is often easier for geneticists to identify disease-causing mutations in exons and, hence, mutation screens often concentrate on examining DNA sequences containing exons.

B. RNA

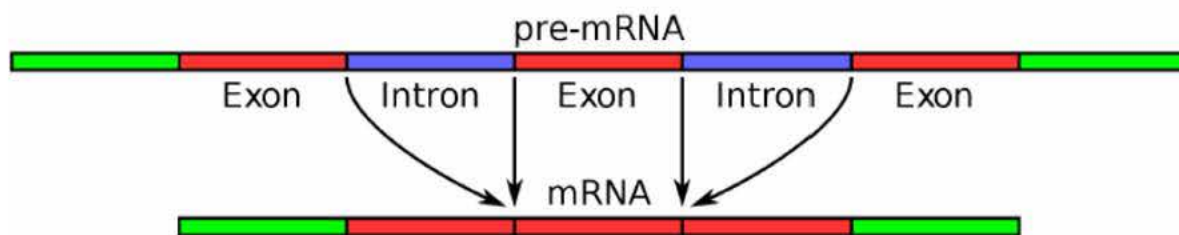
20. Like DNA, RNA – which stands for ribonucleic acid – is a chemical compound. Unlike DNA, however, the four bases that make up RNA are Guanine, Cytosine, Uracil, and Adenine. Thus, instead of the base Thymine, RNA contains Uracil. Common abbreviations of

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. 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. Because of these differences in structure, whereas native DNA forms a double helix, RNA usually exists as a single strand. Moreover, DNA is much more stable than RNA.

21. RNA is generated in the body from native DNA in a process called “transcription.” 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.

22. 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 spliced out are the introns while the remaining segments, exons, are ligated together, or joined to form the intact mRNA molecule. In addition, a chemical “cap” is added to the 5’-end of the RNA. A “tail” of nucleotides that contain the base Adenine is added to the 3’-end. The final mRNA molecule contains only exons, a cap, and a poly-adenosine tail. The following figure is a simplified illustration of the process of pre-mRNA splicing to form mature mRNA. In many cases, the first (5’) and last (3’) exons (or the end sequences of the first and last exons) do not contribute to encoding the protein (green shading). These non-coding exons can influence the

functional properties of the mRNA such as its activity and/or how long it can last in a cell before it is degraded. The internal exons (red) have the sequences that are ultimately translated (see below) into a protein. The number of exons and introns varies for each gene. Even the DNA fragment that encodes a gene can produce different mRNAs with different combinations of exons through a process of alternative splicing.



C. Proteins

23. 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. 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 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.

24. 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 called a ribosome. Once a protein is translated it typically undergoes post-translational or chemical modifications that are important for the protein’s function.

25. 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.

D. cDNA

26. 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.

27. cDNA is structurally different from native DNA. First, cDNA made from an mRNA does not contain introns in contrast to native DNA, which contains intronic sequences. Second, cDNA can contain sequences that correspond to the poly-adenosine 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.

28. 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.

E. Primers

29. A primer is an artificial single-stranded DNA molecule, usually between 15 and 30 nucleotides long, that binds specifically to the target nucleotide sequence. The 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.

30. When its sequence is chosen carefully, a primer will bind to a unique location of the native DNA target, allowing primers to be used for methods that relate to a particular DNA sequence. These methods include producing multiple copies of a specific DNA segment for DNA sequencing reactions or other molecular characterization.

F. Polymerase Chain Reaction

31. Because native DNA gene sequences are generally only present in two copies in each cell (one copy inherited from each parent), and molecular testing methods such as DNA sequencing reactions often require many copies of an input DNA molecule to generate reliable results, geneticists need a method of amplifying DNA products.

32. The most widely used DNA amplification method is the polymerase chain reaction (PCR).¹ PCR involves mixing an input DNA sequence known as the template with a thermostable DNA polymerase enzyme, a pool of all four DNA nucleotides (A, C, T and G), and a great excess of two distinct single-stranded primers. One primer is complementary to one end of the region to be amplified on one strand of the template DNA molecule and the other primer is complementary to the other end of the region to be amplified on the other strand of the template DNA.

33. PCR involves several steps in a cyclical reaction. First, the mixture is heated so that the bonds linking the two strands of the template DNA molecule are overcome and the strands separate (“denaturation”). Second, the mixture is cooled enough to allow one copy of each primer to bind to its complementary template DNA sequence (“annealing”). Third, the DNA polymerase adds nucleotides to the 3’-end of each of the primers in an order complementary to the template DNA. This extension reaction results in the generation of a copy of each strand of the template DNA (“amplifying”). The number of copied DNA molecules doubles with each PCR cycle. A typical PCR runs for 20-30 cycles and results in the accumulation of millions of copies of the template DNA for the interval spanned by the two primers.

34. The ’282 patent discloses the use of PCR to amplify sequences of the BRCA1 gene for screening by allele-specific probes (’282 patent at col. 15, ll. 21-25) and for sequencing BRCA1 segments (’282 patent at col. 16, ll. 23-25). The ’492 patent discloses similar uses of PCR for study of the BRCA2 gene. (See ’492 patent at col. 14, ll. 7-11; *id.* at col. 15, ll. 10-12.)

¹ Basic information about PCR is discussed in Sambrook et al., *Molecular Cloning* (Cold Spring Harbor Laboratory Press 1989), at Chapter 14.

35. I note that Dr. Gregory characterizes the genetic marker D17S855 as “compris[ing] two strands of single-stranded DNA.” (Gregory Decl. ¶ 79.) He also states that “[t]he two strands can be used as a pair of primers in a polymerase chain reaction.” (*Id.*) I disagree with both parts of this characterization. First, rather than describing D17S855 as “two strands of single-stranded DNA,” because the strands are complementary to each other, it is more appropriate to describe D17S855 as a double-stranded DNA molecule. Second, it was well understood by a person of ordinary skill in the early 1990s that PCR involves the use of single-stranded primers that are not complementary to each other to amplify target DNA located between the primers. The result is an amplified PCR product that is double-stranded and incorporates the sequence of the first primer (forward primer) followed by the amplified target sequence, and further followed by the sequence of the second primer (reverse primer). Described differently, the primers are complementary to the ends of the target DNA to be amplified. The end result is amplification of sequences of the target DNA internal to the primers; the PCR product contains the primer sequences and the target DNA sequence.

36. The concept described by Dr. Gregory—separating a double-stranded DNA marker into two complementary single strands of DNA—would not result in an amplified PCR product. The single DNA strands would either exactly align and re-anneal with one another or anneal to the exact same position along the target DNA. In either case there would be no target DNA located between the “primers” to amplify.

37. Dr. Bowcock made similar statements about D17S855 and another marker, D17S932. (Bowcock Decl. at ¶ 83.) I disagree with her position that these double-stranded DNA molecules could have been used as a pair of single-stranded PCR primers for the same reasons.

G. Discovery of the BRCA1 Gene

38. Discovery of the BRCA1 gene was a highly competitive effort that involved multiple groups of scientists with diverse expertise in addition to the inventors of the '282 patent. (See Ex. C, Shattuck Decl. ¶ 9). This discovery effort took place in the early 1990s, when it had been determined that a gene linked to chromosome 17q21, coined "BRCA1," was likely responsible for a large number of familial breast and ovarian cancer.² (See '282 patent at col. 3, ll. 13-29.)

39. Myriad's identification of the BRCA1 gene, as described in the '282 patent, required the application of a positional cloning approach. (Shattuck Decl., ¶¶ 4, 5.; See generally '282 patent ; *id.* at Example 1-8.)

40. Myriad had to take a positional cloning approach because the BRCA1 protein had not been identified. Had the protein been known, they may have been able to use different methods to identify its mRNA and ultimately the gene. Those were methods like immunoprecipitation of the newly made protein while still attached to the ribosome, prokaryotic cloning and expression cloning, and overlapping deletion fragments, which I understand were discussed as conventional prior art techniques for isolating and sequencing a known protein in a case called *In re Kubin* that Defendants mention in their opposition brief. BRCA1 thus had to be identified using positional cloning techniques, which rely upon linkage analyses of familial data to search for the location of the disease-causing gene.

41. After the BRCA1 gene was mapped to chromosome 17 in 1990, intensive study of sets of large families with multiple individuals afflicted with breast and ovarian cancer was needed to narrow the candidate region of chromosome 17 thought to contain BRCA1. (Shattuck

² J. M. Hall, et al., *Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21*, 250 Sci. 1684-89 (1990) (Gregory Ex. H.).

Decl. ¶¶ 9-14.) Myriad had large and informative family data available due to work by Dr. Skolnick. (See Ex. D (Skolnick Dec.) ¶¶ 2-18; '282 patent at col. 8, ll. 15-37.) Having accurate multi-generational pedigrees and availability of DNA samples from these families is instrumental to the positional cloning approach. Families that are not as large or that contain an incorrect diagnosis (including sporadic or non inherited forms of breast cancer— which can sometimes be difficult to differentiate) or a false paternity may not be as useful. One wrinkle in the linkage analysis approach for BRCA1 is that certain families with familial breast cancer showed no linkage to chromosome 17. This suggested a second BRCA gene localized to a different chromosome (ultimately identified as BRCA2).

42. The inventors started with a region that encompassed millions of base pairs. By using a specifically large and informative kindred and other families, the inventors were able to localize BRCA1 to a section of chromosome 17 spanning about 600,000 base pairs. (*Id.* ¶ 12.) This result came in the face of conflicting results from other scientists that had localized BRCA1 to other parts of chromosome 17, as described below. (*See also id.* ¶ 7.)

43. Before candidate breast cancer genes could be isolated for additional study, the inventors needed to create a “physical map” of the putative BRCA1 gene interval on chromosome 17 by obtaining a set of smaller, overlapping cloned DNA molecules that covered the BRCA1 region. (Shattuck Decl. ¶¶ 17-21.) The inventors used a variety of DNA cloning vectors—P1 and BAC clones—in addition to the yeast artificial chromosome systems (YACs). (*Id.* ¶ 17; '282 patent at col. 9, ll. 44-49.) As described further below, the use of P1 and BAC clones was not as well tested at that time.

44. With a set of clones containing pieces of the BRCA1 region, the inventors were then able to put the pieces together and test them as candidate BRCA1 genes. (Shattuck Decl. ¶¶

18-20.) The identification of gene fragments from cloned copies of chromosomal DNA was a challenging process and a likely explanation for the inventor's success in these efforts was the use of a novel gene selection technique. (*See id.* ¶¶ 22-26.)

45. To do this, the inventors isolated mRNA and converted it to cDNA using different primer pairs for PCR. Then they hybridized the synthesized cDNA to genomic segments that were believed to contain the BRCA1 locus. Thirty-nine independent candidate gene fragments by this hybridization selection technique were isolated and ultimately used to identify the full length cDNA of BRCA1. (*See Shattuck Dec.*, ¶¶ 22-26.)

46. The fact that BRCA1 ultimately contained 24 exons (22 coding exons) with a long open-reading frame distributed over 100,000 base pairs made the ultimate identification of the complete cDNA challenging. (*See Shattuck Dec.*, ¶¶ 27-29.) A single DNA sequence error could have resulted in total misunderstanding of the coding reading frame of the cDNA. In addition, the fact that there were multiple mRNA transcripts derived from multiple splicing variants (alternative splicing) transcribed from the BRCA1 gene made the eventual identification of the full cDNA sequence, e.g., mRNA, even more difficult. In fact, without knowing all the alternative splice forms, it would be likely that the full cDNA sequence would not have been correctly assembled and identified, leading to the inability to identify important disease-causing mutations.

47. Proving that a candidate gene fragment identified by the inventors was indeed responsible for an inherited form of breast and ovarian cancer required the identification of DNA sequence mutations that occurred only in family members affected by breast or ovarian cancer. (*See Shattuck Decl.* ¶ 27.) The inventors were able to find such mutations in five families with strong histories of inherited breast and ovarian cancer. (*See Shattuck Decl.* ¶ 15.)

48. Subsequent studies revealed that the BRCA1 gene did not behave in the same manner as other cancer-causing genes. (*See* Shattuck Decl. ¶¶ 30-34.) It was expected that somatic mutations in BRCA1 would be discovered in sporadic breast cancer. Unlike other tumor suppressor genes, they were not. These findings highlighted the unexpected nature of the BRCA1 gene and provided additional evidence that the process of identifying the gene was a substantial scientific accomplishment. (*See id.* ¶ 34.)

H. Discovery of the BRCA2 Gene

49. Identification of the BRCA2 gene, as described in the '492 patent, also involved an approach that was similar to that described above for the identification of the BRCA1 gene (*See* Ex. E, Tavtigian Decl. ¶ 4; *see generally* '492 patent.)

50. The inventors of the '492 patent analyzed 19 families, with multiple members affected by breast cancer, to refine the localization of the BRCA2 gene to a region on chromosome 13. ('492 patent at col. 34, l. 19-col. 36, l. 55 & tbl.1.) This analysis allowed the inventors to reduce the candidate interval on chromosome 13 carrying the BRCA2 gene to 1.5 million base pairs in length. (*Id.* at col. 36, ll. 40-49.)

51. With the narrowed BRCA2 candidate interval in hand, the inventors were then able to construct a physical map of cloned DNA covering the BRCA2 candidate interval. ('492 patent at col. 36, l. 61-col. 37, l. 27 & fig.1.) As was the case for the BRCA1 discovery effort, this physical map used a combination of yeast artificial chromosomes and other DNA cloning vectors to ensure that an accurate physical map was obtained. (*See id.*; *see also* Shattuck Decl. ¶ 17.)

52. The inventors used a range of challenging gene discovery techniques to identify genes that were located in the BRCA2 candidate interval. ('492 patent at col. 37, l. 34-col. 44, l.

5.) These experiments involved the analysis of thousands of clones containing fragments of BRCA2 candidate genes. (*See, e.g., id.* at col. 41, ll. 55-66.)

53. In order to test whether candidate BRCA2 genes might indeed be responsible for inherited breast cancer, the inventors screened candidate DNA sequences for sequence changes that could adversely affect the function of a protein coded for by that candidate. ('492 patent at col. 39, l. 63 to col. 40, l. 28.) More comprehensive study performed after the inventors had sequenced the entire protein-coding portion of the BRCA2 gene identified mutations that segregated with familial breast cancer in nine of the eighteen families screened. (*Id.* at col. 46, ll. 7-62 & tbl.3.) These studies provided convincing evidence that the inventors correctly identified BRCA2, the gene responsible for familial breast cancer on chromosome 13. The protein coded for by BRCA2 was unusually large—being composed of 3418 amino acids—and bore no significant sequence similarities to other known proteins. (*Id.* at col. 45, ll. 11-20.)

III. LEGAL FRAMEWORK

54. In expressing opinions on legal issues, I have applied the following legal standards as described to me by counsel for Plaintiffs.

55. I understand that issued patents are presumed valid and that the party challenging invalidity bears the burden to prove by clear and convincing evidence that a patent is invalid.

A. Anticipation

56. I understand that a patent claim is anticipated by a prior art reference (i.e., it is not “novel” or “new” in view of the prior art reference) if the reference would disclose to one of ordinary skill in the art, either expressly or inherently, each of the limitations of the claim. For a claim limitation to be inherently present in the prior art, I understand it must be necessarily present, not possibly or probably present.

57. I also understand that in order to find a patent invalid on anticipation grounds, the alleged anticipating reference must enable one of ordinary skill in the art in the field of the invention to practice the claimed invention without undue experimentation. I also understand that some amount of experimentation is allowed as long as it is not “undue.” I understand that whether the amount of experimentation required to practice a claimed invention would be “undue” is a fact specific question and can be informed by a number of different factors, including: how much experimentation would be needed, how much guidance is provided in the patent, whether the patent has working examples, the nature of the invention and predictability of the field, the state of the prior art, the level of skill in the field, and how broad the claims are.

B. Obviousness

58. It is my understanding that a patent claim is obvious only if the differences between the claim and the prior art are such that the subject matter of the claim as a whole would have been obvious to one of ordinary skill in the art at the time of the invention. The factors I must consider when evaluating whether the asserted claims would have been obvious to one of ordinary skill in the art include: (1) the scope and content of the prior art, (2) the differences between the prior art and each claim, (3) the level of ordinary skill in the art, and (4) the objective criteria (secondary, or common sense factors) of nonobviousness. These common sense considerations include commercial success, failure of others, praise, long-felt need, and unexpected results.

59. All prior art references must be looked at from the viewpoint of a person of ordinary skill in the art. An obviousness determination is analyzed from the perspective of one of ordinary skill in the art at the time of the invention. One must guard against the use of hindsight. In other words, one must be aware of the distortion caused by hindsight bias, and must be cautious to avoid reading into the prior art the teachings of the claimed invention at issue.

60. I also understand that an obviousness determination requires that there be a reasonable expectation of success in making the invention in light of the prior art.

61. I understand that a party challenging a patent may argue that an invention would have been obvious because it was “obvious to try.” But I understand that an argument based on the idea that an invention was “obvious to try” is not sufficient to show obviousness unless there is evidence that there were a limited number of identified, predictable options available to those skilled in the field, such that a person skilled in the field would have had a reason to select the route that produced the claimed invention.

C. Written Description

62. I understand that for each claim, the patent’s disclosure must describe the invention sufficiently to convey to a person of ordinary skill in the art that the inventor had possession of the claimed subject matter as of the filing date of the application.

D. Person of Ordinary Skill in the Art

63. I have reviewed Dr. Gregory’s definition of a person of ordinary skill in the art (Gregory Decl., ¶ 13), and at this stage do not offer a different view of that hypothetical person.

IV. The Asserted “Primer” Claims are Novel and Not Obvious

64. I have reviewed Defendants’ arguments, including the opinions expressed in the Bowcock and Gregory Declarations, asserting that claims 16 and 17 of the ’282 patent, and claims 29 and 30 of the ’492 patent (collectively, the “primer claims”). I disagree with Defendants’ conclusions.

65. For purposes of my analysis, I have been asked by Plaintiffs’ counsel to apply a construction of the terms “BRCA1 gene” and “BRCA2 gene” as used in the primer claims as encompassing both native DNA and cDNA. In my experience, it is not uncommon for persons of ordinary skill in the art to use the term “gene” to refer to either native DNA or cDNA. For

example, literature in the field at the time of the invention referred to genes as cDNA. (*See* Zhang et al., “High-efficiency gene transfer and high-level expression of wild-type p53 in human lung cancer cells mediated by recombinant adenovirus,” Cancer Gene Therapy, 1994 Mar.; 1(1):5-13 (Exhibit F); Biffi et al., “Lentiviral Hematopoietic Stem Cell Gene Therapy Benefits Metachromatic Leukodystrophy,” Scienceexpress, (July 2013) (Exhibit G).)

66. Claim 16 of the '282 patent recites:

A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.

67. Claim 17 of the '282 patent recites:

The pair of primers of claim 16 wherein said BRCA1 gene has the nucleotide sequence set forth in SEQ ID NO:1.

68. I understand that SEQ ID NO:1 in the '282 patent refers to the cDNA sequence of BRCA1. ('282 patent at col. 53, ll. 4-7.)

69. Claim 29 of the '492 patent recites:

A pair of single-stranded DNA primers of at least 15 nucleotides in length for determination of the nucleotide sequence of a BRCA2 gene by a polymerase chain reaction, the sequence of said primers being isolated from human chromosome 13, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA comprising all or at least 15 contiguous nucleotides of the BRCA2 gene.

70. Claim 30 of the '492 patent recites:

The pair of primers of claim 29 wherein said BRCA2 gene has the nucleotide sequence set forth in SEQ ID NO:1.

71. I understand that SEQ ID NO:1 in the '492 patent refers to the cDNA sequence of BRCA1. ('492 patent at col. 5, ll. 8-9.)

A. The Abel and Anderson Articles Do Not Anticipate Claims 16 and 17 of the '282 Patent

72. The Abel authors “constructed a 800-rad radiation hybrid panel from chromosome 17 to order markers within the BRCA1 region.” (Abel (Gregory Ex. A) at 636.) The Abel article includes a table entitled “PCR conditions for 17q12-q21 STSs” that includes primer sequences associated with different loci. The Abel article does not disclose the sequence of BRCA1 native DNA or cDNA, nor that any of the primers disclosed therein could be used to sequence all or part of BRCA1 native DNA or cDNA. BRCA1 was not discovered before the Abel article published.

73. The Anderson article reports on the construction of a “high-density genetic map of the 8.3-cM interval between D17S250 and GIP on chromosome 17q12-21” to facilitate the positional cloning of BRCA1. (Anderson (Gregory Decl. Ex. B) at abstract.) The authors constructed the map “by developing additional PCR-based polymorphisms and typing these and previously published markers on the CEPH families and on extended kindreds in the breast cancer series.” (Anderson at 618.) The Anderson article includes a table containing different primers associated with different loci in the “BRCA1 Region of Chromosome 17q12-q21.” (Anderson at 619.) The Anderson article does not disclose the sequence of BRCA1 native DNA or cDNA, nor that any of the primers disclosed therein could be used to sequence all or part of BRCA1 native DNA or cDNA. BRCA1 was not discovered before the Anderson article published.

74. Defendants assert that Abel and Anderson articles disclose the same pair of primers associated with locus D17S855, and that that primer pair anticipates claims 16 and 17 of the '282 patent. (*See* Abel at 637; Anderson at 619.) I disagree.³

75. As an initial matter, the claims state that the primers are “for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction.” I have been told by Plaintiffs’ counsel to assume that this claim element is a required part of the invention; i.e., it serves as a separate claim limitation that must be present in the prior art to show that the claim is invalid. With this understanding, it is my opinion that the Abel and Anderson primers do not meet this limitation because they cannot be considered “for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction” because at the time of the Abel and Anderson articles, the sequence of BRCA1—both its native DNA, including the locations of its introns and exons, and its cDNA, was not known. Therefore, it was not known at the time of the articles that the disclosed primer pairs could be used in PCR to amplify all or any part of the BRCA1 native DNA or cDNA. The Anderson and Abel references fail to disclose this claim limitation.

76. I also understand that the primer pair disclosed by Abel and Anderson fall within an intron sequence of BRCA1; they are complementary to only previously unknown and undefined intronic sequences of what was later identified as part of the BRCA1 genomic DNA sequence. This is demonstrated by comparing the placement of the primers within BRCA1 to the exons of BRCA1, as indicated by the capital letters in Figure 10 of the '282 patent. I have annotated Exhibit I from the Bowcock declaration to demonstrate that the Abel and Anderson primer pair falls within an intron of native BRCA1 DNA. (*See* Ex. H) Because the Abel and

³ I offer no opinion about whether the Abel and/or Anderson articles, or any reference discussed herein, qualify as prior art to any claim of the patents-in-suit.

Anderson primers fall within an intron sequence of BRCA1, if used in a PCR reaction, they would synthesize only an intronic portion of what has ultimately been identified by the '282 inventors as BRCA1. Because cDNA contains only exons, the Abel and Anderson articles cannot be used in PCR to synthesize all or part of the sequence of BRCA1 cDNA (i.e., SEQ ID NO:1 of the '282 patent), as required by claim 17.

B. The D17S855 and D17S932 Marker Deposits Do Not Anticipate Claims 16 and 17 of the '282 Patent

77. Defendants argue that the depositing of the D17S855 and D17S932 markers anticipate claims 16 and 17 of the '282 patent. I disagree.

78. First, each of these markers does not separately constitute a pair of single-stranded DNA primers, as required by the claims. Rather, each marker is a double-stranded DNA fragment.

79. Second, even if each of these markers could be separately used as a pair of single-stranded DNA primers (which would first require denaturing the double-stranded DNA fragment into two single-strands of DNA), the markers would not synthesize all or part of the sequence of BRCA1 cDNA (claim 17) by PCR, because they fall within an intron of BRCA1.

80. As described above, PCR involves the use of a pair of single-stranded primers that are complementary to the ends of the target DNA to be amplified that lie between the primers. As was commonly understood in the art before 1994, the 3' ends of the two primers used in a PCR reaction are, relative to the target DNA to be amplified, separated by a stretch of nucleotides ("target DNA") that is not found in either primer. The result is an amplified PCR product that is double-stranded and incorporates the sequence of the first primer (forward primer) followed by the amplified target sequence, followed by the sequence of the second primer (reverse primer).

81. If either of the D17S855 or D17S932 markers was separately used as a pair of single-stranded DNA primers, it would not fit the commonly understood meaning of a pair of primers for PCR. Instead, the two single-strands of DNA either re-anneal to one another (the favored reaction since primers are added in excess) or anneal to the exact same position along the target DNA. In either case, there would be no target DNA lying between them to amplify. If a marker was separated into two single strands of DNA that were used as a pair of primers in PCR, the PCR would not produce a double-stranded, amplified PCR product having the sequence of the first primer, followed by the amplified sequence of the target DNA, followed by the sequence of the second primer. Thus, neither of these markers can be used in PCR to produce the product required by claims 16 and 17 of the '282 patent.

82. Moreover, as described above, the “for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction” language of the claims is must be considered, and neither marker can meet this limitation—even if each used as a pair of single-stranded DNA primers—because the sequence of BRCA1 was unknown before the invention of the '282 patent.

C. The Schutte Article Does Not Anticipate Claims 29 and 30 of the '492 Patent

83. The Schutte article was published on October 15, 1995, and states that the authors “identified a homozygous deletion in a pancreatic carcinoma (DPC) that localized to a 1-cM region at chromosome 13q12.3, which lay within the 6-cM locus of familial breast cancer susceptibility (BRCA2).” (Schutte at abstract.) “In search for the target gene(s) in the DPC/BRCA2 region, the authors “constructed a high-resolution physical map of the region.” (Schutte at 4570.) The Schutte article includes a table of STSs (sequence tagged sites) and a pair of primers associated with each STS.

84. Defendants assert that the primer pairs associated with the “866s186” and “866s239” STSs identified in the Schutte article anticipate claims 29 and 30 of the ’492 patent. I disagree.

85. First, the claims state that the claimed primer pair is “for determination of the nucleotide sequence of a BRCA2 gene by polymerase chain reaction.” I have been told by Plaintiffs’ counsel to assume that this claim element is limiting; i.e., it serves as a separate claim limitation. None of the primer pairs in the Schutte article meet this limitation because they cannot be considered “for determination of a nucleotide sequence of a BRCA2 gene by a polymerase chain reaction” because at the time of the Schutte article the sequence of BRCA2—both its native DNA, including the locations of its introns and exons, and its cDNA, was not known. Therefore, it was not known at the time of the article that the disclosed primer pairs could be used in PCR to amplify all or any part of the BRCA2 native DNA or cDNA. The Schutte article fails to disclose this claim limitation.

86. Second, both Dr. Gregory’s declaration (¶ 242) and Defendants’ Opposition Brief (p.58) state that the “866s186” and “866s239” primer pairs, when used in PCR, synthesize intronic portions of what is now known as BRCA2. Claim 30 requires that the primers, when used in PCR, synthesize of all or part of BRCA2 cDNA (SEQ ID NO:1). The BRCA2 cDNA sequence does not contain any intronic portions of BRCA2 native DNA. Accordingly, the “866s186” and “866s239” primers, when used in PCR, would not result the synthesis of all or at least 15 contiguous nucleotides of BRCA2 cDNA, as required by claim 30.

D. Neither H47777 Nor H48122 Anticipate Claims 29 and 30 of the ’492 Patent

87. Although not addressed in Defendants’ Opposition brief, I understand that Dr. Gregory asserts that claims 29 and 30 are anticipated by the H47777 and H48122 sequences. I

disagree. First, based on the disclosure dates Dr. Gregory alleges, the full sequence of BRCA2 was not known at the time of these deposits, so they cannot be “for determination of a nucleotide sequence of a BRCA2 gene.” Second, these sequences are double-stranded DNA. As such, they are not a pair of single-stranded DNA primers and cannot be used to produce the described PCR product. *See supra* ¶¶ 77-82. I have seen no evidence that these sequences had been used as primers. Accordingly, they cannot and do not anticipate claims 29 and 30.

E. None of Defendants’ References Render the Primer Claims Obvious

88. Although not addressed in Defendants’ Opposition brief, I understand that Defendants are arguing that the asserted primer claims would be obvious in view of various markers. As described more fully below, I disagree with Defendants’ assertion.

89. Essentially, Dr. Gregory suggests that it would have been obvious to design a pair of single-stranded primers, based on the markers D17S855, H47777, or H48122, to use in PCR to amplify the DNA fragment encompassed by that marker. In my view, even if one could design shorter primers to amplify the DNA fragment encompassed by marker D17S855, H47777 or H481222, those primers would still suffer from some of the same shortcomings as using the double-stranded DNA fragment as a pair of single-stranded DNA primers. Those alleged primers would not have been “for determination of a nucleotide sequence” of the BRCA1 or BRCA2 genes by a polymerase chain reaction because, as described above, the nucleotide sequences of BRCA1 and BRCA2 were not known in the art before the filing of the applications that led to the ’282 and ’492 patent were filed.

90. In addition, today we know that the H48122 sequences contain sequences from the 3’UTR (non-protein coding region) and gives no information regarding the protein sequence. Because the sequence of BRCA2 protein was unknown before the inventors’ discovery, this EST could not be used to predict or identify the BRCA2 gene. Likewise, today we know that the

H47777 sequence contains a small region of protein coding and intronic sequence. However until the gene was identified, there would be no way to identify this sequence as encoding a bona-fide protein let alone the BRCA2 protein. Defendants have not identified any reason why persons of ordinary skill in the art would choose these ESTs out of the hundreds or even thousands of ESTs (contained in the region that the BRCA2 gene was believed to map) to design single-stranded primers to determine the sequence of BRCA2 by PCR.

V. The Asserted Method Claims Are Novel and Not Obvious

91. I have reviewed Defendants' arguments, including the opinions expressed in the Bowcock and Gregory Declarations, asserting that claim 5 of the '721 patent, claims 2 and 4 of the '155 patent, claims 7 and 8 of the '441 patent, and claim 4 of the '857 patent are obvious (collectively, the "method claims"). I disagree with Defendants' conclusions.

92. Defendants and their experts suggest that based on the art available at the time of the inventions, all that was required to discover BRCA1 and BRCA2 was to follow known techniques. (*See, e.g.* Gregory Decl. ¶ 22.) For example, Defendants suggest that by 1993, the range of genomic material from which BRCA1 would be isolated had been narrowed, and that the techniques for determining BRCA1 were all known. (Opposition Brief at 61-63.) However, the art Defendants rely on is not so clear cut.

A. The Location of BRCA1 Was Not Predictable or Reasonably Expected Based on the Available Literature

93. In the 1993-1994 timeframe, uncertainty existed in the field about the region in which BRCA1 was located.

94. A 1993 article by Feunteun et al.⁴ suggests that the breast-ovarian cancer locus lies between markers D17S588 and D17S579, a region that is greater than four million base pairs. A 1993 article by Easton et al. (Gregory Dec. Ex. U at abstract) suggests that BRCA1 may be found in a region spanning about 8.3 cM in men and 18 cM in women.

95. A 1993 article by Bowcock et al. (Gregory Ex. V) reports that BRCA1 lay in a 4 CM interval on chromosome 17q12-21 flanked by markers THRA1 and D17S183. (Bowcock at 718.) This region is different than the 4-million base pair region suggested by Feunteun.

96. Later in 1993, the Kelsell et al. article (Gregory Ex. E) identified markers D17S857 and S17S183 as the boundaries for BRCA1. (Kelsell at 1825.) The Kelsell article postulates that BRCA1 therefore lay in a region of 1-1.5 Mb in length based on the mapping information developed in its investigation. (Mb stands for mega base pairs, which is 1,000,000 base pairs.) The region identified by Kelsell is distal to a marker identified by Bowcock et al.

97. A 1994 article by Smith et al.⁵ identifies a different potential region on chromosome 17q for BRCA1. (See Smith at 74.) The Smith article identifies marker D17S702 as the potential proximal marker of BRCA1 and marker EDH17B as the potential distal marker of BRCA1. (*Id.* (“Thus, although not conclusive, the evidence favours the interpretation that BRCA1 lies proximal to EDH17B and distal to D17S702. This is an interval of 1cM or less, and is a significant narrowing of the region over that reported previously (Bowcock et al., 1993; Simare et al., 1993; Kelsell et al., 1993).”).)

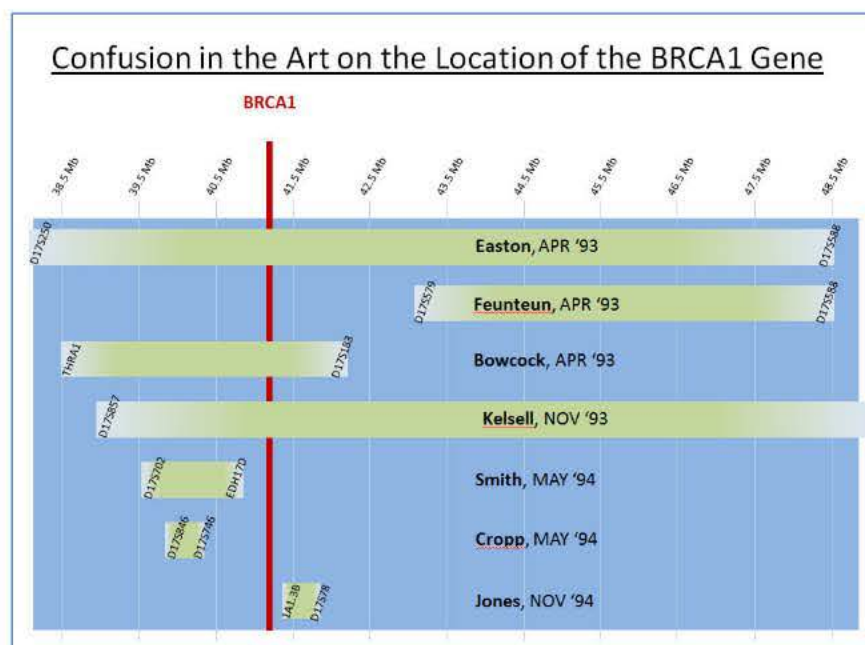
⁴ Feunteun et al., “A Breast-Ovarian Cancer Susceptibility Gene Maps to Chromosome 17q21,” Am. J. Hum. Genet., 52:736-42 (1993) (Ex. I).

⁵ Smith et al., “Localisation of the Breast-Ovarian Cancer Susceptibility Gene (BRCA1) on 17q12-21 to an Interval of >1 cM,” Genes Chromosomes & Cancer, 19:71-76 (1994) (Ex. J).

98. A 1994 article by Cropp et al.⁶ suggested that BRCA1 may fall within the markers D17S846 and D17S746, which is a region of less than 100,000 base pairs. (Cropp at 2549.)

99. Ultimately, Myriad discovered the location of BRCA1, and it does not lie in any of the regions suggested by Feunteun, Smith, Cropp or Jones.

100. As shown in the figure below, when these various regions identified in the literature as potentially containing BRCA1 are compared, there are some regions that overlap, and other regions that do not. In my opinion, based on the art available, a skilled artisan would not have a reasonable expectation of success that any of these regions, or any other region, would contain what was ultimately discovered as BRCA1.



101. And just after Myriad filed its patent, a different set of researchers published an article suggesting that BRCA1 lay in yet a different region of BRCA1.⁷ Jones et al. identified

⁶ Cropp et al., "Evidence for Involvement of BRCA1 in Sporadic Breast Carcinomas," Cancer Research, 54:2548-51 (May 1994) (Ex. K).

⁷ Jones et al., "The detailed characterization of a 400 kb cosmid walk in the BRCA1 region: identification and localization of 10 genes including a dual-specificity phosphatase," Human Mol. Genetics, 3(11):1972-34 (1994) (Ex. L).

BRCA1 as potentially lying within a 400 kB region between markers 1A1.3B and D17S78.

(Jones at 1932.)

102. Because there was confusion about where BRCA1 was located, there would be no reasonable expectation of success as to where BRCA1 was in fact located. A skilled artisan could have proceeded in several different directions to look for BRCA1 based on the available literature with no reasonable expectation of success.

103. The lack of a reasonable expectation of success in identifying BRCA1 is further demonstrated by other commentary in the field suggesting that there existed a number of different candidate genes for BRCA1. For example, in 1990 Dr. King identified a potential region containing BRCA1, but noted that a hundred or more genes likely lay in that region. (Gregory Ex. F at 89.) She also emphasized 17- β hydroxysteroid dehydrogenase as a “most biologically plausible candidate gene,” but it did not turn out to be BRCA1. Also in 1990, Hall identified several plausible candidate genes. (Gregory Ex. H at 1688-89.) In 1992, Hall postulated that there may be more than one gene responsible for inherited breast cancer, and identified several “plausible candidate genes,” none of which turned out to be BRCA1. (Gregory Ex. I at 1240, 1242.)

104. In my opinion, persons of ordinary skill in the art may first desire to investigate these “plausible genes” to determine whether they were BRCA1 and rule them out before selecting a specific chromosomal region to investigate. In fact, I understand that Dr. King herself took this approach and became frustrated when those candidates did not pan out.

105. Further leading to confusion about the nature and location of BRCA1, just two months before Myriad filed the '282 patent, another set of investigators hypothesized that the 17HSDI "pseudogene" was a potential candidate for BRCA1.⁸

106. I also note that the use of positional cloning techniques does not predictably result in identifying the targeted disease-causing gene. For example, in the search for the disease-causing CF gene, the Williamson group used positional cloning techniques based on linkage analyses to identify a chromosomal fragment to identify the disease-causing gene. The results of this work were published in *Nature*, one of the leading scientific publications.⁹ As it turned out, however, the Williamson group's candidate gene was later demonstrated not to be related to cystic fibrosis.¹⁰

B. The Literature Did Not Suggest Clear-Cut Methods For Identifying Genes

107. With respect to the techniques available in the field at the time of the inventions, I disagree that they could be employed in a straightforward manner to identify BRCA1. (*See* Gregory Dec., ¶ 120.)

108. For example, the Bowcock article (Bowcock Ex. G) describes efforts made toward discovering BRCA1, including, for example, looking at familial versus sporadic forms of breast cancer, positional cloning, refinement of the gene location genetically, physical cloning of the region, and using cDNA libraries. The Bowcock article identifies many drawbacks and problems associated with these methods.

⁸ Touitou et al., "17 Beta Hydroxysteroid Dehydrogenase 1 "Pseudogene" Is Differentially Transcribed: Still a Candidate for the Breast-Ovarian Cancer Susceptibility Gene," *Biochem. Biophys. Res. Comm.*, 201(3):1327-32 (June 1994) (Ex. M).

⁹ Estivill et al., "A candidate for the cystic fibrosis locus isolated by selection for methylation-free islands," *Nature*, 326:840-45 (1987) (Ex. N).

¹⁰ Rommens et al., "Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping," *Science*, 245:1059-65 (1989) (Ex. O).

109. Bowcock states that refining the gene location genetically “must be treated with some caution” because, for common diseases like breast cancer, “one cannot discriminate between bona-fide recombinant individuals and individuals who do not carry an altered BRCA1 but develop a non-familial (sporadic) form of the disease.” (Bowcock at 127.)

110. Bowcock identifies physical cloning of the region using YAC screens with STS as a potential technique for discovering BRCA, but states that “YACs are not without their problems,” and goes on to describe some of those problems. (Bowcock at 127-28.) Although not appreciated before Myriad identified BRCA1, the locus in and around BRCA1 contained an unusually high number of Alu repeats. The presence of those sequences would enhance the already limiting property of YACs known as recombination, resulting in YACs that could ultimately provide incorrect ordering of the genome (missing pieces, duplications, noncontiguous chromosome sequences).

111. Bowcock focuses on the use of YACS, but in passing mentions other approaches, like P1 and BAC clones, and remarks that they have not been used “as extensively” in physical mapping projects. (Bowcock at 127.) In fact, the inventors used P1 and BAC DNA cloning vectors to ultimately discover BRCA1. Because of this choice they had to piece together a larger number of DNA fragments to ultimately identify BRCA1. This decreased the recombination events associated with Alu repeats described above with the use of YACs.

112. Bowcock also explains problems with screening for BRCA1 in cDNA libraries. First, the choice of cDNA library is “critical” because “one does not know at the outset in which tissue [BRCA1] is expressed.” Another “issue in screening for genes is that if the gene on is searching for is transiently expressed, the stage at which the RNA is extracted from particular tissue is critical.” Even if the gene is expressed, without knowing the abundance of BRCA1

mRNA, it is not known whether one will be able to detect the mRNA sequence in a cDNA library. The Bowcock article also describes hurdles in searching for mutations in a suitable set of cDNAs. A mutation may be “too small to detect by Southern blotting.” (Bowcock at 131.) Instability of RNA impedes the process. And, if BRCA1 were “encoded by a large gene, it may not be straightforward to identify mutations.” (Bowcock at 131.)

C. Claims 7 and 8 of the '441 Patent Are Not Obvious Nor Anticipated

113. I understand that claim 7 of the '441 patent depends from claim 1, which reads:

A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises 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, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.

114. Claim 7 of the '441 patent recites:

The method of claim 1 wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.

115. Claim 8 of the '441 patent depends from claim 7 and recites:

The method of claim 1 wherein a germline nucleic acid sequence is compared by amplifying all or part of a BRCA1 gene from said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids.

116. I understand that Defendants have asserted that claims 7 and 8 are obvious because they contend that locating the BRCA1 gene would have been obvious given the state of the art in the early-to-mid 1990s. I disagree for the reasons described above. A person of ordinary skill in the art would not have had a reason to select any one of the reported and varying regions within which BRCA1 may lie over other regions because there was confusion and

conflicting reports about where BRCA1 was located. Further, the literature indicated that there were already several postulated “candidate genes,” so a person of ordinary skill in the art may have pursued those candidates in their efforts. Whichever path an artisan ultimately may have chosen, they would not have reasonably expected to successfully find BRCA1. The techniques employed to obtain the gene are imperfect, and missteps along the way can be detrimental. And, even when one thinks they have found the gene, that may still turn out to be wrong, as in the case of the cystic fibrosis gene described above.

117. I understand that Defendants have asserted that claim 8 is anticipated by Bowcock’s February 1993 article. (Opposition Brief at 70, footnote 16; Bowcock Dec., ¶¶ 93-94.) I disagree. The Bowcock article does not disclose the sequence of wild-type BRCA1 gene, which is an element of claim 1, and thus claim 8. Accordingly, it cannot and does not anticipate claim 8.

D. Claim 4 of the ’857 Patent Is Not Anticipated Nor Obvious

118. Claim 4 of the ’857 patent depends from claim 2, which reads as follows:

A method for diagnosing a predisposition for breast cancer in a human subject which comprises 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, wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer.

119. Claim 4 adds the additional limitation that “the detection in the alteration in the germline sequence is determined by an assay selected from the group consisting of” 13 different assays.

120. I understand that Defendants assert that claim 4 of the ’857 patent is both anticipated and obvious based on the alleged prior art. I disagree.

121. Dr. Gregory argues that claim 4 of the '857 patent is anticipated by the Wooster 1995 article. Claim 4 which requires comparison of a sample sequence against wild-type BRCA2 sequence. The Wooster article does not disclose any DNA sequence for the BRCA2 gene. At least because the Wooster 1995 article does not disclose the BRCA2 sequence it cannot and does not anticipate claim 4.

122. Dr. Gregory also argues that the June 1995 Schutte article anticipates claim 4. Like the Wooster 1995 article, the Schutte June 1995 article does not disclose the DNA sequence of BRCA2. Rather, it discloses that the BRCA2 sequence could possibly be located within a 6 cM region of chromosome 13. At least because Schutte's June 1995 article does not disclose the BRCA2 sequence it cannot and does not anticipate claim 4, which requires comparison of a sample sequence against wild-type BRCA2 sequence.

123. Dr. Gregory asserts that claim 4 is rendered obvious separately by the Wooster 1994 article, a public release of a PAC Contig, and publicly available PAC clones that he alleges he used in the laboratory as part of his contribution to the findings published in the Wooster 1995 article. In my opinion, none of these disclosures renders claim 4 obvious.

124. As Dr. Gregory notes, the Wooster 1994 article identifies a 6 cM region within which he suggested that BRCA2 may ultimately be found. Dr. Gregory identifies a smaller region between D13S260 and D13S267 that he suggests would be a logical starting point to pinpoint BRCA2. But as described above, a person of ordinary skill in the art would not have had any reasonable expectation that they would successfully identify BRCA2 at any of these locations within a 6 cM region. Dr. Gregory implicitly acknowledges this, explaining that a skilled artisan may "walk" between the markers. If one expected to find the gene in a specific location, there would be no need to walk between the markers. Further, the same difficulties and

complexities describe above about positional cloning and other techniques that may be used to identify a gene apply here.

125. The PAC Contig public releases Dr. Gregory identifies (Gregory Exs. K & N) do not provide any sequence information for the PAC Contig. It indicates that sequencing is still in progress. These releases only indicate that the PAC Contig was thought to contain BRCA2. But as described above, in light of the unpredictability in the field and the techniques used to identify genes, in my opinion a person of ordinary skill in the art would not have had a reasonable expectation that this 900 kb region would contain BRCA2, or which sequences in that region were part of the BRCA gene. One would still have to identify whether there are mutations that segregate with disease to identify BRCA2.

126. Dr. Gregory also argues that claim 4 is obvious over publicly available PAC clones that were used in research to try to identify BRCA2 by constructing a PAC contig across D13S260 and D13S267. Dr. Gregory's description omits the steps of identifying the disease-causing mutation. If Dr. Gregory is relying on Dr. Wooster's work to show that he had identified BRCA2 in 1995, I note that his 1995 paper did not publish the DNA sequence of BRCA2, and that sequence was later found incorrect. Had persons of ordinary skill in the art used these same PACs, they may likely have run into the same problems as Wooster and incorrectly identify—and thus not actually identify—the BRCA2 sequence. If people had relied on this sequence, they may not have identified critical disease-causing mutations or may have included mutations that would be irrelevant.

E. Claims 2 and 4 of the '155 Patent Are Not Obvious

127. Claim 2 of the '155 patent reads as follows:

A method of identifying individuals having a BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer comprising:

a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene;

b) sequencing said amplified fragment by dideoxy sequencing;

c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced;

d) comparing the sequence of said amplified DNA to the sequence of SEQ. ID. NO: 1;

e) determining the presence or absence of each of the following polymorphic variations in said individual's BRCA1 coding sequence:

AGC and ACT at position 2201,
TTG and CTG at position 2430,
CCG and CTG at position 2731,
GAA and GGA at position 3232,
AAA and AGA at position 3667,
TCT and TCC at position 4427,
and ACT and GGT at position 4956;

f) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 wherein the presence of any of the said polymorphic variations and the absence of a polymorphism outside of positions 2201, 2430, 2731, 3232, 3667, 4427, and 4956, is correlated with an absence of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

128. Claim 4 of the '155 patent reads as follows:

A method of detecting an increased genetic susceptibility to breast and ovarian cancer in an individual resulting from the presence of a mutation in the BRCA1 coding sequence, comprising:

a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene;

b) sequencing said amplified fragment by dideoxy sequencing;

c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced;

d) comparing the sequence of said amplified DNA to the sequence of SEQ. ID. NO: 1;

e) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 to determine the presence or absence of polymorphisms in said individual's BRCA coding sequences wherein a polymorphism which is not any of the following:

AGC or AGT at position 2201,
 TTG or CTG at position 2430,
 CCG or CTG at position 2731,
 GAA or GGA at position 3232,
 AAA or AGA at position 3667,
 TCT or TCC at position 4427,
 and AGT or GGT at position 4956;

is correlated with the potential of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

129. I understand that SEQ ID NO:1 as used in claims 2 and 4 refers to the BRCA1 consensus DNA sequence. (*See, e.g.*, '155 patent at col. 3, ll. 46-47; *id.* at col. 14, ll. 60-62.) According to the patent, the consensus DNA sequence of BRCA1 was determined by sequencing BRCA1 from five normal individuals. (*See* '155 patent, Example 8.) The consensus sequence is characterized by seven polymorphisms listed in Table IV of the patent. (*See* '155 patent at col. 12, ll. 53-60; *id.* at tbl. iv.)

130. Polymorphisms are one or more variations in a specific sequence of DNA. Polymorphisms can be benign or neutral (i.e., have no effect). Polymorphisms that cause disease are generally referred to as a mutation. (*See* '155 patent at col. 2, ll. ("A Consensus Normal DNA sequence will make it possible for true mutations to be easily identified or differentiated from polymorphisms"); *id.* at col. 3, ll. 49-50 ("Many mutations and normal polymorphisms have already been reported in the BRCA1 gene.")) I understand that the seven polymorphisms listed in claims 2 and 4 of the '155 patent are benign/neutral polymorphisms, and are not disease causing. *See id.* at Table IV (describing seven polymorphic changes in "BRCA1 normal genes").

131. I understand that Defendants have asserted that claim 2 and 4 of the '155 patent are obvious based on the Miki article, the Friedman article and the '282 patent. I disagree.

132. The Miki article (Bowcock Decl., Ex. H) reports on probable predisposing mutations segregating with BRCA1. Those mutations include a base pair deletion, a base pair insertion, a stop codon, a missense substitution, and a regulatory mutation. (Miki at 68.) Miki also reports a few neutral polymorphisms in BRCA1. (Miki at 69, tbl. 3.) None of the neutral polymorphisms disclosed in Miki correspond to the claimed neutral polymorphisms in the '155 patent. Miki does not disclose a consensus sequence of BRCA1.

133. The Friedman article (Bowcock Decl., Ex. L) reports on additional probable predisposing mutations segregating with BRCA1. Friedman also reports a handful of neutral polymorphisms, including a few of the normal polymorphisms identified in claim 2. Friedman at Table 3. Friedman does not disclose a consensus sequence of BRCA1.

134. The '282 patent discloses the BRCA1 sequence and states that 11 common polymorphisms were identified in screening 5 kindreds to determine the BRCA1 sequence. *See* '282 patent Example 8; *id.* at col. 56, ll. 29-30. The '282 patent does not describe what those 11 common polymorphisms were, and does not disclose a consensus sequence of BRCA1.

135. In my opinion, the disclosures of Miki, Friedman and the '282 patent do not render the methods of claims 2 and 4 obvious. First, none of these references suggest determining the consensus sequence of BRCA1 or using it to determine whether or not an individual may be at risk of cancer. Second, even if a person of ordinary skill in the art would have had a reason to construct a consensus sequence, that person would not have had a reasonable expectation about what common polymorphisms would be encompassed by the consensus sequence. Indeed, none of these references identified the seven common

polymorphisms that the inventors determined comprised the consensus sequence. And given the variability of polymorphisms reported among these references, it is not predictable which polymorphisms would make up the consensus sequence. The Miki article itself states that “[t]he large size and fragmented nature of [BRCA1] coding sequence will make exhaustive searches for new mutations challenging.” (Miki at 172.) Friedman also speaks to the complexities of screening for inherited BRCA1 mutations. (Friedman at 403.) Moreover, depending on what polymorphisms are seen in working towards creating a consensus sequence, one cannot always predict if a polymorphism resulting in a change in the amino acid sequence would be neutral or not. For example, sometimes non-conserved amino acids do not implicate disease, other times they do. BRCA1 is illustrative: some of the neutral polymorphisms are conserved amino acid changes (e.g., position 3667, LYS → ARG), whereas others are non-conserved amino acid changes (e.g., position 2731, PRO → LEU).

136. Beyond finding a polymorphism, a skilled artisan would also have to determine its effect. Polymorphisms in introns could cause changes in splicing or expression control, and one of skill in the art could only determine if such a polymorphism had a deleterious effect by observing the effect of the polymorphism in familial population. For polymorphisms found in exons, one would have to determine whether the polymorphism caused a change in the amino acid sequence. If it did, they would have to go back to family data to see if there is correlation between polymorphism and disease.

137. Given the above, it would not have been obvious to develop the methods of claims 2 and 4 based on Miki, Friedman, or the '282 patent.

138. I also understand that Dr. Gregory has asserted that the method of claim 2 is not new in view of either of Miki, Friedman, or the '282 patent (i.e., is anticipated by any of those

references) because each “necessarily determined the presence or absence of sequence variations in the BRCA1 coding sequence listed at the positions in claim 2.” *See* Gregory Dec., ¶¶ 140, 149, 157. This argument ignores that the method of claim 2 requires comparing an individual’s sequence against the consensus sequence and the seven listed normal polymorphisms. None of these references identifies the consensus sequence or the seven listed normal polymorphisms, so none of these references can or do disclose the method of claim 2.

F. Claim 5 of the ’721 Patent Is Not Obvious

139. Claim 5 of the ’721 patent depends from claim 1, which reads as follows:

A method for determining an omi haplotype of a human BRCA1 gene comprising: (a) determining the nucleotide sequence of the BRCA1 gene or fragment thereof from at least one female individual with a family history which indicates a predisposition to breast cancer, (b) comparing the determined nucleotide sequence from said female individual to SEQ ID NO: 263, and (c) determining the presence of the following nucleotide variations: thymine at nucleotides 2201 and 2731, cytosine at nucleotides 2430 and 4427, and guanine at nucleotides 3232, 3667 and 4956, wherein the presence of the nucleotide variations in the determined nucleotide sequence indicates the omi1 haplotype.

140. Claim 5 adds this additional limitation to claim 1:

The method of claim 1 wherein the BRCA1 gene or fragment thereof is amplified prior to nucleotide sequencing.

141. I understand SEQ ID NO:263 to correspond to the omi¹ sequence of BRCA1. *See* ’721 patent, col. 4 at 7-8. The patent describes this sequence as “a normal sequence which is the most likely sequence to be found in the majority of the normal population.” *Id.* at col. 4, ll. 29-32. The patent also states that two additional haplotypes, BRCA1^{omi2} and BRCA2^{omi3} had been identified. *Id.* at col. 25, ll. 10-12. These haplotypes depend on the frequency with which an allelic variation occurs at 7 neutral polymorphic sites in a normal individual. *See id.* at col. 23, l. 63 to col. 25, l. 38.

142. I understand that Defendants assert that the method of claim 5 of the '721 patent is obvious over each of Miki, Freidman, and the '282 patent, each of which disclose some neutral polymorphisms, but none of which discloses the DNA sequence of SEQ ID NO:263 nor suggests determining the omi¹ sequence. I disagree for the same reasons that I do not consider claims 2 and 4 of the '155 patent obvious.

G. Objective Considerations Support the Nonobviousness of the Asserted Claims

143. As described above, I understand from Plaintiffs' counsel that a determination of whether a patent claim is obvious requires consideration of what is known as objective evidence of non-obviousness. This evidence includes such common sense factors as commercial success, fulfillment of a long-felt need, failure of others to make the claimed inventions, and praise for the invention by others in the field. It is my opinion that all of these factors further support my opinion that the asserted claims of the patents are not obvious.

144. In my opinion, there was a long-felt need for the claimed inventions, which allow, for the first time, patients to learn their risk for hereditary breast or ovarian cancers and plan appropriate treatment and prevention strategies with their physicians. This long-felt need is also shown by the large number of researchers who were attempting to discover the BRCA genes in the same timeframe as Myriad. The failure of those other researchers to achieve the inventions also demonstrates the difficulty and unpredictability of the field and the non-obviousness of the inventions.

145. I am also aware of substantial praise and recognition for the claimed inventions in the field. The sequencing of the BRCA genes and development of the first genetic test for mutations in those genes has been widely hailed as a significant medical advance.

146. It is also my understanding Myriad's BRACAnalysis® tests that use the claimed inventions have been very successful and a source of significant revenue.

VI. CLAIM 4 OF THE '155 PATENT IS SUPPORTED BY AN ADEQUATE WRITTEN DESCRIPTION

147. I understand that Defendants assert that the specification of the '155 patent does not adequately describe a sufficient number of mutations that lead to increased susceptibility to breast cancer. I further understand that because of this alleged deficiency, Defendants contend that claim 4 of the '155 patent is not properly described in the patent.

148. Claim 4 of the '155 patent reads in full:

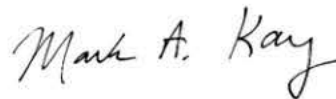
A method of detecting an increased genetic susceptibility to breast and ovarian cancer in an individual resulting from the presence of a mutation in the BRCA1 coding sequence, comprising:

- a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene;
- b) sequencing said amplified fragment by dideoxy sequencing;
- c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced;
- d) comparing the sequence of said amplified DNA to the sequence of SEQ. ID. NO: 1;
- e) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 to determine the presence or absence of polymorphisms in said individual's BRCA coding sequences wherein a polymorphism which is not any of the following:

- AGC or AGT at position 2201,
- TTG or CTG at position 2430,
- CCG or CTG at position 2731,
- GAA or GGA at position 3232,
- AAA or AGA at position 3667,
- TCT or TCC at position 4427,
- and AGT or GGT at position 4956;

is correlated with the potential of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

149. In my opinion, Defendants' written description argument is based on a reading of claim 4 with which I disagree. As I read claim 4, the method ultimately provides that if after comparing an individual's coding sequence of BRCA1 with the sequence of SEQ ID NO:1 (the consensus sequence, '155 patent, col. 2, ll. 19-20; *id.* at col. 3, ll. 45-46), any polymorphism is found that is not one of the seven listed in the claim, then that person has a potential of increased genetic susceptibility to breast or ovarian cancer. Based on my reading of the claim, the written description adequately describes claim 4. The specification describes the seven polymorphisms in the claim and identifies them as normal. '155 patent at tbl. iv; *id.* at col. 15, l. 48 to col. 16, l. 2; *id.* at col. 16, l. 67 to col. 17, l. 5; *id.* at col. 18, ll. 26-41. Since the claim only requires identification of any polymorphism aside from these, there is no need for the patent to describes examples of them; it is clear what those polymorphisms would be.



Dated: August 30, 2013

Signed: _____

Mark A. Kay, M.D., Ph.D.

CERTIFICATE OF SERVICE

On this 30th day of August 2013, I certify that I electronically filed the foregoing DECLARATION OF MARK ALLAN KAY, M.D., PH.D. with the Clerk of Court using the CM/ECF system that will send an electronic notification to counsel of record for all of the parties.

/s/ David G. Mangum