

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEDX, INC.
Petitioner

v.

UNIVERSITY OF UTAH *et al.*
Patent Owner

U.S. Patent No. 5,753,441

Inter Partes Review Case No. Unassigned

DECLARATION OF MADHURI HEGDE, PH.D., FACMG

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I, Madhuri Hegde, Ph.D., FACMG, hereby declare as follows.

I. Introduction

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been retained as an expert witness on behalf of GENEDX, INC. for the above-captioned *inter partes* review (IPR). I am being compensated for my time in connection with this IPR at my standard legal consulting rate, which is \$350 per hour.

3. I understand that the petition for *inter partes* review involves U.S. Patent No. 5,753,441 ("the '441 patent"), GDX1001, which resulted from U.S. Appl. No. 08/488,011 ("the '011 application"), filed June 7, 1995¹, which is a continuation-in-part of U.S. Appl. No. 08/409,305, filed March 24, 1995, which is a continuation-in-part of U.S. Appl. No. 08/348,824, filed November 29, 1994, which is a continuation-in-part of U.S. Appl. No. 08/308,104, filed September 16, 1994, which is a continuation-in-part of U.S. Appl. No. 08/300,266, filed September 2, 1994, which is continuation-in-part of U.S. Appl. No. 08/282,221, filed August 12, 1994. The '441 patent lists Mark H. Skolnick, David E. Goldgar,

¹ The filing date of the '011 application was corrected to June 7, 1995 in a Certificate of Correction. GDX1009, p. 507.

Yoshio Miki, Jeff Swenson, Alexander Kamb, Keith D. Harshman, Donna M. Shattuck-Eidens, Sean V. Tavtigian, Roger W. Wiseman, and P. Andrew Futreal as inventors. The '441 patent issued on May 19, 1998 from the '011 application. I understand that, according to the USPTO records, the '441 patent is currently assigned to University of Utah Research Foundation and United States of America as represented by the secretary of the Department of Health and Human Services (collectively, "the patent owner").

4. In preparing this Declaration, I have reviewed the '441 patent and each of the documents cited herein, in light of general knowledge in the art. In formulating my opinions, I have relied upon my experience, education and knowledge in the relevant art. In formulating my opinions, I have also considered the viewpoint of a person of ordinary skill in the art ("POSA") (*i.e.*, a person of ordinary skill, defined further below in Section IV) prior to August 12, 1994 or June 7, 1995.

II. My Background and Qualifications

5. I am an expert in the field of recombinant DNA technology, medical genetics, and genetic diagnostics. I received my B.S. and M.Sc. in Microbiology/Genetics from the University of Bombay, Bombay, India in 1987 and 1992, respectively. I was a Senior Research Fellow at University Hospital, University of Bombay, Bombay, India in 1992-1995 and Scientific Officer at DNA

Diagnostic Laboratory, Auckland Hospital, Auckland, New Zealand in 1995-1996. I received my Ph.D. in Applied Science, with thesis titled "Molecular-Based Diagnostics of Inherited Disorders: Multiple Exon and Trinucleotide Repeat Expansion Analysis," from the University of Auckland, Auckland, New Zealand in 2000 and I was a Postdoctoral Fellow in Clinical Molecular Genetics at the Department of Human Genetics at Baylor College of Medicine, Houston, Texas in 2000-2003.

6. I became an Assistant Professor in the Department of Human Genetics at Baylor College of Medicine, Houston, Texas in 2003, and then an Assistant Professor in the Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia in 2006. I was an Associate Professor in the Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia in 2009-2013, and I became a Professor in the Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia in 2013. I am currently an Adjunct Associate Professor since 2004, at the School of Health Sciences, University of Texas M.D. Anderson Cancer Center, Houston, Texas.

7. I have also been a Scientific Director at DNA Diagnostic Laboratory, Auckland Hospital, Auckland, New Zealand in 1996-2000; an Assistant Laboratory Director in 2001-2006 and a Co-Director in 2006 at DNA Diagnostic Laboratory, Department of Human Genetics, Baylor College of Medicine,

Houston, Texas; and, a Senior Laboratory Director in 2006-2010 and Scientific Director in 2010-2012 at Emory Genetics Laboratory, Atlanta, Georgia. Since, 2012, I am an Executive Director at Emory Genetics Laboratory, Atlanta, Georgia.

8. I am American Board of Medical Genetics certified Clinical Molecular Geneticist. I have received numerous grants and awards related to my research in recombinant DNA technology, medical genetics, and genetic diagnostics. I have published more than 74 research articles and several book chapters related to recombinant DNA technology, medical genetics, and genetic diagnostics, with a focus on novel gene discovery and functional analysis of sequence variants in disease associated genes. I also have an extensive research experience related to recombinant DNA technology, medical genetics, and genetic diagnostics.

9. Accordingly, I am an expert in the field of recombinant DNA technology, medical genetics, and genetic diagnostics. My full background is detailed in my *curriculum vitae*. GDX1003.

III. List of Documents I Considered in Formulating My Opinions

10. In formulating my opinions, I have considered all the documents cited herein, including the following documents. I have reviewed the Declarations of Mark Allan Kay, M.D., Ph.D. (GDX1015) and Gregory C. Critchfield, M.D.

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(GDX1014), and I disagree with their conclusions. For the reasons set forth in detail below, I reach the conclusions offered herein.

<i>GDX Exhibit #</i>	<i>Description</i>
1001	U.S. Patent No. 5,753,441 (filed on January 5, 1996; issued on May 19, 1998)
1004	Friedman, L.S., <i>et al.</i> , "Confirmation of <i>BRCA1</i> by analysis of germline mutations linked to breast and ovarian cancer in ten families," <i>Nature Genetics</i> 8: 399-404 (1994)
1005	Miki, Y., <i>et al.</i> , "A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene <i>BRCA1</i> ," <i>Science</i> 266: 66-71 (1994)
1006	Bowcock, A.M., "Molecular cloning <i>BRCA1</i> : a gene for early onset familial breast and ovarian cancer," <i>Breast Cancer Research and Treatment</i> 28: 121-135 (1993)
1007	Kelsell, D.P., <i>et al.</i> , "Genetic analysis of the <i>BRCA1</i> region in a large breast/ovarian family: refinement of the minimal region containing <i>BRCA1</i> ," <i>Human Mol. Genetics</i> 2: 1823-1828 (1993)
1008	Easton, D.F., <i>et al.</i> , "Genetic Linkage Analysis in Familial Breast and Ovarian Cancer: Results from 214 Families," <i>Am. J. Hum. Genet.</i> 52: 678-701 (1993)
1009	File History for U.S. Patent No. 5,753,441
1010	File History for U.S. Patent Publ. Appl. No. 08/409,305
1011	File History for U.S. Patent Publ. Appl. No. 08/300,266
1012	PACER List of Associated Cases for 14-md-02510, available at https://ecf.utd.uscourts.gov/cgi-bin/qryAscCases.pl?89779 (last accessed on August 15, 2014)
1013	Myriad Genetics 2013 Annual Report, <i>downloaded from</i> http://files.shareholder.com/downloads/MYGN/3399011197x0x699241/42B88246-0E90-4F5C-9697-3DF98027C46D/2013_Annual_Report.pdf
1014	Declaration of Dr. Gregory C. Critchfield, filed December 23, 2009, in <i>Assoc. for Molecular Pathology v. U.S. Patent & Trademark Office</i> , No. 09-cv-04515-RWS (S.D.N.Y.)
1015	Declaration of Mark Allan Kay, M.D., Ph.D., filed August 31, 2013, in <i>University of Utah Research Foundation v. Ambry Genetics Corp.</i> , No. 13-cv-00640-RJS (D. Utah)

1016	Eng, C., <i>et al.</i> , "Interpreting epidemiological research: blinded comparison of methods used to estimate the prevalence of inherited mutations in <i>BRCA1</i> ," <i>J. Med. Genet.</i> 38: 824-833 (2001)
1017	Bowcock, A.M., "Molecular cloning of <i>BRCA1</i> : a gene for early onset familial breast and ovarian cancer," <i>Breast Cancer Res Treat</i> 28: Abstract (1993)
1018	Cotton, R.G., "Current method of mutation detection," <i>Mutation Research</i> 285: Abstract (1993)
1019	Sambrook, J., <i>et al.</i> , "Molecular Cloning, A Laboratory Manual," 2 nd Ed., Cold Spring Harbor Laboratory Press, §§ 5.28-5.32, 6.36-6.48, 13.6-13.77, and 14.5-14.21 (1989)
1020	Cotton, R.G.H., "Current methods of mutation detection," <i>Mutation Research</i> 285: 125-144 (1993)
1021	File History for U.S. Patent Publ. Appl. No. 08/308,104
1022	File History for U.S. Patent Publ. Appl. No. 08/289,221
1023	Kelsell, D.P. <i>et al.</i> , "Genetic analysis of the <i>BRCA1</i> region in a large breast/ovarian family: refinement of the minimal region containing <i>BRCA1</i> ," <i>Hum. Mol. Genet.</i> 2: Abstract (1993)
1024	Smith <i>et al.</i> , "Complete Genomic Sequence and Analysis of 117 kb of Human DNA Containing the Gene <i>BRCA1</i> ." <i>Genome Research</i> 6(11): 1029-49 (Nov. 1996)
1025	Alberts, <i>et al.</i> , "Molecular Biology of the Cell," 3 rd Ed., pp. 98-99, 104-106, 242-243, 292-293, 314-317, 337, 339, 1072-1073, G-5-G-6, G-10, G-17 (1994)
1026	" <i>BRCA1</i> gene," <i>Genetics Home Reference: Your Guide to Understanding Genetic Conditions</i> , National Library of Medicine's Website for Consumers, available at http://ghr.nlm.nih.gov/gene/BRCA1 (last accessed Jul. 22, 2014)
1027	King, "Breast Cancer genes: how many, where and who are they?," <i>Nature Genetics</i> 2: 89-90 (October 1992)
1028	Hall, J., <i>et al.</i> , "Linkage of early-onset familial breast cancer to chromosome 17q21," <i>Science</i> 21: 1684-1689 (1990)
1029	Bowcock, A.M., <i>et al.</i> , "THRA1 and D17S183 Flank an Interval of <4 cM for the Breast-Ovarian Cancer Gene (<i>BRCA1</i>) on Chromosome 17q21," <i>Am J. Hum. Genet.</i> 52: 718-722 (1993)

1030	"Centimorgan," <i>Genetics Home Reference: Your Guide to Understanding Genetics Conditions</i> , National Library of Medicine's Website for Consumers, available at http://ghr.nlm.nih.gov/glossary=centimorgan (last accessed Aug. 12, 2014)
1031	"Homo sapiens BRCA1 (BRCA1) gene, complete cds; ribosomal protein L21-like protein (rpL21) pseudogene, complete sequence; Rho7 (Rho7) and Vatl (Vatl) genes, complete cds; and unknown (ifp35) gene, exons 1 through 3 and partial cds," <i>National Center for Biotechnology Information</i> available at http://www.ncbi.nlm.nih.gov/nuccore/1698398 (last accessed on Aug. 12, 2014)
1032	Cropp, C., <i>et al.</i> , "Evidence for Involvement of BRCA1 in Sporadic Breast Carcinomas," <i>Cancer Research</i> 54: 2548-2551 (1994)
1033	Smith, S., <i>et al.</i> , "Localisation of the Breast-Ovarian Cancer Susceptibility Gene (BRCA1) on 17112-21 to an Interval of ≤ 1 cM," <i>Genes, Chromosomes & Cancer</i> 10: 71-76 (1994)
1034	Jones, K., <i>et al.</i> , "The detailed characterization of a 400 kb cosmid walk in the <i>BRCA1</i> region: identification and localization of 10 genes including a dual-specificity phosphatase," <i>Human Molecular Genetics</i> 3:1927-1934(1994)
1035	File History for U.S. Patent Publ. Appl. No. 08/348,824

IV. Person of Ordinary Skill in the Art

11. I understand that a person of ordinary skill in the art ("POSA") is a hypothetical person who is presumed to be aware of all the pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the subject matter of the '441 patent, a POSA would typically have had (i) a Ph.D. in genetics, molecular genetics, or molecular biology, or in a related field in the biological sciences, and have experience in recombinant DNA technology, medical genetics, or genetic diagnostics; or (ii) a Master's degree in

genetics, molecular genetics, or molecular biology, or in a related field in the biological sciences, and have at least 2 year of experience in recombinant DNA technology, medical genetics, or genetic diagnostics. A POSA would have known how to research the scientific literature regarding recombinant DNA technology, medical genetics, or genetic diagnostics. Also, a POSA may be comprised of a multidisciplinary team with each member drawing upon not only his or her own skills, but also taking advantage of certain specialized skills of others in the team, *e.g.*, to solve a given problem. For example, a molecular biologist and a physician may have been part of the team.

12. Before August 12, 1994, a POSA in the art of recombinant DNA technology, medical genetics, or genetic diagnostics would have had knowledge of scientific literature concerning methods for identifying and cloning of genes or gene sequences and methods for screening or detecting alterations in the genes. Such a POSA would have had knowledge of strategies for identifying and cloning the genes or gene sequences and for screening or detecting alterations in the gene.

V. The '441 Patent Specification

13. This declaration is being submitted together with a petition for *inter partes* review of claims 7, 8, 12, and 23 of the '441 patent.

14. I have reviewed the '441 patent and its parent applications (U.S. Appl. Nos. 08/409,305; 08/348,824; 08/308,104; 08/300,266; and 08/282,221), along

with their file history. GDX1001; GDX1009; GDX1010; GDX1035; GDX1021; GDX1011; GDX1022. And, in assessing the '441 patent, I have considered the teachings of the scientific literature as of August 12, 1994, in light of general knowledge in the art as of that date.

15. The '441 patent is directed to methods for isolating and detecting human breast and ovarian cancer predisposing gene (BRCA1). GDX1001, Abstract, 1:20-41, 4:36-55; 6:9-30, 6:64-7:5. The patent is also directed to screening (or detecting) alterations (*e.g.*, mutations or polymorphisms) in the BRCA1 gene, and using the mutations for diagnosing a predisposition to breast and ovarian cancer. *Id.*

VI. Overview of the Claims of the '441 patent

16. The claims of the '441 patent are generally directed to methods for screening or detecting the germline alterations in the BRCA1 gene comprising comparing the germline sequence of the BRCA1 gene, RNA, or cDNA from a subject with the sequence of the wild-type BRCA1 gene, RNA, or cDNA, wherein a difference in the sequences indicates an alteration in the BRCA1 gene. The challenged claims recite specific, well-known methods for screening or detecting the alterations, *e.g.*, amplifying and sequencing the BRCA1 gene.

17. Claim 1 of the '441 patent recites:

1. 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.

Claim 7 recites:

7. 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.

Claim 8 recites:

8. 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.

Claim 12 recites:

12. The method of claim 1 wherein a germline nucleic acid sequence is compared by amplifying BRCA1 nucleic acids from said sample to produce amplified nucleic acids, hybridizing the amplified nucleic acids to a BRCA1 DNA probe specific for a BRCA1 allele and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said allele in the subject.

Claim 20 recites:

20. A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 11 and 12 which comprises analyzing a sequence of the BRCA1 gene or BRCA1 RNA from a human sample or analyzing the sequence of BRCA1 CDNA made from mRNA from said sample.

Claim 23 recites:

23. The method of claim 20 wherein a germline alteration is detected by amplifying all or part of a BRCA1 gene in said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids.

GDX1001, 155:17-25, 15:57-67, 156:44-50, 157:11-17, 157:32-35.

VII. Claim Construction

18. I understand that terms of the claims are to be given their broadest reasonable interpretations in light of the specification and prosecution history of the '441 patent.

19. "**Germline**". While the '441 patent and prosecution history do not explicitly define the term, the specification states: "[s]omatic mutations . . . occur only in certain tissues, . . . and are not inherited . . . Geimline [sic] mutations can be found in any of a body's tissues and are inherited." GDX1001, 12:44-47. Thus, a POSA would interpret "**germline**" as related to nucleic acid sequences and alterations (defined below) as sequences and alterations that are inherited, are present in the genomic DNA of all nucleated cells, and are likely to be passed on to

progeny. In contrast, somatic alterations are not inherited, are present in the genomic DNA of only certain cells, and are not passed on to progeny.

20. **"Alteration"**. The '441 patent specification defines "alteration" as: "[a]lteration of a wild-type gene' encompasses all forms of mutations . . . in the coding and noncoding regions.. Deletions may be of the entire gene or of only a portion of the gene." GDX1001, 12:39-41. The specification also states: "To exclude the possibility that the mutations were simply common polymorphisms in the population, ASOs [allele-specific oligonucleotides] for each mutation were used[.]" *Id.*, 58:65-67. During prosecution, the patent owner stated: "Dr. Skolnick . . . discussed the utility for other alterations including polymorphisms." GDX1009, 312 (Amendment filed September 12, 1996, pg. 7). Thus, a POSA would interpret "**alteration**" to include mutations and polymorphisms.

21. **"BRCA1 gene probe"** and **"BRCA1 DNA probe"**. The '441 patent specification in its definitions section states: "[p]robes for BRCA1 alleles may be derived from the sequences of the BRCA1 region . . . The probes may be of any suitable length, which span all or a portion of the BRCA1 region, and which allow specific hybridization to the BRCA1 region." GDX1001, 21:52-56. And, the specification states: "polymorphisms associated with BRCA1 alleles . . . are detected by hybridization . . . which forms a stable hybrid . . . under stringent to moderately stringent . . . conditions." *Id.*, 21:36-41. The specification also states:

"polynucleotide . . . having at least about eight nucleotides, . . . from a polynucleotide sequence encoding BRCA1 are preferred as probes." *Id.*, 22:20-24.

22. An allele is an alternative form of a gene and can be either a wild-type or mutant allele. Thus, a POSA would interpret "**BRCA1 gene probe**" as a polynucleotide of any suitable length that specifically hybridizes to the BRCA1 region under stringent to moderately stringent conditions. The BRCA1 gene probe may be specific to a wild-type BRCA1 allele or a mutant allele.

23. A gene (and an allele) is composed of DNA. Thus, a BRCA1 allele is composed of BRCA1 DNA. As such, a POSA would interpret "**BRCA1 DNA probe**" similarly to "BRCA1 gene probe," *i.e.*, a polynucleotide of any suitable length that specifically hybridizes to the BRCA1 region under stringent to moderately stringent conditions.

24. "**Primers**". While neither the '441 patent specification nor its prosecution history explicitly define the term, the specification states: "[t]he primer pairs . . . are useful for determination of the nucleotide sequence of a particular BRCA1 allele using PCR. The pairs . . . can be annealed to sequences within or surrounding the BRCA1 gene . . . to prime amplifying DNA synthesis of the BRCA1 gene[.]" GDX1001, 16:30-35 (emphasis added). Thus, a POSA would interpret "**primers**" to encompass primers that are complementary to and anneal to

sequences within or surrounding the BRCA1 gene on the chromosome and amplify the BRCA1 gene.

25. **"Screening" and "Detection"**. While neither the '441 patent specification nor its prosecution history explicitly define the terms, the specification states: "[a]lteration of wild-type BRCA1 genes can also be detected by screening for alteration of wild-type BRCA1 protein." GDX1001, 15:62-64. Claims 1, 7, and 12 recite: "[a] method for screening . . . an alteration . . . by detecting the presence of a hybridization product[.]" *Id.* 156:17-25, 57-62, 156:44-50. Claim 27, similarly, is directed to a method for screening an alteration by detecting a BRCA1 polypeptide. *Id.*, 158:3-14. Thus, a POSA would understand that the terms are used interchangeably in the '441 patent and are synonymous.

26. Any term I have not expressly interpreted above, I have given its plain and ordinary meaning to a POSA.

VIII. State of the Art as of August 12, 1994

27. The '441 patent relates to the methods for isolating and detecting human breast and ovarian cancer predisposing gene (BRCA1). GDX1001, Abstract, 1:20-41, 4:36-55; 6:9-30, 6:64-7:5. The patent also relates to screening (or detecting) alterations (*e.g.*, mutations or polymorphisms) in the BRCA1 gene, and using the mutations for diagnosing a predisposition to breast and ovarian cancer. *Id.* Breast and ovarian cancers are common cancers in women and, like

many cancers, are influenced by an individual's genetic makeup or heredity. GDX1007, 1:1. The hereditary information in an individual exists as genome in almost every cell of the body and consists of approximately 22,000 genes that are packed into 23 pairs of chromosomes. Alberts, et al., "Molecular Biology of the Cell," 3rd Ed., 1994; (GDX1025), 16. The genes form the basis of human hereditary traits and are composed two complementary strands of DNA (or deoxy ribonucleic acid) molecules that contain 4 different chemical units called nucleotide bases or nucleotides, adenosine (A), thymine (T), cytosine (C), and guanine (G), arranged in a predetermined linear order (called gene sequence). GDX1025, 3-5. The complementarity of the two strands is determined by specific binding of A to T and G to C. GDX1025, 4. The DNA present in an individual's genome is called genomic DNA. GDX1025, 22.

28. A gene sequence encodes (*i.e.*, contains information necessary to produce) a protein. A protein is produced after a) transcription of the gene into an mRNA (or messenger ribonucleic acid) molecule and, b) translation of the mRNA molecule into a protein molecule. Only some regions of a gene, called exons, encode a protein and are present in the mRNA. GDX1025, 6-7. Other gene parts, called introns, which are interspersed between the exons, do not encode a protein and are not present in mRNA. GDX1025, 21. DNA, RNA, and cDNA are collectively called **nucleic acids**. GDX1025, 23.

29. An individual's germline DNA sequence is inherited from the individual's parents and is present in all nucleated cells types in the body. GDX1025, 22. Alterations or variations can arise in a gene sequence. GDX1025, 18-19. Some alterations are common in a population and are not linked to a disease or a risk of developing a disease. Such non-disease linked alterations are called polymorphisms. Other alterations are linked to a disease or a risk of developing a disease and are called mutations. GDX1025, 18-19. A germline mutation is present in genomic DNA of all nucleated cells, is inherited by an individual from his or her parents, and can be passed on to the individual's progeny. GDX1025, 22. In contrast, a somatic mutation is present in the genomic DNA of only certain cells and is not passed on to progeny. *Id.* In cancer genetics, somatic mutations are generally thought to arise in specific cells randomly or due to environmental factors. GDX1025, 8. Because of alterations in its sequence, a gene can exist in alternative forms within a population. These alternate forms of a gene are called alleles. The most common nucleotide sequence not linked to a disease risk is often called a wild-type sequence. GDX1025, 18.

30. Before August 12, 1994, a POSA was able to extract DNA, mRNA, or proteins from cells using conventional methods. Such methods allowed a POSA to isolate a specific segment of genomic DNA, such as a gene or a part of a gene, for further study or use. Such conventional methods also allowed a POSA to

synthetically create DNA, RNA, or cDNA. DNA, RNA, and cDNA are collectively called nucleic acids. GDX1025, 23.

31. Before August 12, 1994, positional cloning was a commonly-used approach to identify a gene. GDX1006, 3:2, 6:3, Fig. 2; GDX1025, 14. Before the BRCA1 gene was identified, "[p]ositional cloning [had] been used effectively [to isolate] several important human disease genes such as cystic fibrosis, familial adenomatous polyposis, and Huntington's disease." GDX 1006, 6:3; GDX1025, 14. In positional cloning, a disease gene is first localized to a particular chromosomal region by determining a chromosomal region associated with inheritance of the disease in affected (linked) families by mapping and genetic analysis. GDX1006, 3:2, 3:5-6, 6:3, Fig. 2, 7:2. After the disease-linked chromosomal region is sufficiently narrowed genetically, the gene can be identified and characterized by standard molecular biology techniques. GDX1006, 3:2, 6:3, Fig. 2, 7:3-11:3. Positional cloning is an iterative process. Rather, vicissitudes are expected on the course to gene discovery and are part of the normal process towards the inevitable identification of a gene once its chromosomal location is determined.

32. Typically, positional cloning starts with physically mapping the gene location on a chromosome by linkage analysis. *See* GDX1006, 3:5-6, 6:3, Fig. 2. Linkage analysis aims to find the location of a gene of interest on a chromosome

relative to a marker DNA sequence, whose position on the chromosome is already known. "Linkage analysis relies on the identification of a marker or markers that segregate [in families] with disease predisposition." GDX1006, 3:6. In other words, by identifying the presence of certain markers in family members with disease, and the absence of the same marker in members without disease, researchers can determine that a certain genetic region correlates with the disease. Before August 12, 1994, linkage analysis was routinely used to map genes. GDX1006, 3:5-4:3, 6:3, Fig. 2. Researchers performed multiple rounds of linkage analysis, with each round finding genetic markers that were incrementally closer to the gene location. *Id.* Thus, by using this technique, a gene was located to a relatively narrow chromosomal region flanked by the identified markers. *Id.* The genetic region is then genetically refined further by identifying closer markers. *Id.*, 6:3, Fig. 2, 7:2.

33. Once the chromosomal region can no longer be refined further genetically, "the only viable approach [] to obtaining the gene is to capture the linked region physically, search for all the genes within it, and see which is altered consistently in linked families[.]" *Id.*, 6:3. About 1 Mb region was understood to be sufficiently narrow to allow straightforward identification of the gene of interest. For example, King explains that the presence of several markers in the BRCA1 region "should permit BRCA1 to be localized to roughly 1cM [approx. 1 Mb on

human chromosome] by gene mapping" and then "it will be tedious, but straight forward to identify all of the transcripts [corresponding to candidate genes] in the [locus], and comparing sequences of these genes among susceptible versus not susceptible relatives." GDX1027, 3:3-4:1. And Kelsell, after identifying a 1-1.5 Mb locus, considered it to be sufficiently narrow to start analyzing the genes known to be located within the region and suggests analyzing other sequences in the region that did not correspond to known genes in order to identify the BRCA1 gene. GDX1007, 4:2. Further steps involve: 1) physically placing the genetic region of interest into laboratory host organisms, such as yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), P1 phages, and cosmids, in a commonly used process known as cloning to obtain several clones containing overlapping sequences from within the region; 2) screening the clones to identify the ones carrying genes potentially linked to the disease (candidate genes); and 3) screening the candidate genes for mutations linked to the disease. GDX1006, 3:2, 6:3, Fig. 2.

34. Before August 12, 1994, YACs, BACs, P1 phages, and cosmids were commonly used laboratory tools to clone segments of genomic DNA. GDX1006, 6:3, 7:2-8:3. The clones were then used to screen cDNA libraries from appropriate tissue to identify the cDNAs corresponding to the candidate gene located within the region by using conventional techniques: direct hybridization, exon trapping,

CpG island trapping (HTF island analysis), and zooblots. GDX1006, 8:4-11:2, Fig. 4.

35. Once a set of cDNAs corresponding to candidate genes were identified, they were analyzed for alterations that cosegregate with the disease in a linked family. GDX1006, 11:4-12:2. This means that researchers would determine whether affected members of a linked the family had different versions of the gene compared to non-affected members of the family. Various methods for screening alterations were commonly and routinely used before August 12, 1994. Such methods include hybridization methods (*e.g.*, hybridization using allele-specific oligonucleotide probes) and sequencing methods. GDX1006, 11:4-12:2; GDX1020, 3:Abstract, 11:9-12:1.

36. Hybridization methods detect an alteration in a nucleic acid (called target or template) by sequence-specific binding (based on complementarity) of the target nucleic acid with another nucleic acid (called a probe). An allele-specific oligonucleotide (ASO) probe is a short nucleic acid that is complementary to the target sequence, particularly an allele. GDX1020, 11:9-12:1. Allele-specific oligonucleotide hybridization uses ASO probes to specifically detect a particular allele.

37. Before August 12, 1994, sequencing techniques were well established and routinely practiced. Sequencing methods generally used amplified nucleic

acids obtained from DNA, particularly genomic DNA, to determine the gene sequence. GDX1006, 11:4-12:1; GDX1019, 21-40. Before August 12, 1994, polymerase chain reaction (PCR) was routinely used to amplify a DNA fragment (gene or gene fragment) (called template), particularly genomic DNA. GDX1006, 11:4-12:1; GDX1019, 93-109. PCR amplification uses short DNA fragments (called primers, typically a pair of primers) that contain a sequence complementary to the ends of the target sequence in a template.

38. Breast or ovarian cancer susceptibility was known to be inherited, and identification of the susceptibility gene for diagnosis or prognosis of breast or ovarian cancer was of enormous interest. GDX1005: Abstract; GDX1007, 1:1; GDX1028, Abstract; GDX1006, Abstract, 11:3. Similar to several other genes, such as the cystic fibrosis gene and the Huntington's disease gene, the BRCA1 gene was identified by positional cloning. GDX1005, 1:4-2:3. In 1990, the gene for breast cancer susceptibility, Breast Cancer Susceptibility Gene 1 (BRCA1) locus, was mapped to the long arm of chromosome 17 (17q21) by linkage analysis. GDX1007, 1:1; GDX1028. The locus was also found to be linked to ovarian cancer. GDX1005; GDX1007; GDX1008.

39. In 1993, three years after the mapping of the BRCA1 gene to chromosome 17q21, Easton *et al.*, as part of Breast Cancer Linkage Consortium study, narrowed down the BRCA1 locus to "an interval whose genetic length [was]

estimated to be 8.3 cM² in males and 18.0 cM in females" between markers D17S588 and D17S250 by using conventional mapping techniques. GDX1008: Abstract. Soon thereafter, in April 1993, Bowcock *et al.* narrowed down the locus to < 4cM region between markers THRA1 and D17S183, which lie within the markers disclosed in Easton. GDX1029, Abstract (also acknowledging GDX1008). By November 18, 1993, Kelsell *et al.* narrowed the BRCA1 locus further to a 1-1.5 Mb region between markers D17S857 and D17S183, which lie within markers disclosed in Bowcock. GDX1007, Abstract. As a result of these works of different groups, the BRCA1 gene was repeatedly mapped to a region that included Kelsell's 1-1.5 Mb region, indicating that there was a high likelihood that the BRCA1 gene was located in Kelsell's region. Within a short period, several other groups, such as Smith, Cropp and Jones, identified sub-regions within Kelsell's region. GDX1033; GDX1032; GDX1034. In fact, these groups took Kelsell's region as a reference to establish that their sub-regions accurately identified the BRCA1 gene location. *Id.* As such, Kelsell's region was accepted as the likely location for the BRCA1 gene.

40. On November 7, 1994, about 4 years after the mapping of the BRCA1 gene to chromosome 17, Miki published detailing the identification of BRCA1 gene "composed of 22 coding exons distributed over roughly 100 kb of genomic

² 1 cM "translates to approximately one million base pairs of DNA sequence in the human genome." GDX1030.

DNA," producing "a single transcript of 7.8 kb," GDX1005, 2:1-2, Fig. 2, 3. The benefit of detecting the BRCA1 mutations for diagnosing breast or ovarian cancer was well understood in the art and genetic diagnostic techniques to screen for mutations linked to a disease were commonly used. GDX1005, Abstract; GDX1006:Abstract, 13:3. In fact, several mutations and polymorphisms in the BRCA1 gene were identified. GDX1005, 4:Tables 2, 3; GDX1004, 4. Exemplary relevant art includes the references discussed below.

41. **Miki** published before June 7, 1995, on October 7, 1994. Miki discloses identification of the BRCA1 gene by positional cloning. GDX1005, Abstract, 1:5-2:4. Specifically, Miki identifies that the BRCA1 gene spans 100 kb genomic DNA and comprises 22 exons, and predicts a BRCA1 amino acid sequence. *Id.*, 2:1-2, 2:Figure 2. Miki also discloses methods for screening the germline alterations in the BRCA1 gene – allele specific probe hybridization, PCR amplification, and sequencing, and identifies various mutations and polymorphisms in the BRCA1 gene. *Id.*, 4:Tables 2 and 3.

42. **Kelsell** published before August 12, 1994. To verify the publication month of Kelsell, I conducted a PubMed search for Kelsell. GDX1023 is a web printout from a PubMed search and discloses that Kelsell was published in November 1993. Therefore, I understand that Kelsell was published in November, 1993.

43. Kelsell uses positional cloning to identify the BRCA1 gene, suggesting it as an approach for the BRCA1 gene identification. GDX1007, Abstract. It uses linkage analysis to narrow down the BRAC1 region to a 1-1.5 Mb region, identifies two genes known to be located within the region (not previously ruled out) as candidate genes, and screens the two genes for breast or ovarian cancer linked germline mutations to determine whether one of the genes is the BRCA1 gene. GDX1007, Abstract, 3:2-4:2. After determining that the genes were not the BRCA1 gene, Kelsell suggests analyzing (by sequencing) "the remainder of the normally untranslated region or identifying a recombination between this locus and BRCA1" to identify the BRCA1 gene in the region. *Id.*, 4:2.

44. **Bowcock** published before August 12, 1994. To verify the publication month of Bowcock, I conducted a PubMed search for Bowcock. GDX1017 is a web printout from a PubMed search and discloses that Bowcock was published in November 1993. Therefore, I understand that Bowcock was published in November, 1993.

45. Bowcock provides a specific approach for identifying the BRCA1 gene by positional cloning. GDX1006, 3:2; 6:3. Specifically, Bowcock describes conventional techniques for narrowing down the BRCA1 locus on chromosome 17, identifying candidate genes within the narrowed-down locus, and analyzing the candidate genes by screening them for mutations linked to breast or ovarian

cancers in order to determine whether a candidate gene is in fact the BRCA1 gene. GDX1006, 1:Summary, 3:2, 6:3. Bowcock also reviews conventional techniques for isolating and sequencing the BRCA1 gene and detecting mutations linked to breast and ovarian cancers in the gene. *Id.*, 11:4-12:1.

46. **Cotton** published before August 12, 1994. To verify the publication month of Cotton, I conducted a PubMed search for Cotton. GDX1018 is a web printout from a PubMed search and discloses that Cotton was published in January 1993. Therefore, I understand that Cotton was published in January, 1993. Cotton reviews techniques that were commonly used for detecting mutations in 1993, particularly allele-specific oligonucleotide (ASO) hybridization. GDX1020, Abstract, 11-12.

IX. My Understanding of Written Description Requirement and Priority

47. It is my understanding that in order to provide an adequate written description of an invention, a patent specification must describe the invention in sufficient detail such that a POSA can clearly conclude that the inventor had invented the claimed invention. In other words, the inventor must have had possession of the claimed invention, though possession does not necessarily require having a tangible embodiment of the invention. The description cannot merely provide enough detail to make the invention obvious, but instead must

provide enough detail so that a POSA reading the disclosure understands what the invention is.

48. It is my understanding that a patent claim may claim priority benefit to the filing date of one or more previously-filed patent applications if, among other things, the earlier-filed application(s) provide(s) an adequate written description of the patent claim's subject matter. I understand that the adequate written description must be provided in each application in the chain of applications leading to the patent.

49. I have reviewed the parent applications of the '441 patent, Appl. Nos. 08/409,305 ("the '305 application") (GDX1010), 08/348,824 ("the '824 application") (GDX1035), 08/308,104 ("the '104 application") (GDX1021), 08/300,266 ("the '266 application") (GDX1011), and 08/289,221 ("the '221 application") (GDX1022). For the reasons discussed below, a POSA would conclude that the parent applications do not fully describe the BRCA1 gene sequence, and thus the BRCA1 gene probes, BRCA1 DNA probes, or primers required in claims 7, 8, 12, and 23. Accordingly, the parent applications do not show possession of the methods of claims 7, 8, 12, and 23.

50. Claim 7 is directed to a method that requires hybridizing a *BRCA1 gene probe* to sample genomic DNA. GDX1001, 155:57-62. Claim 12 is directed to a method that requires hybridizing a *BRCA1 DNA probe* to amplified BRCA1

nucleic acids. GDX1001, 156:44-50. The terms "BRCA1 gene probe" and "BRCA1 DNA probe" are construed as a polynucleotide of any suitable length that specifically hybridizes to the *BRCA1* region under stringent to moderately stringent conditions.

51. Each of claims 8 and 23 is directed to a method that includes a step of amplifying nucleic acids from the BRCA1 gene. GDX1001, 155:63-67. Claims 8 and 23 explicitly require *primers* for amplification. Claim 12 requires "amplifying" BRCA1 nucleic acids, but does not explicitly require primers. However, amplifying includes amplifying by any technique, including PCR which requires primers. The term "primers" is construed to encompass primers that are complementary to and anneal to sequences *within or surrounding* the BRCA1 gene. *Id.*

52. The complete sequence of the BRCA1 gene was not published until 1996 and is 81,188 bps. GDX1024, 2:3 ("We present the complete sequence and analysis of a 117,143-bp region of human chromosome 17 that encompasses the 81-kb *BRCA1* gene."); *see also*, GDX1026 (noting that the BRCA1 gene is located on chromosome 17 at base pairs 43,044,294 to 43,125,482, indicating that the BRCA1 gene is 81,188 bps).

53. None of the parent applications disclose the entire BRCA1 gene sequence. The '305 application states: "[f]igures 10A–10H show genomic sequence

of BRCA1. The lower case letters denote intron sequence while the upper case letters denote exon sequence. Uncertainty about sequence at an intron/exon boundary is indicated by vvvvv. Indefinite intervals (between introns) are designated with vvvvvvvvvvvvvv. The intron between exons 6 and 7 is not included." GDX1010, 12:26-29. The BRCA1 genomic DNA sequence (*i.e.*, BRCA1 gene sequence) disclosed in Figs. 10A-10H is 21,820 bps long and includes several indefinite intervals unknown sequence and length, *e.g.*, at nucleotides 1966-1978 and 2504-2516 in Fig. 10A and at nucleotides 15377-15389, 16836-16848, 17338-17350, and 18286-18298 in Fig. 10F. The BRCA1 genomic DNA sequence in Figs. 10A-10H also does not disclose specific nucleotides at various positions, *e.g.*, at positions 2323-2325, 2329, and 2500 in Fig. 10A and at positions 13596-13597, 14071, 14343, and 14353-14354 in Fig. 10E.

54. The '305 application also discloses a partial BRCA1 gene sequence as SEQ ID NO: 14. GDX1010, 82:17-18. The sequence disclosed as SEQ ID NO: 14 is 21,715 bps long and includes several indefinite intervals of unknown sequence and length, *e.g.*, at nucleotides 1958-1970, 2496-2508, 15335-15347, 16770-16782, 17258-17270, and 18196-18208. The sequence disclosed as SEQ ID No:14 also does not disclose specific nucleotides at various positions, *e.g.*, at positions 4751-4752, 4755, 4762-4763, 4765, 14280, 14339, 14501-14502, 14516, and

14968. Thus, the BRCA1 gene disclosed in the '305 application is at most 21,820 bps (out of total 81,188 bps), with several stretches of unknown intervals with unknown sequence and length and several missing nucleotides within the BRCA1 gene. As such, the '305 application does not disclose the complete sequence of the BRCA1 gene.

55. Similarly, the sequences of the BRCA1 gene disclosed in the '824 and '104 applications are 21,820 bps, the sequence of the BRCA1 gene disclosed in the '266 application is 21,715 bps, and the sequence of the BRCA1 gene described in the '221 application is 10,952 bps, all with several indefinite intervals of unknown sequence and length and several missing nucleotides. GDX1035, 167-174, SEQ ID NO: 14; GDX1021, 115-126, SEQ ID NO: 14; GDX1011, 112-123, SEQ ID NO:13; GDX1022 101-108, SEQ ID NO: 11.

56. The '824 and '104 applications states: "[p]artial genomic DNA sequences determined for BRCA1 are set forth in SEQ ID NO: 14. The lower case letters denote intron sequence while the upper case letters denote exon sequence. Uncertainty about sequence at an intron/exon boundary is indicated by vvvvv. Indefinite intervals (between introns) are designated with vvvvvvvvvvvvvv." GDX1035, 85:13-16; GDX1021, 80:13-16. The partial BRCA1 gene sequences disclosed as SEQ ID NO: 14 in the '824 and '104 applications are 21,820 bps long and include several indefinite intervals of unknown sequence and length, e.g., at

nucleotides 1966-1978, 2504-2516, 15377-15389, 16836-16848, 17338-17350, and 18286-18298. The sequences also do not disclose specific nucleotides at various positions, *e.g.*, at positions 2323-2325, 3027-3029, 13707, 13730-13731, 13922, 13924, and 13945. Thus, the '824 and '104 applications do not disclose the complete sequence of the BRCA1 gene.

57. The '266 application states: "[p]artial genomic DNA sequences determined for BRCA1 are set forth in SEQ ID NO:13. The lower case letters denote intron sequence while the upper case letters denote exon sequence. Uncertainty about sequence at an intron/exon boundary is indicated by vvvvv. Indefinite intervals (between introns) are designated with vvvvvvvvvvvvvv." GDX1011, 80:4-7. The partial BRCA1 gene sequence disclosed as SEQ ID NO: 13 is 21,715 bps long and includes several indefinite interval of unknown sequence and length, *e.g.*, at nucleotides 1958-1970, 2496-2508, 15335-15347, 16770-16782, 17258-17270, and 18196-18208. The sequence also does not disclose specific nucleotides at various positions, *e.g.*, at positions 3019-3020, 4950, 4974, 10922, 13806-13807, 13897, 13921, 13931, 14055-14057, 14719, and 14435. Thus, the '266 applications do not disclose the complete sequence of the BRCA1 gene.

58. The '221 application discloses that "[t]he genomic DNA sequences determined for BRCA1 is set forth in SEQ ID NO:11, in which the exons have

been identified." GDX1022, 78:27-28. The BRCA1 genomic DNA sequence disclosed as SEQ ID NO: 11 is 10,952 bps long and includes several stretches of unknown nucleotides, *e.g.*, at nucleotides 610-719, 4441-4454, 5125-5135, 6450-6474, 6686-6699, 6743-6755, 7866-7893, 7920-8126, 8277-8289, 9151-9161, 9726-9735, 10303-10315, and 10506-10518. Because the BRCA1 gene sequence in SEQ ID NO:11 is only 10,952 bps, the stretches of unknown nucleotides must be of indefinite length in order to arrive at the full 81,188 kb sequence of the BRCA1 gene. The sequence also does not disclose specific nucleotides at various positions, *e.g.*, at positions 5311, 5320, 5357, 5577, 5836, 6139, and 6142. Thus, the parent applications also do not disclose the complete sequence of the BRCA1 gene.

59. Thus, the parent applications disclose only a fraction of the entire BRCA1 gene sequence (which is 81,188 bps) – the '305, '824, and '104 applications describe a BRCA1 gene sequence that is only 21,820 bps (26.9% of the entire sequence); the '266 application describes a BRCA1 gene sequence that is only 21,715 bps (26.7% of the entire sequence); and the '221 application describes a BRCA1 gene sequence that is only 10,952 bps (13.5% of the entire sequence). And, even those partial BRCA1 sequences are interspersed with several indefinite intervals with unknown sequence and length and several unknown nucleotides. Therefore, even if the BRCA1 sequence in the parent applications were not

missing sequences, the parent applications disclose, at most, about 27% of the entire BRCA1 gene sequence. The parent applications also do not disclose the sequences surrounding the BRCA1 gene in the BRCA1 region.

60. As such, the parent applications do not disclose the entire BRCA1 gene sequence and the sequences surrounding the BRCA1 gene in the BRCA1 region. As discussed above, claims 7, 8, 12, and 23 require "BRCA1 gene probe," "BRCA1 DNA probe," and/or "primers." GDX1001, 155:57-62, 156:44-50, 157:32-35. "BRCA1 gene probe" and "BRCA1 DNA probe" are construed as a polynucleotide of any suitable length that specifically hybridizes to the *BRCA1 region* under stringent to moderately stringent conditions. And, "primers" is construed to encompass primers that are complementary to and anneal to sequences *within or surrounding* the BRCA1 gene. Because the parent applications fail to disclose the entire BRCA1 gene sequence and the sequences surrounding the gene in the BRCA1 region, they also fail to disclose all the "primers," "BRCA1 gene probes" and "BRCA1 DNA probes" required by claims 7, 8, 12, and 23.

61. In light of the above, a POSA reading any of the parent applications would not have understood that the patent owner had possession of the methods of claims 7, 8, 12, and 23. Therefore, it is my understanding that the '441 patent is not entitled to filing dates of the parent applications.

X. *Summary Chart of Analysis Over the Art*

62. The challenged claims are directed to methods for screening the germline of a subject for an alteration in the BRCA1 gene or methods for detecting a germline alteration in the BRCA1 gene of a sample. Miki discloses every element of the challenged claims, arranged as claimed. Miki also provides sufficient detail for these elements such that a POSA could have practiced the claimed methods without undue experimentation in light of the general knowledge in the art. In addition, as of August 12, 1994, each claim would have been obvious over Bowcock and Kelsell together or further in view of Cotton, which show that a person of ordinary skill in the art ("POSA") would have had a reason to arrive at the methods of the challenged claims, with a reasonable expectation of success. GDX1007, 1006, 1020. The chart below summarizes this analysis.

Ground	Basis	References	'441 Patent Claims
1.	Anticipation	Miki	7, 8, 12, and 23
2.	Obviousness	Bowcock and Kelsell	8 and 23
3.	Obviousness	Kelsell, Bowcock, and Cotton	7 and 12

XI. *Basis of my Analysis with Respect to Anticipation*

63. It is my understanding that a reference anticipates a claim if it discloses each and every element recited in the claim, arranged as in the claim, so as to enable one of skill in the art to make and use the claimed invention without the need for undue experimentation in light of the general knowledge available in

the art. The factors that I have considered in determining whether a reference sets forth the elements of a claim in a sufficient manner such that a POSA could have made and used the claimed invention without undue experimentation include: the breadth of the claim, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the reference, the existence of working examples, and the quantity of experimentation needed to make or use the invention claimed.

XII. The Basis of my Analysis with Respect to Obviousness

64. I understand that an obviousness analysis involves comparing a claim to the prior art to determine whether the claimed invention would have been obvious to a person of ordinary skill in the art in view of the prior art, and in light of the general knowledge in the art. I also understand when a person of ordinary skill in the art would have reached the claimed invention through routine experimentation, the invention may be deemed obvious. I also understand that obviousness can be established by combining or modifying the teachings of the prior art to achieve the claimed invention. It is also my understanding that where there is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of doing so successfully. I understand that the reason to combine prior art references can come from a variety of sources, not just the prior art itself or the specific problem the patent owner was

trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the modification needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not necessarily require explication in any reference.

65. I understand that when considering the obviousness of an invention, one should also consider whether there is any objective evidence that supports the nonobviousness of the invention. I understand that objective evidence of non-obviousness (also known as secondary considerations of nonobviousness) includes factors such as failure of others, copying, unexpectedly superior results, praise in the industry, commercial success, and long-felt but unmet need.

XIII. Ground 1: Miki Discloses Every Limitation of Claims 7, 8, 12, and 23, Arranged as Claimed, and Without Necessitating Undue Experimentation

66. I understand that Miki is prior art to the '441 patent. The claim charts and discussion below show that Miki discloses each and every element of claims 7, 8, 12, and 23, arranged as claimed. Miki also provides sufficient detail for these elements such that a POSA could have practiced the claimed methods without undue experimentation in light of the general knowledge in the art.

A. Claim 7

67. The claim chart below shows where each and every element of claim 7 is disclosed in Miki, arranged as claimed. Claim 7 depends from claim 1 and thus

contains each and every element of claim 1. Thus, claim 1 is included in the claim chart below to enumerate all the elements of claim 7.

Claim 7	Disclosure of Miki (GDX 1005) ³
<p>[1. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises</p> <p>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,</p> <p>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.]</p>	<p>"[I]n kindred 2035, cDNA and genomic DNA from carriers in the kindred were compared for heterozygosity for polymorphic sites." (4:3)</p> <p>"Fig. 6. . . . (C) Inferred regulatory mutation in kindred 2035. ASO [Allele Specific Oligonucleotide] analysis of haplotype carriers and noncarriers used two different polymorphisms, PM1 and PM7 (Table 3). Samples were examined for heterozygosity in the germ line . . . The top two rows of each panel contain PCR products amplified from genomic DNA, . . . "A" and "G" are the two alleles detected by the ASOs. The dark spots indicate that a particular allele is present in the sample. The first three lanes of the lower panel represent the three genotypes from unrelated individuals." (5: Fig. 6 Legend)</p>
7. The method of claim 1	See claim 1 above in this chart
wherein a germline	"Fig. 6. . . . (C) Inferred regulatory mutation in

³ Boldface type in the claim charts indicates that emphasis was added to the disclosure.

<p>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</p> <p>detecting the presence of a hybridization product,</p> <p>wherein a presence of said product indicates the presence of said allele in the subject.</p>	<p>kindred 2035. ASO [Allele Specific Oligonucleotide] analysis of haplotype carriers and noncarriers used two different polymorphisms, PM1 and PM7 (Table 3). Samples were examined . . . in the germ line . . . PCR products amplified from genomic DNA, . . . two alleles detected by the ASOs. The dark spots indicate that a particular allele is present in the sample." (5: Fig. 6 Legend)</p> <p>"PCR products were generated as described [n26] . . . were then blotted onto Hybond membrane . . . Wild-type and mutant ASOs were labeled . . . used in an overnight hybridization reaction . . . Blots were exposed to x-ray film[.]" (6:n27)</p>
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68. As shown in the claim chart above, Miki discloses *screening* the germline genomic DNA of carriers and noncarriers of a breast or ovarian cancer susceptibility allele within a BRCA1-linked family for polymorphisms ("A" or "G" allele) by *hybridizing* the allele-specific oligonucleotide (ASO) probes for the "A" or "G" allele to PCR products amplified from the genomic DNA of the carriers and noncarriers and *detecting* the presence of the hybridization product (as dark spots on x-ray film). As discussed above, polymorphisms are alterations. Section VII. ASO probes are polynucleotides that specifically hybridize to a particular allele of the gene (here BRCA1 gene). GDX1020, 11-12. And, carriers and noncarriers are family members that carry the mutant or wild-type BRCA1 gene (alleles), respectively. Thus, Miki discloses *screening* the germline genomic DNA of carriers (subject with mutant BRCA1 gene sequence) and noncarriers (with wild-

type BRCA1 gene sequence) for BRCA1 gene alterations by *hybridizing* BRCA1 gene probe that specifically hybridizes to an allele to PCR products and *detecting* the presence of the hybridization product. (Also, Miki discloses screening control population having wild-type BRCA1 sequence by *amplifying* genomic DNA to produce PCR products and *hybridizing* the products with ASO probes to determine whether the identified alterations were polymorphisms. GDX1005, 4:4, 6:n27.)

69. PCR amplifies a target sequence in a template, such as a gene, by using short DNA fragments, called primers, that specifically bind to the sequence. The reaction is carried out by mixing nucleotides, primers, template, and amplifying enzyme to produce PCR products. Thus, the PCR products contain the amplified nucleic acids (that are a copy of the target sequence) and template. Miki used genomic DNA as template to produce PCR products and hybridizes ASO probes with the PCR products directly, without purifying the amplified nucleic acids from the PCR products. GDX1005, n27. Thus, the probes in Miki hybridized to both the amplified nucleic acids and the genomic DNA template. In addition, the amplified nucleic acids are a true copy of the genomic DNA template. As such, Miki discloses *screening* the germline of a human subject for an alteration in the BRCA1 gene by *hybridizing* a BRCA1 gene probe that specifically hybridizes to a BRCA1 allele to genomic DNA isolated from a carrier (subject with mutant BRCA1 gene sequence) and a noncarrier (with wild-type BRCA1 gene sequence).

70. In order to screen for alterations in carriers and noncarriers by ASO probes, Miki discloses comparing the hybridization patterns of carriers and noncarriers, such that a difference in the hybridization patterns indicates hybridization to different alleles, *i.e.*, to different BRCA1 gene sequences. GDX1005, 5:Fig. 6C. In fact, the presence of a hybridization product with a specific ASO probe in Miki indicates the presence of its corresponding allele. *Id.* As such, Miki discloses comparing the BRCA1 gene sequence of the subject and the wild-type BRCA1 gene sequence, wherein a difference in the sequences indicates an alteration in the sequence. And, the presence of the hybridization product with an ASO probe indicates the presence of the corresponding allele. Thus, Miki discloses each and every element of claim 7, arranged as claimed.

71. Further, the disclosure of Miki is sufficient to have allowed a POSA to perform the method of claim 7 without undue experimentation. First, ASO probe hybridization was a conventional, routinely-used technique before August 12, 1994. GDX1020, 11:9-12:4. Second, Miki provides guidance and working examples (e.g., Figure 6C) by explicitly using the technique to detect the germline alterations in the BRCA1 gene, and by providing reagents for the technique. GDX1005, 5:Fig. 6C, 71, n26-n27. Third, Miki is specifically directed to screening for alterations in the BRCA1 gene. GDX1005, 2:3-4:4, Tables 2, 3, Fig. 6C. And, finally, although the technique was well-known, Miki further explains how to use

it to detect the germline alterations in the BRCA1 gene. *Id.*, Fig. 6C, 6:n26-n27.

Therefore, a POSA could have performed the method of claim 7 without undue experimentation.

B. Claim 8

72. Claim 8 depends from claim 1 and thus contains each and every element of claim 1. Thus, claim 1 is included in the claim chart below to enumerate all the elements of claim 8.

Claim 8	Disclosure of Miki (GDX1005)
<p>[1. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises</p> <p>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,</p> <p>wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type</p>	<p>"Germline BRCA1 mutations in 17q-linked kindreds." (2:4)</p> <p>"In the initial screen for predisposing mutations in BRCA1, DNA from one individual carrying the predisposing haplotype from each kindred was tested. The 21 coding exons and associated splice junctions were amplified from either genomic DNA samples . . . When the amplified DNA sequences were compared to the wildtype sequence, four of the eight kindred samples were found to contain sequence variants (Table 2). . . . Five common polymorphisms were also identified in the BRCA1 coding sequence (Table 3)." (68:2)</p> <p>Table 2 discloses predisposing mutations in the BRCA1 gene. (4:Table 2)</p> <p>Table 3 discloses neutral polymorphisms in the BRCA1 gene. (4:Table 3)</p>

indicates an alteration in the BRCA1 gene in said subject.]	
8. 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.	<p><i>See claim 1 above in this claim chart</i></p> <p>"In the initial screen for predisposing mutations in BRCA1, DNA from one individual carrying the predisposing haplotype from each kindred was tested. . . . were amplified from . . . genomic DNA samples [by PCR using a set of PCR primers as described in n26] . . . When the amplified DNA sequences were compared to the wildtype sequence, . . . found to contain sequence variants (Table 2)." (3:2)</p> <p>"The templates for PCR were . . . genomic DNA from members . . . who carried the predisposing haplotype. Sequences of PCR primers used to amplify each exon of BRCA1. . . . The PCR products were . . . analyzed by cycle sequencing[" (6: n26)</p>

73. As shown in the claim chart above, Miki discloses *screening* the germline of an individual with predisposing haplotype (subject) for mutations in the BRCA1 gene of the individual by *amplifying* the genomic DNA of the individual, *sequencing* the amplified nucleic acids, and *comparing* the sequence of the amplified nucleic acids with the wild-type sequence. As discussed above, mutations are alterations. Thus, Miki discloses screening the germline genomic DNA of a subject for an alteration in the BRCA1 gene by *comparing* the germline sequence of the BRCA1 gene of the subject with the germline sequence of wild-type BRCA1 gene by *amplifying* all or part of the BRCA1 gene of the subject by

using a set of primers to produce amplified nucleic acids and *sequencing* the amplified nucleic acids.

74. In order to determine the differences between the subject BRCA1 gene sequence and the wild-type sequence, Miki discloses comparing the amplified DNA sequences (from the subject BRCA1 gene) with the wild-type sequences such that a difference between the sequences indicated an alteration in BRCA1 gene of the subject. Thus, Miki teaches each and every element of claim 8, arranged as claimed.

75. Further, the disclosure of Miki is sufficient to have allowed a POSA to perform the method of claim 8 without undue experimentation. First, amplification using primers and sequencing were conventional, routinely-used techniques before August 12, 1994. GDX1006, 11:4-12:1. Second, Miki provides guidance and working examples by explicitly using the techniques together to detect the germline alterations in the BRCA1 gene, and by providing reagents for the techniques. GDX1005, 3:2, 6:n26-n27. Third, Miki is specifically directed to screening for alterations in the BRCA1 gene. GDX1002, 2:3-4:4, Tables 2, 3. And, finally, although the techniques were well-known, Miki further explains how to use them together to detect the germline alterations in the BRCA1 gene. GDX1005, 6:n26. Therefore, a POSA could have performed the method of claim 8 without undue experimentation.

C. Claim 12

76. Claim 12 depends from claim 1 and thus contains each and every element of claim 1. Elements of claim 1 are discussed above, under claim 7 discussion.

Claim 12	Disclosure of Miki (GDX1005)
12. The method of claim 1 wherein a germline nucleic acid sequence is compared by amplifying BRCA1 nucleic acids from said sample to produce amplified nucleic acids,	<i>See claim 1 above under claim 7 discussion.</i>
hybridizing the amplified nucleic acids to a BRCA1 DNA probe specific for a BRCA1 allele and	"Fig. 6. . . . (C) Inferred regulatory mutation in kindred 2035. ASO [Allele Specific Oligonucleotide] analysis of haplotype carriers and noncarriers used two different polymorphisms, PM1 and PM7 (Table 3). Samples were . . . in the germ line . . . PCR products amplified from genomic DNA , and . . . two alleles detected by the ASOs . The dark spots indicate that a particular allele is present in the sample." (5: Fig. 6 Legend)
detecting the presence of a hybridization product,	" PCR products were generated as described [n26] . . . were then blotted onto Hybond membrane . . . Wild-type and mutant ASOs were labeled . . . used in an overnight hybridization reaction . . . Blots were exposed to x-ray film for 40 min[.]" (6:n27)
wherein the presence of said product indicates the presence of said allele in the subject.	

77. As discussed under claim 7 above, Miki teaches each and every element of claims 1 and 7. As such, Miki discloses *screening* the germline of a subject for BRCA1 gene alterations by *hybridizing* allele-specific BRCA1 gene probe to subject's genomic DNA and *detecting* the presence of hybridization product, wherein the presence of the product indicates the presence an allele.

BRCA1 gene probe, used in claim 7, and BRCA1 DNA probe, used in claim 12, are construed similarly. See Section VII. As shown in the chart above, Miki discloses hybridizing ASO probes to amplified PCR products, which include amplified nucleic acids (and genomic DNA template). GDX1005, 70: Fig. 6 Legend. As such, Miki discloses *screening* the germline genomic DNA of subject for BRCA1 gene alterations by *amplifying* BRCA1 nucleic acids from the subject, *hybridizing* an allele-specific BRCA1 DNA probe to *amplified nucleic acids*, and *detecting* the presence of hybridization product, wherein the presence of the product indicates the presence an allele.

78. As discussed under claim 7, Miki discloses comparing the BRCA1 gene sequence of the subject and the wild-type BRCA1 gene sequence, wherein a difference in the sequences indicates an alteration in the sequence. Thus, Miki teaches each and every element of claim 12, arranged as claimed.

79. Further, the disclosure of Miki is sufficient to have allowed a POSA to perform the method of claim 12 without undue experimentation. First, amplification and ASO probe hybridization were conventional, routinely-used techniques before August 12, 1994. GDX1006, 11:4-12:1; GDX1020, 11:9-12:4. Second, Miki provides guidance and working examples (e.g., Figure 6C) by explicitly using the techniques together to detect the germline alterations in the amplified nucleic acids from the BRCA1 gene, and by providing reagents for the

techniques. GDX1005, 5:Fig. 6C, 71, n26-n27. Third, Miki is specifically directed to screening for alterations in the BRCA1 gene. GDX1005, 2:3-4:4, Tables 2, 3, Fig. 6C. And, finally, although the techniques were well-known, Miki further explains how to use them to detect the germline alterations in the BRCA1 gene. *Id.*, Fig. 6C, 6:n26-n27. Therefore, a POSA could have performed the method of claim 12 without undue experimentation.

D. Claim 23

80. Claim 23 depends from claim 20 and thus contains each and every element of claim 1. Thus, claim 23 is included in the claim chart below to enumerate all the elements of claim 23.

Claim 23	Disclosure of Miki (GDX 1005)
<p>[20. A method for detecting a germline alteration in a BRCA1 gene,</p> <p>said alteration selected from the group consisting of the alterations set forth in Tables 11 and 12 which comprises</p> <p>analyzing a sequence of the BRCA1 gene or BRCA1 RNA from a human sample or analyzing the sequence of BRCA1 CDNA made from mRNA from said</p>	<p>"Probable predisposing mutations have been detected in five of eight kindreds presumed to segregate BRCA1 susceptibility alleles." (11-12. Abstract)</p> <p>"Germline BRCA1 mutations in 17q-linked kindreds." (2:4)</p> <p>"In the initial screen for predisposing mutations in BRCA1, DNA from one individual carrying the predisposing haplotype from each kindred was tested. The 21 coding exons and associated splice junctions were amplified from . . . genomic DNA samples . . . When the amplified DNA sequences were compared to the wildtype sequence, four of the eight kindred samples were found to contain sequence variants (Table 2)." (3:2)</p>

sample.]	
23. The method of claim 20	<i>See claim 20 above in this claim chart</i>
wherein a germline alteration is detected by amplifying all or part of a BRCA1 gene in said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids.	"In the initial screen for predisposing mutations in BRCA1, DNA from one individual carrying the predisposing haplotype from each kindred was tested. . . . were amplified from . . . genomic DNA samples [by PCR using a set of PCR primers as described in n26] . . . amplified DNA sequences were compared to the wildtype sequence , . . . samples were found to contain sequence variants (Table 2)." (3:2) "The templates for PCR were . . . or genomic DNA from members of BRCA1 kindreds who carried the predisposing haplotype. . . . PCR primers used to amplify each exon of BRCA1. . . . The PCR products were . . . analyzed by cycle sequencing[.] " (6: n26)

81. As discussed above under claim 8 and shown in the claim chart above, Miki discloses *screening* the germline of a subject for an alteration in the BRCA1 gene by *comparing* the germline sequence of the BRCA1 gene of the subject with the germline sequence of the wild-type BRCA1 gene by *amplifying* all or part of the BRCA1 gene of the subject by using a set of primers to produce amplified nucleic acids and *sequencing* the amplified nucleic acids. And, "analyzing a sequence" includes comparing the sequence from a sample with a control (wild-type) sequence; and detecting and screening are synonymous. Thus, Miki discloses *detecting* the germline alteration in the BRCA1 gene by *analyzing* the sequence of the BRCA1 gene from a sample by *amplifying* all or part of the BRCA1 gene from

the sample by using a set of primers to produce amplified nucleic acids, and *sequencing* the amplified nucleic acids.

82. Miki successfully detects several mutations, listed in Table 2, which are also listed in Table 11 of the '441 patent. GDX1005, 4; GDX1001, 56. And, one of these mutations (in codon 1775 of Kindred 2099, in Table 2) is also listed in Table 12 of the '441 patent. Thus, Miki teaches each and every element of claim 23, arranged as claimed.

83. Further, the disclosure of Miki is sufficient to have allowed a POSA to perform the method of claim 23 without undue experimentation. First, amplification using primers and sequencing were conventional, routinely-used techniques before August 12, 1994. GDX1006, 11:4-12:1; GDX1019, 21-40; 93-109. Second, Miki provides guidance and working examples by explicitly using the techniques together to detect the germline alterations in the BRCA1 gene, and by providing reagents for the techniques. GDX1005, 3:2, 71:n26-n27. Third, Miki is specifically directed to screening for alterations in the BRCA1 gene. *Id.*, 2:3-4:4, Tables 2, 3. And, finally, although the techniques was well-known, Miki further explains how to use them together to detect the germline alterations in the BRCA1 gene. *Id.*, 6:n26. Therefore, a POSA could have performed the method of claim 23 without undue experimentation.

84. Miki explicitly discloses the method that is encompassed within claim 23, and thus a POSA could have performed the method of claim 12 without undue experimentation.

85. In view of the facts discussed above and my understanding with respect to anticipation, it is my understanding that claims 7, 8, 12, and 23 are anticipated by Miki.

XIV. Ground 2: Bowcock and Kelsell Provide a Reason to Arrive at the Invention of Claims 8 and 23 with a Reasonable Expectation of Success

86. I understand that Bowcock and Kelsell are considered to be prior art to the '441 patent even if the '441 patent is entitled to the benefit of the filing date of one or more of its parent applications. The claim charts and discussion below show that Bowcock and Kelsell teach or suggest each and every element of claims 8 and 23.

87. A POSA would have been motivated to arrive at the claimed methods for screening or detecting the germline alterations in the BRCA1 gene, e.g., to identify women at risk for developing breast cancer. GDX1006, Abstract, 13:3; *See* ¶38, above. Bowcock suggests that "[t]he isolation of BRCA1 and the elucidation of the mutations resulting in breast and ovarian cancer predisposition will allow identification of women who have inherited germ-line mutations in BRCA1." GDX1006, Abstract. Bowcock also discloses that "methods may be developed to detect very early lesions in this gene [that] would permit diagnosis of very early

tumors or pre-malignant lesions." *Id.*, 13:3. Indeed, POSAs commonly diagnosed other genetic diseases by screening for or detecting mutations in other genes. As such, a POSA would have been motivated to arrive at methods for screening or detecting the germline alterations in the BRCA1 gene.

88. A POSA looking to develop methods for screening or detecting the germline alterations in the BRCA1 gene would have had a reason to combine Bowcock and Kelsell, because Kelsell determined that the BRCA1 gene is found within a 1-1.5Mb region and chromosome 17, and Bowcock provides methods for identifying the BRCA1 gene within such a locus. GDX1007, Abstract; GDX1006, 3:2, 6:3, Fig. 2, *see also* generally. Bowcock provides "approaches [for] isolating BRCA1, and outlines positional cloning approaches in general." GDX1006, 3:2. Bowcock also discloses examples of several conventional methods that could be applied for screening (or detecting) "alterations in DNAs from a variety of sources." GDX1006, Abstract, 11:4-12:2. Kelsell uses a positional cloning approach to narrow down the BRCA1 locus to a 1-1.5 Mb region on chromosome 17. GDX1007, Abstract, 3:2-4:2. Kelsell also applies the techniques disclosed in Bowcock (PCR amplification and sequencing) for screening for alterations in the candidate genes for the BRCA1 gene. GDX1007, 2:8, 5:7. A POSA looking to develop methods for screening or detecting the germline alterations in the BRCA1 gene would have used the conventional methods disclosed in Bowcock, and

applied in Kelsell, to screen or detect alterations in the BRCA1 gene. GDX1006, Abstract, 11:4-12:2; GDX1007, Abstract, 3:2-4:2; *See* ¶38, 87. A POSA would also have used the positional cloning approach disclosed in Bowcock to analyze Kelsell's 1-1.5 Mb region to identify the BRCA1 gene. GDX1006, Abstract, 3:2, 6:3, Fig. 2, *see also* generally; GDX1007, Abstract, 3:2-4:2; *See* ¶¶38, 87. As such, a POSA looking to develop methods for screening or detecting the germline alterations in the BRCA1 gene, as recited in claims 8 and 23, would have had a reason to combine Bowcock and Kelsell.

89. As discussed below, a POSA would also have had a reasonable expectation of successfully arriving at the subject matter of claims 8 and 23. *See* ¶¶90-106.

A. Claim 8

90. Claim 8 depends from claim 1 and thus contains each and every element of claim 1. Accordingly, claim 8 is included in the claim chart below to enumerate all the elements of claim 8. The claim chart below shows where Bowcock and Kelsell disclose every element of claim 8.

Claim 8	Disclosure of Bowcock (GDX 1006) and Kelsell (GDX1007)
[1. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises	"Once a set of cDNAs within the region likely to contain BRCA1 have been identified, they will be studied to see if they detect alterations in DNAs from a variety of sources affected members in linked families, tumors from linked-family members, and sporadic tumors demonstrating loss

<p>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,</p> <p>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.]</p>	<p>of heterozygosity at BRCA1." (GDX1006, 11:4)</p> <p>"Combining this information with previously published mapping information suggests that BRCA1 is contained in a region estimated at 1 - 1.5 Mb in length." (GDX1007, Abstract)</p> <p>"In this study we have performed sequence analysis of [two candidate genes known to be located in the identified locus]. No mutations were detected in the coding region of either gene in the germline DNA from three affected individuals from the family." (GDX1007, 4:2)</p> <p>"Genomic DNA from . . . affected gene carriers (3550, 3543 and 3677) and one unaffected noncarrier (3079) were sequenced. . . for detection of disease-causing mutations in their constitutive DNA. No variation from the published sequences was detected." (GDX1007, 2:8)</p>
<p>8. The method of claim 1</p>	<p><i>See claim 1 above in this chart</i></p>
<p>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</p> <p>sequencing the amplified nucleic acids.</p>	<p>"One sure method of detecting mutations is by DNA sequencing. However, this can be a laborious task, particularly if the gene is very large. Sequencing can be performed on a genomic DNA template or a cDNA template prepared from RNA by reverse transcriptase. PCR allows one to sequence rapidly and directly from a complex template, but problems still remain [with sequencing cDNA]." (GDX1006, 11:5)</p> <p>"Genomic DNA . . . was sequenced directly following PCR amplification." (GDX1007, 5: 7)</p> <p>"Genomic DNA from . . . affected gene carriers (3550, 3543 and 3677) and one unaffected noncarrier (3079) were sequenced. . . for</p>

	detection of disease-causing mutations in their constitutive DNA. No variation from the published sequences was detected." (GDX1007, 2:8)
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91. Based on the teachings of Bowcock and Kelsell, a POSA would have been motivated to *screen* the germline alterations in the BRCA1 gene of a human subject by *amplifying* all or part of a BRCA1 gene of the subject using a set of primers to produce amplified nucleic acids, and *sequencing* the amplified nucleic acids, using techniques that were well within a POSA's technical grasp and selected from a finite number of available options. ¶¶91-106. Bowcock suggests developing methods for screening individuals for predisposing mutations in the BRCA1 gene and discloses examples of several conventional methods that can be applied for screening (or detecting) "alterations in DNAs from a variety of sources [(human subjects)]." GDX1006, Abstract, 13:3, 11:4-12:2. Among those methods, Bowcock specifically discloses DNA sequencing as "[o]ne sure method for detecting mutations" and notes that "[s]equencing can be performed on a genomic DNA template." *Id.*, 11:5. Bowcock also discloses that "PCR allows one to sequence rapidly and directly from a complex template...." *Id.* Kelsell applies the techniques disclosed in Bowcock for screening alterations in the candidate genes for the BRCA1 gene. GDX1007, 2:8, 5:7. Specifically, Kelsell discloses PCR amplifying the genomic DNA of individuals affected or unaffected with breast or

ovarian cancer by using primers to produce amplified nucleic acids, followed by sequencing the amplified nucleic acids to detect disease-causing alterations. *Id.*

92. PCR was a conventional technique to amplify a DNA fragment, and sequencing was a conventional technique to determine sequence of a DNA fragment, particularly genomic DNA. GDX1006, 11:4-12:1; GDX1019, 21-40; 93-109. In fact, the '441 patent itself acknowledges that mutations can be detected by using "techniques well known in the art" and "gene sequences can be amplified directly from genomic DNA . . . using known techniques." GDX1001, 14:9-14. As such, a POSA would have been motivated to screen for the germline alterations in the BRCA1 gene of a human subject by PCR *amplifying* the BRCA1 gene of the subject using a set of primers to produce amplified nucleic acids, and *sequencing* the amplified nucleic acids, using techniques that were well within a POSA's technical grasp from among a finite number of available techniques. GDX1006, 11:4-12:1; ¶37.

93. And a POSA would have had a reason to compare the germline sequence of the BRCA1 gene of a subject with wild-type BRCA1 gene sequence to screen for alterations in the BRCA1 gene sequence. GDX1006, Abstract, 13:3, 11:4-12:1; GDX1007, 2:8, 5: 7. As exemplified in Kelsell, a POSA would have had a reason to amplify and sequence the BRCA1 gene of the subject to detect mutations by compare the sequence of the amplified nucleic acids from the subject

BRCA1 gene with the wild-type sequences. *Id.* Kelsell discloses PCR amplifying the genomic DNA of individuals affected or unaffected with breast or ovarian cancer by using primers to produce amplified nucleic acids, followed by sequencing the amplified nucleic acids to detect disease-causing mutations. GDX1007, 2:8, 5: 7. Kelsell then compares the sequences of the amplified nucleic acids with the published (wild-type) sequences to identify any variations. *Id.*, 2:8.

94. As such, based on the teachings of Bowcock and Kelsell, a POSA would have *compared* the germline sequence of the BRCA1 gene of a subject with the wild-type BRCA1 gene sequence to *screen* for alterations in the BRCA1 gene sequence of a subject by *amplifying* the subject's BRCA1 gene sequence to obtain amplified nucleic acids and *sequencing* the amplified nucleic acids. And a POSA would have understood that a difference between the germline sequence of the BRCA1 gene of a subject and the wild-type BRCA1 gene sequence indicates an alteration in BRCA1 gene of the subject.

95. Thus, a POSA would have been motivated to arrive at the claimed method for *screening* the germline alterations in the BRCA1 gene of a subject by *comparing* the sequence of the BRCA1 gene of the subject with the wild-type BRCA1 gene sequence by *amplifying* all or part of the BRCA1 gene from the subject with a set of primers to produce amplified nucleic acids and *sequencing* the amplified nucleic acids, wherein a difference in the sequences indicated an

alteration in the gene. As such, based on the combined teachings of Bowcock and Kelsell, a POSA would have been motivated to arrive at the method of claim 8.

96. And a POSA would have had a reasonable expectation of success in arriving at the claimed invention. POSAs knew that breast and ovarian cancer susceptibility was inherited. GDX1007, 1:1; GDX1028, Abstract. Thus, POSAs had substantial interest in identifying the breast or ovarian cancer susceptibility gene so that conventional methods could be used for determining a subject's diagnosis or prognosis for breast or ovarian cancer. GDX1005, Abstract; GDX1006, Abstract, 13:3. POSAs also understood that the BRCA1 gene existed in a 1-1.5 Mb region on chromosome 17. GDX1007, Abstract. Given the motivation to develop screening methods for alterations in the BRCA1 gene, mapping of the BRCA1 gene to a 1-1.5 Mb region on chromosome 17, and conventional techniques to identify a gene, identifying the BRCA1 gene was inevitable.

97. In 1990, researchers mapped the Breast Cancer Susceptibility Gene 1 (BRCA1) locus to chromosome 17q21. GDX1007, 1:1 By 1993, the location of the BRCA1 gene was progressively narrowed down to a 1-1.5 Mb region on chromosome 17 via the efforts of several groups utilizing the conventional and well-known positional cloning approach. GDX1007, Abstract. Kelsell's region was located within the regions that were previously identified as the BRCA1 region, and it was used as a reference for later-identified regions (which also fell within

Kelsell's region) to establish that the later-identified regions were reliable. *See* ¶¶38-39. As such, Kelsell's 1-1.5 Mb region was considered the likely location for the BRCA1 gene in the art. *Id.*

98. A POSA would have reasonably expected to succeed in identifying the BRCA1 gene by using a positional cloning approach to further analyze the 1-1.5 Mb locus. Before August 12, 1994, positional cloning was a conventional, routinely-used approach for identifying genes. GDX1006, Abstract, 6:3, Fig. 2; GDX1007, Abstract, 2:6, 3:2; GDX1025, 14; *see* ¶¶31-37. In fact, several genes, such as cystic fibrosis, familial adenomatous polyposis, and Huntington's disease, had already been successfully identified by positional cloning. GDX1006, 6:3; GDX1025, 14. Bowcock provides a roadmap specifically for identifying the BRCA1 gene by positional cloning, involving: (1) genetically localizing the gene to a chromosomal locus, (2) physically capturing the locus when the locus can no longer be genetically narrowed further, (3) searching for the genes located within the locus (candidate genes), and (4) identifying the genes with mutations linked to breast or ovarian cancer. GDX1006, 3:2; 6:3; Fig. 2.

99. It was also generally understood in the art that once the BRCA1 gene had been localized to about a 1 Mb locus (the smallest definable linked interval on human chromosome), it would be straightforward to identify the genes located within the locus and compare their sequences within a linked family to identify

genes with breast or ovarian cancer linked mutations. For example, the King reference articulates this general knowledge in the art. King explains that the presence of several markers in the BRCA1 region "should permit BRCA1 to be localized to roughly 1cM [approx. 1 Mb on human chromosome] by gene mapping" and then "it will be tedious, but straight forward to identify all of the transcripts [corresponding to candidate genes] in the [locus], and comparing sequences of these genes among susceptible versus not susceptible relatives." GDX1027, 3:3-4:1.

100. Further, because of the small size of Kelsell's region, a POSA would have expected a small number of genes to be located within the region⁴. In fact, Kelsell itself found the 1-1.5 Mb region to be sufficiently small to start analyzing the genes known to be located within the region and suggested analyzing other sequences in the region that did not correspond to known genes in order to identify the BRCA1 gene. GDX1007, 4, 2 (To eliminate completely this locus as a candidate for BRCA1 requires sequencing the remainder of the normally untranslated region[.]). Thus, a POSA would have understood Kelsell's 1-1.5 Mb region to be a sufficiently small region to identify and analyze genes within the

⁴ Kelsell's determination that two candidate genes located within its 1-1.5 Mb locus were not the BRCA1 gene helped narrow down the number of candidate genes within the 1-1.5 Mb locus further.

region, and would have reasonably expected to successfully identify the BRCA1 gene from amongst the candidate genes by using the next steps of positional cloning. *See* ¶¶31-37. (Although a POSA would have successfully identified the BRCA1 gene in Kelsell's 1-1.5 Mb region by using the next steps of positional cloning (as practiced and suggested by Kelsell), a POSA could have routinely narrowed down the region further by using "a number of polymorphisms [that had] been identified," allowing further genetic analysis of the region (as suggested by Kelsell). GDX1007, 4:2.).

101. Thus, based on the combined teachings of Bowcock and Kelsell in view of the knowledge in the art and high level of interest in the BRCA1 gene, a POSA would have applied the conventional positional cloning approach, as specifically applied to the BRCA1 gene in Bowcock, to Kelsell's 1-1.5 Mb region to physically capture the region and perform the next steps of positional cloning.

102. "[T]o capture the linked genetic region [*i.e.*, the BRCA1 locus] physically," Bowcock suggests cloning the BRCA1 locus in a "large but manipulable form" once the locus is small enough and can no longer be genetically refined further. GDX1006, Abstract, 6:3. Specifically, Bowcock suggests using yeast artificial chromosomes (YACs) (that can accommodate 200 Kb-2 Mb DNA segments), BACs (that can accommodate 150-350 Kb DNA segments), or P1 phage (that can accommodate approx. 100 Kb DNA segments) to clone large

segments of the BRCA1 region, and using cosmids (that can accommodate approx. 40 Kb DNA segments) to clone smaller overlapping segments of the BRCA1 region. *Id.* YACs, BACs, P1 phages, and cosmids were commonly used laboratory tools to clone segments of genomic DNA. *Id.*

103. Bowcock suggests using routine, conventional techniques to identify the candidate gene located within the region after obtaining the clones. GDX1006, 8:4-11:3, Fig. 4. After identifying the candidate genes, Bowcock suggests screening the genes for the germline mutations that are only present in individuals with breast or ovarian cancer or in tumors. *Id.*, Abstract, 11:4-12:2. Bowcock discloses various conventional techniques, such as hybridization methods, sequencing methods (*e.g.*, polymerase chain reaction (PCR), or PCR followed by sequencing) to identify genes with breast or ovarian cancer linked mutations. *Id.* In fact, the '441 patent itself acknowledges that mutations can be detected by using "techniques well known in the art" and "gene sequences can be amplified directly from genomic DNA . . . using known techniques." GDX1001, 14:9-14.

104. As such, based on the combined teachings of Bowcock and Kelsell and common practice in the art, a POSA looking to isolate the BRCA1 gene would have been motivated to apply a conventional positional cloning approach, as disclosed by Bowcock, to identify the BRCA1 gene within the narrow 1-1.5 Mb BRCA1 region of Kelsell with a reasonable expectation of success, because such

methods use conventional techniques that have been used successfully for other genes (*e.g.*, cystic fibrosis). GDX1006, Abstract, 3:2, 6:3, Fig. 2, Fig. 4. Vicissitudes on the course to identifying the BRCA1 gene are expected and are part of the expected process towards inevitable identification of a disease gene from its known chromosomal location. ¶31. In fact, these vicissitudes further the gene identification process. *Id.* For example, Kelsell's determination that two candidate genes located within its 1-1.5 Mb locus were not actually the BRCA1 gene helped narrow down the number of candidate genes within the 1-1.5 Mb locus further.

105. In sum, Kelsell discloses a narrow 1-1.5 Mb BRCA1 locus that would have contained a finite number of genes within the locus. And, Bowcock directs using a conventional and routine positional cloning approach for identifying the BRCA1 gene within a locus, which involves using a standard combination of routine, well-known techniques. And, in view of the BRCA1 gene-specific guidance provided in Bowcock, general knowledge in the art and common sense, a POSA would have used Bowcock's positional cloning approach to BRCA1 identification to inevitably identify the BRCA1 gene within Kelsell's 1-1.5 Mb region.

106. Having identified the BRCA1 gene, a POSA would have had a reasonable expectation of successfully screening the germline of a human subject

for alterations in the BRCA1 gene, by amplifying all or part of the gene from the subject to obtain amplified nucleic acids and sequencing the amplified nucleic acids. PCR amplification and sequencing were conventional techniques routinely used in the art before August 12, 1994. GDX1006, 11:3-12:2, GDX1007, 5:7; ¶37. In fact, the '441 patent itself acknowledges that mutations can be detected by using "techniques well known in the art" and "gene sequences can be amplified directly from genomic DNA . . . using known techniques." GDX1001, 14:9-14. And, Kelsell discloses successful screening of candidate genes for mutations by PCR amplifying the gene from genomic DNA, followed by sequencing. GDX1007, 5:7 (although the candidate genes were determined to be not BRCA1 gene, the screening by itself was successful and brought a POSA closer to finding the BRCA1 by eliminating 2 of the candidate genes in the 1-1.5 Mb region). As such, a POSA would have had a reasonable expectation of successfully *screening* the germline of a human subject for alterations in the *BRCA1* gene by *amplifying* all or part of the gene from the subject to get amplified nucleic acids and *sequencing* the amplified nucleic acids. That is, a POSA would have had a reasonable expectation of successfully arriving at the method of claim 8.

B. Claim 23

107. Claim 23 depends from claim 20 and thus contains each and every element of claim 20. Accordingly, claim 20 is included in the claim chart below to

enumerate all the elements of claim 23. The claim chart below shows where Bowcock and Kelsell disclose every element of claim 8.

Claim 23	Disclosure of Bowcock (GDX1006) and Kelsell (GDX1007)
<p>[20. A method for detecting a germline alteration in a BRCA1 gene,</p> <p>said alteration selected from the group consisting of the alterations set forth in Tables 11 and 12 which comprises</p> <p>analyzing a sequence of the BRCA1 gene or BRCA1 RNA from a human sample or analyzing the sequence of BRCA1 CDNA made from mRNA from said sample.]</p>	<p>"Once a set of cDNAs within the region likely to contain BRCA1 have been identified, they will be studied to see if they detect alterations in DNAs from a variety of sources affected members in linked families, tumors from linked-family members, and sporadic tumors demonstrating loss of heterozygosity at BRCA1." (GDX1006, 11:4)</p> <p>" BRCA1 is contained in a region estimated at 1 - 1.5 Mb in length." (GDX1007, Abstract)</p> <p>"In this study we have performed sequence analysis of [two candidate genes known to be located in the identified locus]. No mutations were detected in the coding region of either gene in the germline DNA from three affected individuals from the family." (GDX1007, 4:2)</p> <p>"Genomic DNA from lymphoblastic cell lines from three affected gene carriers (3550, 3543 and 3677) and one unaffected noncarrier (3079) were sequenced for the whole coding region of both . . . genes . . . for detection of disease-causing mutations in their constitutive DNA. No variation from the published sequences was detected " (GDX1007, 2:8)</p>
<p>23. The method of claim 20</p>	<p><i>See claim 20 above in this chart</i></p>
<p>wherein a germline alteration is detected by amplifying all or part of a BRCA1 gene in said</p>	<p>"One sure method of detecting mutations is by DNA sequencing. However, this can be a laborious task, particularly if the gene is very large. Sequencing can be performed on a</p>

<p>sample using a set of primers to produce amplified nucleic acids and</p> <p>sequencing the amplified nucleic acids.</p>	<p>genomic DNA template or a cDNA template prepared from RNA by reverse transcriptase. PCR allows one to sequence rapidly and directly from a complex template, but problems still remain [with sequencing cDNA]." (GDX1006, 11:5)</p> <p>"Genomic DNA . . . was sequenced directly following PCR amplification." (GDX1007, 5: 7)</p> <p>"Genomic DNA from . . . affected gene carriers (3550, 3543 and 3677) and one unaffected noncarrier (3079) were sequenced . . . for detection of disease-causing mutations in their constitutive DNA. No variation from the published sequences was detected." (GDX1007, 2:8)</p>
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108. As discussed above under claim 8, based on the combined teachings of Bowcock and Kelsell, a POSA would have been motivated to arrive at a method for *screening* the germline alterations in the BRCA1 gene of a sample by *comparing* the sequence of the BRCA1 gene in the sample with the wild-type BRCA1 gene sequence by *amplifying* all or part of the BRCA1 gene from the sample with a set of primers to produce amplified nucleic acids and *sequencing* the amplified nucleic acids, wherein a *difference* in the sequences indicated an alteration in the gene, with a reasonable expectation of success. ¶¶91-106.

109. As construed above, the '441 patent interchangeably uses "screening" and "detecting," and these terms are synonymous. Also, "analyzing a sequence " is understood to include determining the sequence of the BRCA1 gene in the human

sample and comparing the sequence from the sample with a control (wild-type) sequence. As such, a POSA would have been motivated to arrive at a method for *detecting* a germline alteration in a BRCA1 gene by *analyzing* the BRCA1 gene sequence from a human sample by *amplifying* all or part of a BRCA1 gene from the sample using a set of primers to produce amplified nucleic acids and *sequencing* the amplified nucleic acids, with a reasonable expectation of success.

110. A POSA would have had motivation to identify the exact alterations in the BRCA1 gene that are recited in claim 23 (listed in Tables 11 and 12 of the '441 patent), with a reasonable expectation of success. While the exact identity of these alterations may not have been known, a POSA would have expected these mutations inherited nature of breast or ovarian cancer. GDX1007, 1:1; GDX1028, Abstract ; ¶96. And, a POSA would have been motivated to identify such mutations in view of the inherited nature of breast or ovarian cancer, inevitable identification of the BRCA1 gene, the use of mutations in other genes for diagnosing diseases, and the desire for screening methods for BRCA1 alterations. ¶¶96-105. In addition, a finite number of conventional and routine methods (*e.g.*, PCR amplification and sequencing) to screen alterations were available, as noted above under claim 8 discussion. GDX1006, 11:3-12:1; ¶103. Thus, a POSA would have been motivated to identify the new alterations, such as the alterations listed in Tables 11 and 12 of the '441 patent (and recited in claim 23), using techniques that

were well within a POSA's technical grasp and were selected from a finite number of available options. Given that such conventional and routine methods had previously been used to screen for additional alterations in genes, *e.g.*, in Miki and Kelsell, a POSA would have had a reasonable expectation of successfully identifying alterations in the BRCA1 gene. GDX1005, 3:2, 6:n26; GDX1007, 2:8, 5:7; GDX1006, 6:3.

111. Given the desire for methods to screen for BRCA1 alterations to diagnose breast or ovarian cancer, a POSA would have been motivated to screen previously analyzed or new patients with breast or ovarian cancer or patients with family history of breast or ovarian cancer to identify any additional alterations. GDX1005, Abstract; GDX1006, Abstract, 13:3. As discussed above for claim 8, a finite number of conventional methods for screening alterations were known. And, a POSA would have screened only a limited number of patients using conventional methods selected from a finite number of available options to identify at least one of the BRCA1 alterations required in claim 23. Thus, a POSA would have screened a finite number of patients using conventional techniques selected from a finite number of options to successfully identify at least one of the mutations recited in claim 23.

112. As such, a POSA would have had a reasonable expectation of successfully arriving at a method for detecting the germline alteration in the

BRCA1 gene by *analyzing* the BRCA1 gene sequence from a human sample by *amplifying* all or part of a BRCA1 gene from the sample using a set of primers to produce amplified nucleic acids and *sequencing* the amplified nucleic acids, wherein the alteration was selected from the alterations listed in Table 11 and 12 of the '441 patent.

113. And, in view of the facts discussed above and my understanding with respect to obviousness, it is my understanding that claims 8 and 23 would have been obvious in view of Bowcock in combination with Kelsell.

XV. Ground 3: Bowcock, Kelsell, and Cotton Provide a Reason to Arrive at the Invention of Claims 7 and 12 with a Reasonable Expectation of Success

114. I understand that Kelsell, Bowcock, and Cotton are considered to be prior art to the '441 patent even if the '441 patent is entitled to the benefit of the filing date of one or more of its parent applications. The claim charts and discussion below show that Bowcock, Kelsell, and Cotton teach or suggest each and every element of claims 7 and 12.

115. As discussed above under Ground 2, a POSA would have had a reason to combine the teachings of Bowcock and Kelsell. Bowcock and Kelsell disclose conventional methods for identifying the BRCA1 gene and methods for screening the BRCA1 gene for alterations after the BRCA1 has been identified. GDX1006, Abstract, 3:2, 6:3, Fig. 2; GDX1007, 2:8, 5:9. As discussed above

under claim 8, based on the combined teachings of Bowcock and Kelsell, a POSA would have would have been motivated to identify the BRCA1 gene and would have screened for alterations in the gene using conventional techniques disclosed in the references. ¶¶86-106. Cotton discloses commonly-used techniques for detecting mutations before August 12, 1994, particularly allele-specific oligonucleotide (ASO) hybridization. GDX1020, Abstract, 11:9-12:1. As such, a POSA looking to detect alterations in the BRCA1 gene would have had a reason to use ASO hybridization disclosed in Cotton in a method for screening the germline alterations in the BRCA1 gene disclosed in the combined teaching of Bowcock and Kelsell. As discussed in detail below, a POSA would also have had a reasonable expectation of successfully arriving at the subject matter of claims 7 and 12.

A. Claim 7

116. Claim 7 depends from claim 1 and thus contains each and every element of claim 1. Claim 1 elements are discussed above under claim 8.

Claim 7	Disclosure of Bowcock (GDX1006), Kelsell (GDX1007) and Cotton (GDX1020)
7. The method of claim 1	<i>See claim 1 above under claim 8 discussion.</i>
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	"Once mutations have been defined they can be searched for repeatedly by methods referred to as diagnostic methods. Such methods include allele-specific oligonucleotide hybridization [" (GDX1020, Abstract) "[Allele-specific oligonucleotide hybridization] is the oldest general targeted method for mutation detection , and relies on mismatches

<p>detecting the presence of a hybridization product,</p> <p>wherein a presence of said product indicates the presence of said allele in the subject.</p>	<p>between mutant target genomic (or PCR amplified) DNA and synthetic wild-type oligonucleotides showing decreased binding of the oligonucleotide relative to a mutant oligonucleotide []." (GDX1020, 11:9-12:1)</p> <p>"Applications [of allele-specific oligonucleotide hybridization] . . . too numerous to require specific examples to be given." (GDX1020, 12:4)</p>
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117. As discussed above under claim 8, based on the teachings of Bowcock and Kelsell, a POSA would have been motivated to arrive at the method of *screening* the germline of a human subject for alterations in the *BRCA1* gene by *amplifying* all or part of the gene from the subject to get amplified nucleic acids and *sequencing* the amplified nucleic acids, wherein a difference in the sequence of the BRCA1 gene from the wild-type gene indicates an alteration in the BRCA1 gene. And, a POSA would have done so with a reasonable expectation of success. That is, based on the teachings of Bowcock and Kelsell, a POSA would have arrived at a method of claims 1 and 8 for screening the germline for alterations in the BRCA1 gene with a reasonable expectation of success.

118. Cotton discloses using allele-specific oligonucleotide (ASO) probe hybridization as one of the conventional techniques to detect specific mutations in genomic DNA. GDX1005, Fig. 6C; GDX1020, 11:9-12:1, 12:4. In fact, the '441 patent acknowledges the use of ASO probes as a well-known technique to confirm presence of a susceptibility allele. GDX1001, 14:9-26. As such, a POSA looking to

screen for alterations of the BRCA1 gene would have been motivated to use the ASO probe hybridization in the methods for screening the germline alterations in the BRCA1 gene (replacing two routine techniques, amplification and sequencing, with another routine technique, ASO probe hybridization).

119. ASO probes are oligonucleotide probes that specifically hybridize to a particular allele of the gene (here BRCA1 gene). And, screening mutations by ASO probes encompasses *hybridizing* the probes to the genomic DNA of a subject and the wild-type control, *detecting* the hybridization product from the two hybridizations, and *comparing* their hybridization patterns. And, a POSA would have understood that a *difference* in the hybridization pattern indicates hybridization to *different alleles, i.e.*, to different BRCA1 gene sequences.

120. Thus, a POSA would have been motivated to *screen* the germline of a subject for an alteration in the BRCA1 gene by *comparing* the germline sequence of the BRCA1 gene of a subject with the wild-type sequence by *hybridizing* a BRCA1 gene probe that specifically hybridizes to a BRCA1 allele to the genomic DNA isolated from the subject and *detecting* the presence of a hybridization product, such that the presence of a hybridization product indicates the *presence* of the allele. A POSA would have understood that a difference in hybridization patterns of BRCA1 gene sequence of the subject from the wild-type sequence after

hybridization with an ASO probe indicates a difference in the two sequences, which in turn correlates to an *alteration*.

121. As such, based on the combined teachings of Kelsell, Bowcock, and Cotton, a POSA would have arrived at the method for *screening* the germline of a subject for an alteration in the BRCA1 gene by *comparing* the germline sequence of the BRCA1 gene of a subject with the wild-type sequence. A POSA would have done so by *hybridizing* an allele-specific BRCA1 gene probe to the genomic DNA isolated from the subject and *detecting* the presence of a hybridization product, such that the presence of a hybridization product indicates the *presence* of the allele, which in turn indicates an alteration in the BRCA1 gene sequence.

122. Further, as discussed in this section above, before August 12, 1994, hybridization methods using allele-specific oligonucleotide probes were conventional and routinely used. GDX1020, Abstract, 11:9-12:4. Therefore, because of the reasons discussed for claims 8 and 23 under Ground 2 and the use of conventional ASO probe hybridization, a POSA would have had a reasonable expectation of successfully arriving at the method.

B. Claim 12

123. Claim 12 depends from claim 1 and thus contains each and every element of claim 1. The elements of claim 1 are discussed above under claim 8.

Claim 12	Disclosure of Bowcock (GDX 1006), Kelsell (GDX1007) and Cotton (GDX1020)
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<p>12. The method of claim 1 wherein a germline nucleic acid sequence is compared by amplifying BRCA1 nucleic acids from said sample to produce amplified nucleic acids,</p> <p>hybridizing the amplified nucleic acids to a BRCA1 DNA probe specific for a BRCA1 allele and</p> <p>detecting the presence of a hybridization product,</p> <p>wherein the presence of said product indicates the presence of said allele in the subject.</p>	<p><i>See claim 1 above under claim 8 discussion.</i></p> <p>"All these methods [including SSCP] are currently performed most successfully after PCR amplification of the region under study." (GDX1006, 12:1)</p> <p>"PCR amplification reactions . . . of genomic DNA . . . All the amplification products were analysed by . . . PCR amplification product was run on a 6% denaturing sequencing gel. The DNA was transferred by blotting . . . followed by 12 hours of hybridisation at 42°C with one of the oligonucleotide primers used in the initial PCR amplification . . . After hybridisation . . . the reaction products were detected by . . . autoradiography." (GDX1007, 5:3)</p> <p>"Once mutations have been defined they can be searched for repeatedly by methods referred to as diagnostic methods. Such methods include allele-specific oligonucleotide hybridization[.]" (GDX1020, Abstract)</p> <p>"[Allele-specific oligonucleotide hybridization] is the oldest general targeted method for mutation detection, and relies on mismatches between mutant target genomic (or PCR amplified) DNA and synthetic wild-type oligonucleotides showing decreased binding of the oligonucleotide relative to a mutant oligonucleotide []." (GDX1020, 11:9-12:1)</p> <p>"Applications [of allele-specific oligonucleotide hybridization] . . . too numerous to require specific examples to be given." (GDX1020, 12:4)</p>
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124. As discussed above under claim 8, based on the teachings of Bowcock and Kelsell, a POSA would have been motivated to arrive at the method of

screening the germline of a human subject for alterations in the *BRCA1* gene by *amplifying* all or part of the gene from the subject to get amplified nucleic acids and *sequencing* the amplified nucleic acids, wherein a difference in the sequence of the *BRCA1* gene from the wild-type gene indicates an alteration in the *BRCA1* gene. And, a POSA would have done so with a reasonable expectation of success. That is, based on the teachings of Bowcock and Kelsell, a POSA would have arrived at the methods of claims 1 and 8 for screening the germline for alterations in the *BRCA1* gene with a reasonable expectation of success.

125. Cotton discloses using allele-specific oligonucleotide (ASO) probe hybridization as one of the conventional techniques to detect specific mutations in nucleic acids. GDX1020, 11:9-12:4; *see also* GDX1019, 99 (suggesting "[u]sing allele-specific oligonucleotide probes to discriminate between amplification products that differ by a single base pair."). In fact, the '441 patent acknowledges ASO probe hybridization as a well-known method. GDX1001, 14:9-26. As such, a POSA looking to screen for alterations of the *BRCA1* gene would have been motivated to use the ASO probe hybridization to screen for alterations in the *BRCA1* gene.

126. As discussed above under claim 7, ASO probes are oligonucleotide probes that specifically hybridize to a particular allele of the gene (here *BRCA1* gene). And, *screening* alterations by ASO probes encompasses *hybridizing* the

probes to amplified nucleic acids from a subject BRCA1 gene and wild-type control, *detecting* the hybridization product from the two hybridizations, and *comparing* their hybridization patterns. And, a POSA would have understood that a difference in the hybridization pattern indicates hybridization to *different alleles*, *i.e.*, to different BRCA1 gene sequences. A POSA would have also understood that a difference in hybridization patterns of BRCA1 gene sequence of the subject from the wild-type sequence after hybridization with an ASO probe indicates a difference in the two sequences, which in turn correlates to an *alteration*.

127. As such, based on the combined teachings of Kelsell, Bowcock, and Cotton, a POSA would have arrived at the method for *screening* the germline of a subject for an alteration in the BRCA1 gene by *comparing* the germline sequence of the BRCA1 gene of a subject with the wild-type sequence by *amplifying* BRCA1 nucleic acids from the subject to produce amplified nucleic acids, *hybridizing* a BRCA1 DNA probe that specifically hybridizes to a BRCA1 allele to the amplified nucleic acids, and *detecting* the presence of a hybridization product, such that the presence of a hybridization product indicates the presence of the allele, which in turn indicates an alteration in the BRCA1 gene sequence.

128. Further, as discussed in this section above, before August 12, 1994, hybridization methods using allele-specific oligonucleotide probes were conventional and routinely used. GDX1020, Abstract, 11:9-12:1, 12:4; *see also*

GDX1019, 99. Therefore, because of the reasons discussed for claims 8 and 23 under Ground 2 and the use of conventional ASO probe hybridization, a POSA would have had a reasonable expectation of successfully arriving at the method of claim 12.

129. And, in view of the facts discussed above and my understanding with respect to obviousness, it is my understanding that claims 7 and 12 would have been obvious in view of Bowcock in combination with Kelsell.

XVI. Objective Indicia of Non-obviousness

130. I understand that in considering the obviousness of an invention, one should also consider whether there are any objective evidence of nonobviousness (also known as secondary considerations of nonobviousness), which include commercial success, long-felt, but unmet need, failure of others, industry praise, unexpectedly superior results and commercial acquiescence through licensing. In reaching my opinions regarding obviousness laid out herein, I also considered whether there were any secondary considerations of non-obviousness.

131. In my review of the prosecution history of the '441 patent, I did not see any allegation of objective evidence of nonobviousness. However, in district court, Myriad provided declarations of Kay (GDX1015) and Critchfield (GDX1014) which included assertions of commercial success, long-felt need and

failure of others, and industry praise. My analysis of the Kay and Critchfield declarations as they relate to secondary considerations follow.

A. No Commercial Success

132. It is my understanding that "commercial success" can be evidence of non-obviousness. I also understand that a finding of commercial success requires evidence of substantial sales, which can be deemed a "success," of the claimed invention and evidence of a nexus (or link) between the "commercial success" and the claims of the patent, *i.e.*, proof that the "sales" are a direct result of the patented technology, as opposed factors unrelated to the claimed invention, such as marketing or lack of competition in the marketplace. I understand that allegations of commercial success based solely on total revenue are insufficient in the absence of a nexus between the sales and the claims of the patent.

133. In reviewing the Kay and Critchfield declarations, I do not find that Myriad has shown facts consistent with commercial success. The Kay and Critchfield declarations point to the BRACAnalysis[®] testing as purportedly showing commercial success of Myriad's collection of patents-in-suit⁵. However,

⁵ The Kay declaration is from *University of Utah Research Foundation v. Ambry Genetics Corp.* Case No. 2:13-cv-00640-RJS and involved Patent Nos. 5,709,999; 5,747,282; 5,753,441; 5,837,492; 6,033,857; 5,654,155; 5,750,400; 6,051,379; 6,951, 721; and 7,250,497. The Critchfield declaration is from

Myriad has not shown that its commercial method is an embodiment of the claims challenged here. GDX1015, 42. Myriad alleges only that “tests that use the claimed inventions have been very successful and a source of significant revenue.” *Id.*, 43. But Myriad has not provided facts stating how any allegedly novel feature of any claim accounts for its alleged commercial success. *Id.*, 42-43.

134. In fact, I note that Myriad’s 2013 Annual Report acknowledged that its sales increase is attributable to Myriad's marketing and education effort: "We believe that our increased sales, marketing, and education efforts resulted in wider acceptance of our molecular diagnostic tests by the medical community and increased patient testing volumes." GDX1013, 52. And according to Dr. Critchfield’s declaration, Myriad’s marketing and education efforts were extensive: (1) By 2009, Myriad had invested more than 200 million dollars in raising patient and physician awareness; (2) By 2009, Myriad had assembled a 300-person sales force (now a 400-person sales force); (3) In just one quarter of 2009, Myriad organized more than 300 "speakers programs" all over the country; (4) Myriad spent millions of dollars on TV and other popular media promotions; and (5) Myriad invested significantly in reimbursement agreements to cover patients' costs for

Association for Molecular Pathology et al. v. Myriad Genetics et al. No. 09 Civ. 4515 (RWS) and involved Patent Nos. 5,710,001; 5,753,441; 5,747,282; 5,837,492; 6,033,857; 5,693,473; and 5,709,999.

genetic testing. GDX1014, 25-31. Accordingly, I did not find that Myriad provides facts showing a nexus between its sales and any challenged claim.

B. No Long-Felt, Unmet Need or Failure of Others

135. It is my understanding that a showing of a long-felt unmet need requires three factors. First, the need must have been a persistent one that was recognized in the prior art by those of ordinary skill in the art. Second, the long-felt need must not have been satisfied by another before the invention. Third, the invention must in fact satisfy the long-felt need. I understand a showing of long-felt need requires a showing of all three factors.

136. In reviewing the Kay and Critchfield declarations, I do not find that Myriad has shown facts consistent with long-felt need. Myriad asserted that *BRACAnalysis*® filled a long-felt unmet need for a test to accurately evaluate a patient's risk of developing hereditary breast and ovarian cancers. GDX1015, 42. However, Myriad did not identify any particular art that articulates a long-felt, unmet need for the claimed invention. GDX 1015, 42. And Myriad has only generally alleged a long-felt, unmet need for its testing services, without tying the need to the merits of the particular challenged claims. *Id.* Also, Myriad has not provided evidence showing that the subject matter of the claims challenged here meets any long-felt, unmet need. *Id.*

137. Regarding its allegation of failure of others, Myriad has provided no

evidence that there was a lack of know-how for solving any technical problem related to any of the challenged claims. *Id.* Rather, Myriad seems to allege that because it determined the gene sequence of BRCA1, other researchers failed to arrive at the claimed invention. But Myriad does not show that any researchers failed for technical reasons, or even that other researchers attempted to arrive at any challenged claim. *Id.* Myriad's allegation that it determined a partial gene sequence cannot establish failure of others to arrive at the claimed invention. Rather, vicissitudes are expected on the course to gene discovery and are part of the normal process towards the inevitable identification of a gene once its chromosomal location is determined, as discussed above in ¶¶31-37, 96-105.

C. No Evidence of Industry Praise

138. I understand that evidence of industry praise must establish a nexus between the alleged praise and the claimed invention. But in reviewing the Critchfield and Kay declarations, I did not find that Myriad articulated any industry praise with a nexus to any of the challenged claims. GDX1015, 42; GDX1014, 18.

139. And if Myriad were to assert that there had been praise for the original BRCA1 sequencing work, such praise would lack a nexus to the merits of the challenged claims. The challenged claims are not directed to sequencing the BRCA1 gene, but are directed to screening or detecting alterations in the BRCA1 gene. And neither the Critchfield nor the Kay declarations show that that any

praise for BRACAnalysis® is due to features of the challenged claims. GDX1015, 42; GDX1014, 18.

140. Myriad has asserted that its BRACAnalysis® test has been recognized in the field as a "gold standard" GDX1014, 18, *citing* Eng et al. S, (GDX1016). However, Eng's statement was not directed to a method for screening or detecting alterations in the BRCA1 gene as recited in the challenged claims. Rather, Eng's statement refers to a broad category of methods for direct nucleotide sequence analysis, not just BRACAnalysis®. Eng stated, "[d]irect nucleotide sequence analysis is considered the gold standard for mutation detection for genes such as BRCA1 and BRCA2." GDX1016, 1:2. But direct nucleotide sequence analysis is not limited to BRACAnalysis®. Direct nucleotide sequence analysis is a technique well known in the prior art and can be used for virtually any nucleotide sequence. And direct nucleotide sequence analysis can be accomplished, for example, using conventional methods such as DNA sequencing, sequence-specific hybridization, or sequence-specific amplification. In reviewing the Critchfield and Kay declarations, I did not observe facts showing a nexus between the alleged praise (for direct nucleotide sequence analysis) and the challenged claims directed to methods for screening or detecting alterations in the BRCA1 gene. GDX 1015, 42; GDX 1014, 18.

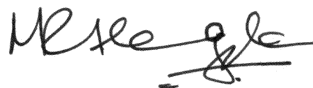
D. No Other Objective Evidence

141. I am not aware of any evidence of unexpectedly superior results of the claimed invention, nor any commercial acquiescence through licensing.

XVII. Conclusion

142. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'MHegde', with a horizontal line drawn underneath it.

Madhuri Hegde

Date: August 18, 2014

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