

IN THE 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 to Skolnick *et al.*

Issue Date: May 19, 1998

Title: 17Q-Linked Breast and Ovarian Cancer Susceptibility Gene

Inter Partes Review No. Unassigned

**Petition for *Inter Partes* Review of U.S. Patent No. 5,753,441 Under 35 U.S.C.
§§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123**

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I. INTRODUCTION

GENEDX, INC. petitions for *inter partes* review, seeking cancellation of claims 7, 8, 12, and 23 of U.S. Patent No 5,753,441 to Skolnick ("the '441 patent") (GDX1001), purportedly owned by UNIVERSITY OF UTAH RESEARCH FOUNDATION AND THE GOVERNMENT OF THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES. On information and belief MYRIAD GENETICS has an interest in the '441 patent. The owners and any potential licensee are referred to collectively as MYRIAD.

II. OVERVIEW

The challenged claims, claims 7, 8, 12, and 23, of the '441 patent are unpatentable over the art identified herein. The '441 patent issued from U.S. Appl. No. 08/488,011 ("the '011 application"), filed June 7, 1995¹, which claims benefit of a series of CIP applications with August 12, 1994 as the earliest filing date. None of the challenged claims are entitled to the benefit of the filing dates of the parent applications. The challenged claims are directed to methods for screening a subject's germline for BRCA1 gene alteration or for detecting a germline alteration in a sample's BRCA1 gene. The claims require a) hybridizing a probe that specifically hybridizes to a BRCA1 allele to the genomic DNA from the sample

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

(claim 7) or amplified nucleic acids obtained from the BRCA1 nucleic acids of the sample (claim 12), and detecting the presence of a hybridization product; or b) amplifying all or part of the BRCA1 gene from the sample to produce amplified nucleic acids and sequencing the amplified nucleic acids (claims 8 and 23). GDX1001, 155-157. Claim 23 also requires specific BRCA1 alterations. *Id.* As of June 7, 1995, each claim is anticipated by Miki *et al.* GDX1005. And as of August 12, 1994, each claim would have been obvious over the combinations of art identified below, showing that a person of ordinary skill in the art ("POSA") would have had a reason to arrive at the claimed methods, with a reasonable expectation of success. GDX1006; GDX1007; GDX1020. Because Petitioner is, at a minimum, reasonably likely to prevail in showing unpatentability, the Petition should be granted and trial instituted on all of the challenged claims.

III. STANDING (37 C.F.R. § 42.104(a)); PROCEDURAL STATEMENTS

Petitioner certifies that (1) the '441 patent is available for IPR and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '441 patent. This Petition is filed in accordance with 37 CFR § 42.106(a). A Power of Attorney and an Exhibit List are filed concurrently herewith. The required fee is paid online via credit card. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Acct. No. 19-0036 (Customer ID No. 45324).

IV. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

Real Parties-In-Interest (37 C.F.R. § 42.8(b)(1)) are: GENEDX, INC. and BIOREFERENCE LABORATORIES, INC.

Related Matters (37 C.F.R. § 42.8(b)(2)): Judicial matters: The '441 patent has been asserted against GeneDx in *Univ. of Utah Research Foundation et al. v. GeneDx*, No. 2-13-cv-00954 (D. Utah Oct. 16, 2013) and against others in cases consolidated into: *In Re: BRCA1- and BRCA2- Based Hereditary Cancer Test Patent Litigation*, No. 2-14-md-02510 (D. Utah Feb. 25, 2014); and in *Invitae Corporation v. Myriad Genetics, Inc.*, No. 3-13-cv-05495 (N. D. Cal. Nov. 26, 2013); *Quest Diagnostics Inc. et al. v. Myriad Genetics, Inc.*, No. 8-13-cv-01587 (C. D. Cal. Oct. 10, 2013); *Counsyl, Inc v. Myriad Genetics, Inc.*, 5-13-cv-04391 (N. D. Cal. Sep. 20, 2013); *Univ. of Utah Research Foundation et al. v. Gene by Gene, Ltd.*, No. 2-13-cv-00643 (D. Utah Jul. 10, 2013). GDX1012. Administrative matters: Petitions for IPR of USPNs 5,654,155; 6,051,379; 6,033,857; 6,083,698; and 6,951,721 are filed concurrently with this petition.

Designation of Counsel (37 C.F.R. § 42.8(b)(3)):

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Notice of Service Information (37 C.F.R. § 42.8(b)(4)): Please direct all correspondence regarding this Petition to lead counsel at the above address. Petitioner consents to service by email at: eellison-PTAB@skgf.com; dsterlin-PTAB@skgf.com; and tpowers-PTAB@skgf.com.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. § 42.22(A))

Petitioner requests IPR and cancellation of claims 7, 8, 12, and 23. A detailed statement of the reasons for the requested relief is in Section VIII.

VI. CLAIM CONSTRUCTION

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretation in light of the specification of the '441 patent. Terms not explicitly discussed below are plain on their face and should be construed to have their ordinary and customary meanings.

"Germline". While the '441 patent and prosecution history do not explicitly define the term, the patent states: "[s]omatic mutations . . . occur only in certain

tissues, . . . are not inherited . . . Geimline [sic] mutations . . . found in any of a body's tissues and are inherited." GDX1001, 12:44-47. So, 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. GDX1002, 19.

"Alteration". The '441 specification defines "alteration" as: "[a]lteration of a wild-type gene' encompasses all forms of mutations . . . in the coding and noncoding regions." 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, 7). Thus, a POSA would interpret "**alteration**" to include mutations and polymorphisms. GDX1002, 20.

"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" *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. 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. GDX1002, 21-22. The BRCA1 gene probe may be specific to a wild-type BRCA1 allele or a mutant allele. 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. *Id.*, 23.

Primers". While neither the '441 patent nor its prosecution history explicitly define the term, the '441 patent 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. So, 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. GDX1002, 24.

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.* 155:17-25, 57-62, 156:44-50. And, claim 27 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. GDX1002, 25.

VII. PERSON OF ORDINARY SKILL IN THE ART AND STATE OF THE ART

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 years of experience in recombinant DNA technology, medical genetics, or genetic diagnostics. GDX1002, 11. A POSA would have known how to research the scientific literature regarding recombinant DNA technology, medical genetics, or genetic diagnostics. *Id.* 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. *Id.* For example, a molecular biologist and a physician may have been part of the team. *Id.* Before August 12, 1994, a POSA 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. *Id.*, 12. 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 genes. *Id.*

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 is 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, like many cancers, are influenced by an individual's genetic makeup. GDX1007, 1:1; GDX1002, 27. An individual's germline DNA sequence is inherited and is present in all nucleated cell types. GDX1025, 22. Alterations or variations can arise in a gene sequence. *Id.*, 18-19. Some alterations are common in a population and are not linked to a disease or a disease risk (polymorphisms).

GDX1002, 29. Other alterations are linked to a disease or a disease risk (mutations). GDX1025, 18-19. A germline mutation is present in genomic DNA of all nucleated cells, is inherited by an individual, and can be passed on to progeny. *Id.*, 22. Because of alterations in its sequence, a gene can exist in alternative forms within a population (alleles), with a wild-type sequence as the most common sequence not linked to a disease risk. GDX1002, 29; GDX1025, 18.

Before August 12, 1994, conventional methods to isolate a genomic DNA segment were known. GDX1002, 30. Positional cloning was a conventional approach to identify genes. *Id.*, 31; GDX1006, 3:2, 6:3, Fig. 2. Before the BRCA1 gene was identified using positional cloning, positional cloning had "been used effectively [to isolate] several important human disease genes such as cystic fibrosis, familial adenomatous polyposis, and Huntington's disease." GDX1006, 6:3; GDX1025, 14; GDX1002, 31.

Positional cloning starts with mapping the gene to a chromosomal location by linkage analysis. GDX1006, 3:5-6, 6:3, Fig. 2; GDX1002, 32. "Linkage analysis relies on the identification of a marker or markers that segregate [in families] with disease predisposition," to map a gene's location relative to the markers. GDX1006, 3:6. Before August 12, 1994, linkage analysis was routinely used to map genes. GDX1006, 3:5-4;3, 6:3, Fig. 2; GDX1002, 32. Researchers performed multiple rounds of linkage analysis to find markers that were close to the gene

location to identify a narrow location. *Id.* The genetic location is then genetically refined further by identifying closer markers. GDX1006, 6:3, Fig. 2, 7:2.

Once the chromosomal region can no longer be genetically refined further, "the only viable approach [] to obtaining the gene is to capture the linked region physically, search for all the genes within it [(candidate genes)], and see which [gene] is altered consistently in linked families[.]" GDX1006, 6:3. About 1 Mb region was understood in the art to be sufficiently narrow to allow straightforward identification of a gene. GDX1002, 33. *E.g.*, 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 [candidate genes] in the [region]." GDX1027, 3:3-4:1. And, Kelsell *et al.* considered a 1-1.5 Mb region to be sufficiently narrow to start analyzing known genes in the region t and suggested analyzing other sequences in the region that did not correspond to the known genes in order to identify the BRCA1 gene. GDX1007, 4: 2; GDX1002, 33.

Before August 12, 1994, genetic regions were routinely physically captured (cloned) into conventional tools, such as bacterial artificial chromosomes (BACs) to obtain clones containing overlapping DNA sequences. GDX1006, 6:3, 7:2-8:3; GDX1002, 34. The clones could then be analyzed using conventional techniques to identify candidate genes within the region. GDX1006, 8:4-11:2, Fig. 4; GDX1002,

34. Once candidate genes were identified, they were screened for alterations linked with a disease using conventional techniques, *e.g.*, allele-specific oligonucleotide (ASO) probe hybridization, PCR amplification, and sequencing. GDX1006, 11:4-12:2; GDX1020, 3:Abstract, 11:9-12:1; GDX1002, 35.

Hybridization methods detect an alteration in the sequence of a target nucleic acid by sequence-specific binding of the target with another nucleic acid (probe). GDX1002, 36. An allele-specific oligonucleotide (ASO) probe is a short nucleic acid complementary to the target sequence in a particular allele, and is used for specifically detecting a particular allele by hybridization. *Id.*, GDX1020, 11:9-12:1. Sequencing determines a DNA sequence by using genomic DNA or amplified nucleic acids as template. GDX1002, 37. Polymerase chain reaction (PCR) amplifies a DNA by short DNA fragments (primers) containing a sequence complementary to the ends of the target sequence. *Id.*

Breast or ovarian cancer susceptibility was known to be inherited, and identification of the susceptibility gene for diagnosing breast or ovarian cancer was of enormous interest. GDX1007, 1:1; GDX1028: Abstract; GDX1005, Abstract; GDX1006: Abstract, 11:3; GDX1002, 38. Like other genes, *e.g.*, the cystic fibrosis gene and the Huntington's disease gene, the BRCA1 gene was identified by positional cloning. GDX1005, 1:4-2:3; GDX1002, 39-40. In 1990, the BRCA1 gene was mapped to chromosome 17q by linkage analysis. GDX1007, 1:1;

GDX1028. The region was also found linked to ovarian cancer. GDX1002, 38.

In 1993, Easton *et al.* narrowed down the BRCA1 region to an interval estimated to be 8.3 cM² in males and 18.0 cM in females by using conventional mapping techniques. GDX1008, Abstract. Soon thereafter, in April 1993, Bowcock *et al.* narrowed down the region further to < 4cM region within Easton's region (based on its marker location). GDX1029, 1:1. In November 1993, Kelsell *et al.* further narrowed the BRCA1 region to a 1-1.5 Mb region within Bowcock's region (based on its marker location). GDX1007, Abstract. Thus, Kelsell's region was located within the previously-identified region. It was also used as a reference for later-identified regions (which fell within Kelsell's region) to establish that the later-identified regions were reliable. GDX1002, 39. So, Kelsell's 1-1.5 Mb region was considered the likely location for the BRCA1 gene in the art. GDX1002, 39.

On November 7, 1994, Miki published the BRCA1 gene sequence with roughly 100 kb of genomic DNA, producing a single transcript of 7.8 kb. GDX1005, 2:1. The desire for 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 alterations in the

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

BRCA1 gene were identified. GDX1005, 4:Tables 2, 3; GDX1004, 4, Table 2a. Exemplary relevant art includes the references discussed below.

Miki published on October 7, 1994 and qualifies as § 102(a) art to the June 7, 1995 filing date. GDX1002, 41. Miki discloses identification of the BRCA1 gene by positional cloning. GDX1005, Abstract, 1:5-2:4. Miki identifies that the BRCA1 gene spans 100 kb genomic DNA and comprises 22 exons, and it 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 it identifies various mutations and polymorphisms in the BRCA1 gene. *Id.*, 4:Tables 2 and 3.

Kelsell published in November 1993 and qualifies as § 102(b) art to the June 7, 1995 filing date and as § 102(a) art to the August 12, 1994 filing date. GDX1002, 42. It uses positional cloning to identify the BRCA1 gene, suggesting it as an approach for the BRCA1 gene identification. *Id.*, 43; GDX1007, Abstract. It genetically narrows down the BRAC1 region to a 1-1.5 Mb region, identifies 2 genes known to be within the region (not previously ruled out) as candidate genes, and screens the genes for breast or ovarian cancer linked germline mutations to determine whether any gene is the BRCA1 gene. GDX1007, 3:2-4:2. After determining that the genes were not the BRCA1 gene, Kelsell suggests analyzing "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.

Bowcock published in November 1993 and qualifies as § 102(b) art to the June 7, 1995 filing date and as § 102(a) art to the August 12, 1994. GDX1002, 44. Bowcock provides a specific approach for identifying the BRCA1 gene by positional cloning and reviews conventional techniques as applicable to the BRCA1 gene identification. *Id.*, 45; GDX1006, 1:Summary, 3:2, 6:3. It discloses narrowing the BRCA1 region; identifying candidate genes within the narrowed-down region; and analyzing the candidate genes by screening them for breast or ovarian cancer linked mutations to determine whether a candidate gene is in fact the BRCA1 gene. *Id.* Bowcock also reviews conventional techniques for isolating and sequencing the BRCA1 gene and screening or detecting BRCA1 mutations linked to breast and ovarian cancers. GDX1006, 11:4-12:1.

Cotton published in January 1993 and qualifies as § 102(b) art to both June 7, 1995 and August 12, 1994 filing dates. GDX1002, 46. Cotton reviews commonly-used techniques for detecting mutations, particularly allele-specific oligonucleotide (ASO) hybridization. *Id.*; GDX1020, Abstract, 11:9-12:5.

VIII. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner requests *inter partes* review of the challenged claims of the '441 patent on the grounds for unpatentability listed in the index below. Per 37 C.F.R. § 42.6(d), copies of the references are filed herewith. In support of the proposed

grounds, this Petition is accompanied by a declaration of expert Dr. Madhuri Hegde (GDX1002), which explains what the art would have conveyed to a POSA.

Ground	35 U.S.C. Section (pre-3/16/2013)	Index of References	'441 Patent Claims
1.	§ 102	Miki	7, 8, 12, and 23
2.	§ 103	Bowcock and Kelsell	8 and 23
3.	§ 103	Bowcock, Kelsell, and Cotton	7 and 12

Grounds 1-3 are not redundant. Although Miki anticipates claims 7, 8, 12, and 23, it is § 102(a) art and could potentially be removed as prior art. Even if Miki were removed as prior art, Bowcock and Kelsell render claims 8 and 23 obvious, and Bowcock, Kelsell, and Cotton render claims 7 and 12 obvious.

1. Claims 7, 8, 12, and 23 Are Not Entitled to the Benefit of the Filing Date of Any of the Parent Applications

Claims 7, 8, 12, and 23 are not entitled to the benefit of the filing dates of any of the parent applications of the '441 patent, Appl. Nos. 08/409,305 (GDX1010); 08/348,824 (GDX1035); 08/308,104 (GDX1021); 08/300,266 (GDX1011); or 08/289,221 (GDX1022) ("parent applications"). Each of the parent applications fails to show possession of the entire BRCA1 gene sequence and its surrounding sequences in the BRCA1 region, and thus fails to show possession of the probes and primers required by the claims. Thus, the parent applications fail to provide written description for the full scope of the claimed methods.

The priority date entitled to a particular claim depends upon when the subject matter necessary to support the claim under § 112 was first disclosed in an

application in the priority chain. *See In re Daniels*, 144 F.3d 1452, 1456 (Fed. Cir. 1998). The invention is properly disclosed where the "application . . . reasonably conveys to a [POSA] that the inventor had possession of the claimed subject matter at the time of the earlier filing date." *Eiselstein v. Frank*, 52 F.3d 1035, 1039 (Fed. Cir. 1995). A written description must show that the applicant is in possession of the entire scope of the claim. *Regents of the Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Courts consider several factors, including the nature and scope of the invention at issue, existing knowledge in the field, extent and content of the prior art, maturity of the field, predictability of the aspect at issue, and any other appropriate considerations. *Capon v. Eshhar*, 418 F.3d 1349, 1357-59 (Fed. Cir. 2003). "Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed." *In re Huston*, 308 F.3d 1267, 1277 (Fed. Cir. 2002) (quoting *Lockwood v. Am. Airlines Inc.*, 107 F.3d 1565 (Fed. Cir. 1997)).

Claim 7 method requires hybridizing a *BRCA1 gene probe* to genomic DNA. GDX1001, 155:57-62. Claim 12 method requires hybridizing a *BRCA1 DNA probe* to amplified BRCA1 nucleic acids. GDX1001, 156:44-50. Claims 8 and 23 methods require amplifying nucleic acids from the BRCA1 gene. GDX1001, 155:63-67, 157:34-35. Claims 8 and 23 explicitly require *primers* for amplification; claim 12 includes amplification with *primers*. GDX1002, 51.

The complete BRCA1 gene sequence was published in 1996 and is 81,188 bp long. GDX1024, 2:3; GDX1026; GDX1002, 52. None of the parent applications disclose the entire BRCA1 gene sequence. GDX1002, 53-59. As Dr. Hegde explained, the '305 application discloses only a partial BRCA1 gene sequence in Figs. 10A-10H and as SEQ ID NO: 14. GDX1002, 53-54; GDX1010, Figs. 10A-10H; 82:17-18. The BRCA1 gene sequence in Figs. 10A-10H is only 21,820 bps long with several indefinite intervals of unknown sequence and length, *e.g.*, at 1966-1978 and 2504-2516 in Fig. 10A, and several missing nucleotides, *e.g.*, at nucleotides 2323-2325, 2329, and 2500 in Fig. 10A. GDX1002, 53; GDX1010, Figs. 10A-10H; 82:17-18. And, SEQ ID NO: 14 is only 21,715 bps with several indefinite intervals of unknown sequence and length, *e.g.*, at nucleotides 1958-1970, 2496-2508, and 18196-18208, and several missing nucleotides, *e.g.*, at nucleotides 4751-4752, 14516, and 14968. *Id.*, 54. Thus, the '305 application discloses the BRCA1 gene sequence that is at most 21,820 bps (out of total 81,188 bps), with several stretches of indefinite intervals of unknown sequence and length and several missing nucleotides. GDX1002, 54.

The BRCA1 gene sequences disclosed in the '824 and '104 applications are 21,820 bps, the sequence in the '266 application is 21,715 bps, and the sequence in the '221 application is 10,952 bps, all with several indefinite intervals of unknown sequence and length and several missing nucleotides. GDX1002, 55-58;

GDX1010; SEQ ID NO: 14; GDX1021, SEQ ID NO: 14; GDX1011, SEQ ID NO:13; GDX1022, SEQ ID NO: 11.

So, the parent applications disclose only a fraction of the entire BRCA1 gene sequence (81,188 bps) – the '305, '824, and '104 applications disclose a BRCA1 gene sequence with only 21,820 bps (26.9% of the entire sequence); the '266 application discloses a BRCA1 gene sequence with only 21,715 bps (26.7% of the entire sequence); and the '221 application discloses a BRCA1 gene sequence with only 10,952 bps (13.5% of the entire sequence). GDX1002, 53-59. And, even those partial BRCA1 sequences are interspersed with several indefinite intervals of unknown sequence and length and several unknown nucleotides. *Id.* 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. *Id.* The parent applications also do not disclose the sequences surrounding the BRCA1 gene in the BRCA1 region. *Id.*, 59. Although the importance of the BRCA1 gene in breast or ovarian cancer diagnosis was recognized in the art as of the filing dates of the parent applications, the BRCA1 gene sequence itself was not predictable. So, the parent applications do not fully describe the BRCA1 gene sequence.

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 describe the entire *BRCA1* gene sequence and the sequences surrounding the gene in the *BRCA1* region, they also fail to describe all the "primers," "BRCA1 gene probes," and "BRCA1 DNA probes" required by claims 7, 8, 12, and 23. GDX1002, 53-60. So, the parent applications fail to provide description for the full scope of the claimed methods.

While it would have been obvious to a POSA reading the parent applications in view of the art to determine the entire *BRCA1* gene sequence and the sequences surrounding the gene in the *BRCA1* region, it is not disclosed in the parent applications. And, "[e]ntitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed." *In re Huston*, 308 F.3d at 1277; *See also Lockwood*, 107 F.3d at 1572. As such, the claims are not entitled to the priority benefit of the parent applications' filing dates.

2. Miki Is § 102(a) Art, and Kelsell, Bowcock, and Cotton Are § 102(b) Art to the June 7, 1995 Filing Date

As stated above, claims 7, 8, 12, and 23 are not entitled to the priority benefit of the parent applications. Miki *et al.* published an article entitled "A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene *BRCA1*" in *Science* on October 7, 1994 ("Miki"; GDX1005). Thus, Miki published before

June 7, 1995, the filing date of the '011 application that matured to the '441 patent. So, Miki qualifies as § 102(a) art to the June 7, 1995 filing date. Miki lists 45 authors, with 35 authors being different from the inventors listed on the '441 patent. Thus, Miki is "by others" within the meaning of § 102(a).

Kelsell *et al.* published an article entitled "Genetic analysis of the BRCA1 region in a large breast/ovarian family: refinement of the minimal region containing BRCA1" in *Human Molecular Genetics* in November 1993. ("Kelsell"; GDX1007). GDX1002, 42. Bowcock published an article entitled "Molecular cloning of BRCA1: a gene for early onset familial breast and ovarian cancer" in *Breast Cancer Research and Treatment* in November 1993 ("Bowcock"; GDX1006). GDX1002, 44. Cotton published an article entitled "Current methods of mutation detection" in *Mutation Research* in January 1993. ("Cotton"; GDX1020). GDX1002, 46. Thus, Kelsell, Bowcock, and Cotton published more than a year before June 7, 1995, the filing date of the '011 application that matured to the '441 patent. So, they qualify as § 102(b) art to the June 7, 1995 filing date. Also, Bowcock and Kelsell qualify as § 102(a) art and Cotton qualifies as § 102(b) art to the August 12, 1994 filing date.

3. Ground 1: Claims 7, 8, 12, and 23 Are Anticipated by Miki

The charts and discussion below show, as confirmed by Dr. Hegde, that Miki discloses every element of claims 7, 8, 12, and 23, arranged as claimed. And,

Miki discloses these elements in sufficient detail to enable a POSA to practice the methods without undue experimentation. As such, Miki anticipates these claims.

Claim 7: Claim 7 depends from claim 1 and contains every element of claim

1. Thus, claim 1 is included in the claim chart to enumerate all claim 7 elements.

Claim 7	Disclosure of Miki (GDX1005) 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." (5: Fig. 6 Legend)</p>
7. The method of claim 1	See claim 1 above in this chart
wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe	"Fig. 6. . . . (C) Inferred regulatory mutation in kindred 2035. ASO [Allele Specific Oligonucleotide] analysis of

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

<p>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>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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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). GDX1002, 68. Polymorphisms are alterations. *Id.*; Section VI. ASO probes are oligonucleotide probes that specifically hybridize to a particular allele of a gene (here BRCA1 gene). GDX1002, 68. And, carriers and noncarriers are family members that carry the mutant or wild-type BRCA1 gene (alleles), respectively. GDX1002, 68. Thus, Miki discloses *screening* the germline genomic DNA of carriers (mutant BRCA1 gene) and noncarriers (wild-type BRCA1 gene) 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. *Id.* (Also, Miki discloses screening control population (with wild-type BRCA1 sequence) by *amplifying* genomic DNA to produce PCR products and *hybridizing* the products with ASO probes to determine if the identified alterations were polymorphisms. GDX1005, 4:4, 6:n27.)

As Dr. Hegde explained, PCR products contain the genomic DNA template that was used for amplification (with the amplified nucleic acids), unless the PCR products are purified to remove the template. *Id.*, 69. In addition, the amplified nucleic acids are a true copy of the genomic DNA template. *Id.* Miki does not disclose purifying the PCR products to remove template before using the PCR products for hybridization with probes. GDX1005, n27; GDX1002, 69. Thus, the probes in Miki hybridized to both the amplified nucleic acids and the genomic DNA template. *Id.* So, Miki discloses *screening* the germline of a subject for a BRCA1 gene alteration by *hybridizing* a BRCA1 gene probe that specifically hybridizes to a BRCA1 allele to genomic DNA isolated from a carrier (subject; mutant BRCA1 gene) and a noncarrier (wild-type BRCA1 sequence).

As Dr. Hegde explained, Miki *compares* 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. *Id.*, 70; GDX1005, 5:Fig. 6C. In fact, the presence of a hybridization product with a 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. *Id.* And, the presence of the hybridization product with an ASO probe indicates the presence of its corresponding allele. *Id.* Thus, Miki teaches each and every element of claim 7, arranged as claimed. GDX1002, 68-70.

Further, the disclosure of Miki is sufficient to have allowed a POSA to practice the method of claim 7 without undue experimentation. ASO probe hybridization was a conventional, routinely-used technique before August 12, 1994. GDX1020, 11:9-12:4. 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, 6, n26-n27. Miki is specifically directed to screening for alterations in the BRCA1 gene. GDX1005, 2:3-4:4, Tables 2, 3; GDX1002, 71. And, although the technique was well-known, Miki further explains how to use it to detect the germline alterations in the BRCA1 gene. GDX1005, Fig. 6C, 6:n26-n27; GDX1002, 71. So, Miki provides an enabling disclosure and anticipates claim 7.

Claim 8: Claim 8 depends from claim 1 and contains every element of claim

1. Thus, claim 1 is included in the claim chart to enumerate all claim 8 elements.

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 indicates an alteration in the BRCA1 gene in said subject.]</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 . . . amplified from either genomic DNA samples . . . When the amplified DNA sequences were compared to the wildtype sequence, . . . were found to contain sequence variants (Table 2). . . . Five common polymorphisms were also identified in the BRCA1 coding sequence (Table 3)." (3:2)</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>
<p>8. The method of claim 1</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><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. . . 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.</p>

	Sequences of PCR primers used to amplify each exon of BRCA1. . . . The PCR products were . . . analyzed by cycle sequencing[.] " (6: n26)
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As 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. GDX1002, 73. Mutations are alterations. *Id.*; Section VI. Thus, Miki discloses *screening* the germline genomic DNA of a subject for a BRCA1 gene alteration 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. GDX1002, 73.

As Dr. Hegde explained, 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 indicates an alteration in BRCA1 gene of the subject. *Id.*, 74. Thus, Miki teaches each and every element of claim 8, arranged as claimed. *Id.*, 73-74.

Further, Miki's disclosure is sufficient to have allowed a POSA to perform claim 8 method without undue experimentation. Amplification using primers and

sequencing were routine, conventional techniques before August 12, 1994. GDX1006, 11:4-12:1. Miki provides guidance and working examples by explicitly using the techniques together to detect germline BRCA1 gene alterations, and by providing their reagents. GDX1005, 3:2, 6:n26. Miki is specifically directed to screening alterations in the BRCA1 gene. GDX1002, 2:3-4:4, Tables 2, 3; GDX1002, 75. And, although the techniques were well-known, Miki explains how to use them together to detect BRCA1 gene alterations. GDX1005, 6:n26; GDX1002, 75. So, Miki provides an enabling disclosure and anticipates claim 8.

Claim 12: Claim 12 depends from claim 1 and contains 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	<i>See claim 1 above under claim 7 discussion</i>
wherein a germline nucleic acid sequence is compared by amplifying BRCA1 nucleic acids from said sample to produce amplified nucleic acids,	"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)
hybridizing the amplified nucleic acids to a BRCA1 DNA probe specific for a BRCA1 allele and	
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
wherein the presence of said product indicates the presence	

of said allele in the subject.	exposed to x-ray film for 40 min[.]" (6:n27)
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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. GDX1002, 77. BRCA1 gene probe, used in claim 7, and BRCA1 DNA probe, used in claim 12, are construed similarly. *Id.*; Section VI. 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, 5: Fig. 6 Legend. As such, Miki discloses *screening* the germline 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. GDX1002, 77.

As discussed for 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 sequence alteration . GDX1002, 78. So, Miki teaches every element of claim 12, arranged as claimed. GDX1002, 77-78.

Also, the disclosure of Miki is sufficient to have allowed a POSA to perform the method of claim 12 without undue experimentation. Amplification and ASO

probe hybridization were conventional, routinely-used techniques before August 12, 1994. GDX1006, 11:4-12:1; GDX1020, 11:9-12:4. 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, 6, n26-n27. Miki is specifically directed to screening for alterations in the BRCA1 gene. GDX1005, 2:3-4:4, Tables 2, 3, Fig. 6C; GDX1002, 79. And, although the techniques were well-known, Miki further explains how to use them to detect the germline alterations in the BRCA1 gene. GDX1005, Fig. 6C, 6:n26-n27; GDX1002, 79. So, Miki provides an enabling disclosure and anticipates claim 12.

Claim 23: Claim 23 depends from claim 20 and contains every element of claim 20. So, claim 20 is included in the chart to enumerate all claim 23 elements.

Claim 23	Disclosure of Miki (GDX1005)
[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	"Probable predisposing mutations have been detected [.]" (Abstract) " Germline BRCA1 mutations in 17q-linked kindreds." (67:4) "In the initial screen for predisposing mutations in BRCA1 , DNA from one individual carrying the predisposing haplotype. . . were amplified from . . . genomic DNA samples . . . When the amplified DNA sequences were compared to the wildtype sequence . . . were found to contain sequence variants (Table 2)." (68:2)

mRNA from said sample.]	Table 2 discloses predisposing mutations in BRCA1 gene. (69:Table 2)
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.	<p>"In the initial screen for predisposing mutations in BRCA1, DNA from one individual carrying the predisposing . . . 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)." (68:2)</p> <p>"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[" (71: n26)</p>

As discussed for claim 8 and shown in the claim chart, Miki discloses *screening* the germline of a subject for BRCA1 gene alterations 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. "Analyzing a sequence" includes comparing the sequence from a sample with a wild-type sequence; and detecting and screening are synonymous. GDX1002, 81. Thus, Miki discloses *detecting* a germline alteration in the BRCA1 gene by *analyzing* the BRCA1 gene sequence 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. *Id.* Miki successfully detects several mutations, listed in Table 2, which are also listed in Table 11 of the '441 patent. GDX1005, 4; GDX1001, 56; GDX1002, 81. One mutation (codon 1775 in Table 2) is also listed in Table 12 of the '441 patent. GDX1005, 4; GDX1001, 60; GDX1002, 81. So, Miki teaches each and every element of claim 23, arranged as claimed. GDX1002, 81-82.

Further, the disclosure of Miki is sufficient to have allowed a POSA to perform the method of claim 23 without undue experimentation. Amplification using primers and sequencing were conventional, routinely-used techniques before August 12, 1994. GDX1006, 11:4-12:1; GDX1019. 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. Miki is specifically directed to screening for BRCA1 gene alterations. GDX1005, 2:3-4:4, Tables 2, 3; GDX1002, 83. And, although the techniques was well-known, Miki further explains how to use them together to detect the germline alterations in the BRCA1 gene. GDX1005, 6:n26; GDX1002, 83. So, Miki provides an enabling disclosure and anticipates claim 23.

4. Ground 2: Claims 8 and 23 Would Have Been Obvious Over Bowcock and Kelsell

As discussed above, Bowcock and Kelsell qualify as § 102(b) art to the June 7, 1995 filing date and as § 102(a) art to the August 12, 1994. Claims 8 and 23

would have been obvious in view of the combination of Bowcock and Kelsell.

Prior art references must be "considered together with the knowledge of one of ordinary skill in the pertinent art." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). In that regard, "it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). That is because an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

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; GDX1002, 38, 87. 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.

GDX1002, 87. So, a POSA would have been motivated to arrive at methods for screening or detecting alterations in the BRCA1 gene. *Id.*

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 on chromosome 17, and Bowcock provides methods for identifying the BRCA1 gene within such a region. GDX1007, Abstract; GDX1006, 3:2, 6:3, Fig. 2, *see also* generally; GDX1002, 88. 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; GDX1002, 88. Kelsell uses a positional cloning approach to narrow down the BRCA1 region to a 1-1.5 Mb region on chromosome 17. GDX1007, Abstract, 3:2-4:2; GDX1002, 88. Kelsell also applies the techniques disclosed in Bowcock (PCR amplification and sequencing) to screen for alterations in the BRCA1 candidate genes. GDX1007, 2:8, 5:7. A POSA looking to develop methods for screening the germline alterations in the BRCA1 gene would have used the conventional methods 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; GDX1002, 35-

37, 87-88. 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; GDX1002, 38-39, 87-88. 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. GDX1002, 38, 87-88. As discussed below, and explained by Dr. Hegde, a POSA would have had a reasonable expectation of successfully arriving at claims 8 and 23. *See* GDX1002, 89-106.

Claim 8: Claim 8 depends from claim 1 and contains every element of claim

1. So, claim 1 is included in the claim chart to enumerate all claim 8 elements.

Claim 8	Disclosure of Bowcock (GDX1006) 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[.]" (GDX1006, 11:4)
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	" BRCA1 is contained in a region estimated at 1 - 1.5 Mb in length." (GDX1007, Abstract) "In this study we have performed sequence analysis of [two candidate genes known to be located in the identified region] . No mutations were detected in the coding region of either gene in the germline DNA from three affected individuals[.]" (GDX1007, 4:2)

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.]	" 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)
8. The method of claim 1	<i>See claim 1 above in this chart</i>
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>"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 . . . 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 . . . DNA. No variation from the published sequences was detected." (GDX1007, 2:8)</p>

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. GDX1002, 86-95. 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." GDX1006, Abstract, 13:3, 11:4-12:2; GDX1002, 91. 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." GDX1006, 11:5; GDX1002, 91. 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; GDX1002, 91. 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.*

As Dr. Hegde explained, 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; GDX1002, 37, 92. In fact, the '441 patent itself acknowledges that mutations can be detected by using "techniques well known in

the art" and "sequences can be amplified directly from genomic DNA . . . using known techniques." GDX1001, 14:9-14. So, a POSA would have been motivated to screen for BRCA1 gene alterations in 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 well within a POSA's technical grasp from among a finite number of available techniques. GDX1006, 11:4-12:1; GDX1002, 37, 91-92. As the Court explained in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007), "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a [POSA] has a good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."

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 BRCA1 gene sequence alterations. GDX1006, Abstract, 13:3, 11:4-12:1, GDX1007, 2:8, 5: 7; GDX1002, 93. As Dr. Hegde explained, and exemplified in Kelsell, a POSA would have had a reason to amplify and sequence the BRCA1 gene of the subject to detect mutations and compare the sequence of the amplified nucleic acids with the wild-type sequences. *Id.* Kelsell discloses 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 mutations. GDX1007, 2:8, 5:7; GDX1002, 93. Kelsell then compares the sequences of the amplified nucleic acids with the wild-type sequences to identify variations. *Id.*, 2:8, GDX1002, 93.

So, based on the teachings of Bowcock and Kelsell, a POSA would have *compared* the germline sequence of the subject's BRCA1 gene with the wild-type BRCA1 gene sequence to *screen* for alterations in the subject's BRCA1 gene sequence by *amplifying* the subject's sequence to obtain amplified nucleic acids and *sequencing* the amplified nucleic acids. GDX1002, 91-94. A POSA would have understood that a difference between the subject's BRCA1 sequence and wild-type BRCA1 sequence indicates an alteration in the subject's gene. *Id.*

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 gene alteration. GDX1002, 86-95. So, based on the combined teachings of Bowcock and Kelsell, a POSA would have been motivated to arrive at the method of claim 8. *Id.*

And a POSA would have had a reasonable expectation of success in arriving

at the claimed invention. GDX1002, 96-106. POSAs knew that breast and ovarian cancer susceptibility was inherited. GDX1007, 1:1; GDX1028, Abstract. So, 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 BRCA1 gene alterations, 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. GDX1006:Abstract, 13:3, 3:2, 6:3, Fig. 2, *see also* generally; GDX1007, Abstract; GDX1002, 96-106.

As Dr. Hegde explained, 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. GDX1002, 38-39, 97. This 1-1.5 Mb region was identified in Kelsell. 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. GDX1002, 38-39, 97. So, Kelsell's 1-1.5 Mb region was considered the likely location for the BRCA1 gene in the art. *Id.*

A POSA would have reasonably expected to succeed in identifying the BRCA1 gene by using positional cloning to further analyze the 1-1.5 Mb region. GDX1002, 98-105. 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; GDX1002, 31-37, 98. 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 specific approach for identifying the BRCA1 gene by positional cloning. GDX1006, 3:2; 6:3; Fig. 2. Bowcock reviews conventional techniques as applicable to BRCA1 gene identification, involving: (1) genetically localizing the gene to a chromosomal region, (2) physically capturing the region when it can no longer be genetically narrowed further, (3) searching for the genes located within the region (candidate genes), and (4) identifying the genes with mutations linked to breast or ovarian cancer. GDX1006, 3:2, 6:3, Fig. 2; GDX1002, 31-37, 98.

It was generally understood in the art that once the BRCA1 gene had been localized to about a 1 Mb region, it would be straightforward to identify the genes in the region and compare their sequences within a linked family to identify genes with breast or ovarian cancer linked mutations. GDX1002, 33, 98. *E.g.*, the King reference articulates this general knowledge. *Id.*; GDX1027, 3:3-4:1. 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 [of candidate genes] in the [region], and comparing sequences of these genes among susceptible versus not susceptible relatives." GDX1027, 3:3-4:1.

Further, due to the small size of Kelsell's region, a POSA would have expected a small number of genes within the region⁴. *Id.*, 100. In fact, Kelsell itself considered the 1-1.5 Mb region to be sufficiently small to start analyzing the genes known to be located in 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; GDX1002, 100. So, a POSA would have understood Kelsell's 1-1.5 Mb region to be sufficiently small to identify and analyze genes in it, and would have reasonably expected to successfully identify the BRCA1 gene from among the candidate genes by using the next steps of positional cloning. GDX1007, Abstract, 3:2, 6:3, Fig. 2; GDX1002, 31-37, 96-105. (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

⁴ Kelsell's determination that two candidate genes located within its 1-1.5 Mb region were not the BRCA1 gene helped narrow down the number of candidate genes within the 1-1.5 Mb region further. GDX1002, 100, 106.

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; GDX1002,100.).

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. *Id.*

"[T]o capture the linked genetic region physically," Bowcock suggests cloning the BRCA1 region in a "large but manipulable form" once the region is small enough and can no longer be genetically refined further. GDX1006, Abstract, 6:3. Bowcock suggests using yeast artificial chromosomes (YACs), BACs, or P1 phage to clone large segments of the BRCA1 region, and using cosmids to clone smaller overlapping segments of the BRCA1 region. GDX1006, 6:3, 7:3-8:3. YACs, BACs, P1 phages, and cosmids were commonly-used laboratory tools to clone segments of genomic DNA. *Id.*; GDX1002, 34, 102.

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.

So, based on the teachings of Bowcock and Kelsell and common knowledge 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 Kelsell's narrow 1-1.5 Mb region with a reasonable expectation of success, because such methods use conventional techniques that have been used successfully for other genes (*e.g.*, cystic fibrosis). GDX1002, 96-105; GDX1006, Abstract, 3:2, 6:3, Fig. 2, Fig. 4. Also as Dr. Hegde explained, vicissitudes experienced in the process of identifying the BRCA1 gene would have been expected, and in fact, would have brought the researchers closer to identifying the BRCA1 gene. GDX1002, 31, 104.

Any potential counterargument that this combination presents the type of "obvious to try" situation that does not rise to the level of *prima facie* obviousness must fail. The *KSR* court reaffirmed the principle that a combination that was

obvious to try may in fact be obvious. The Court instructed:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, *[POSA]* has a good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR International Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007). (emphasis added). On occasions, the Federal Circuit has cited to two exceptions when something that is "obvious to try" would *not* be considered obvious under 35 U.S.C. § 103. *See, e.g., Bayer Schering Pharma AG v. Barr Labs.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009); *In re Kubin*, 561 F.3d 1351, 1359-61 (Fed. Cir. 2009). These exceptions were originally noted in *In re O'Farrell* 853 F.2d 894 (Fed. Cir. 1988). The *O'Farrell* court instructed:

The admonition that "obvious to try" is not the standard under § 103 has been directed mainly to two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of

experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id., 853 F.2d at 903.

Neither of the two *O'Farrell* exceptions applies here. As discussed above, Kelsell discloses a narrow 1-1.5 Mb BRCA1 region that would have contained a finite number of genes within the region. GDX1007, Abstract, 3:2; GDX1002, 100, 105. And, Bowcock directs using a conventional and routine positional cloning approach for identifying the BRCA1 gene within a region, which involves using a standard combination of routine, well-known techniques. GDX1006, 3:2, 6:3, Fig. 2; GDX1002, 31-37, 98, 102-105. And, in view of the BRCA1 gene-specific guidance provided in Bowcock, general knowledge in the art and common sense, and a strongly-motivated field, 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. GDX1006, 3:2, 6:3, Fig. 2; GDX1002, 96-105.

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. GDX1006, 11:3-12:2, GDX1007, 5:7; GDX1002, 37, 106. As Dr. Hegde explained, PCR amplification and sequencing were conventional techniques routinely used before August 12, 1994. GDX1002, 37, 91-92. 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); GDX1002, 91-106.

So, 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. GDX1002, 91-106. That is, a POSA would have had a reasonable expectation of successfully arriving at claim 8. *Id.* In sum, claim 8 would have been obvious over Bowcock in view of Kelsell, even in light of any allegation of objective indicia of non-obviousness. Objective indicia of non-obviousness are addressed as to all the claims in Section VIII.6., below.

Claim 23: Claim 23 depends from claim 20 and contains its every element.

Claim 20 is included in the claim below to enumerate all claim 23 elements.

Claim 23	Disclosure of Bowcock (GDX1006) and Kelsell (GDX1007)
[20. A method for detecting a germline	"Once a set of cDNAs within the region likely to contain BRCA1 have been identified, they will be

<p>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>studied to see if they detect alterations in DNAs from a variety of sources[.] (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 region]. No mutations were detected in . . . either gene in the germline DNA from three affected individuals [.] (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 . . . 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 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 . . . 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 . . . DNA. No variation from the published sequences was detected." (GDX1007, 2:8)</p>

As discussed 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. *See also*, GDX1002, 86-106.

"Screening" and "detecting," are synonymous. Section VI. Also, "analyzing a sequence" includes comparing the sequence with a wild-type sequence. GDX1002, 109. A POSA would have been motivated to arrive at a method for *detecting* the germline BRCA1 gene alterations by *analyzing* the BRCA1 gene sequence from a 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. *Id.*, 86-109.

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. *Id.*, 110-112. While the exact identity of these alterations may not have been known, a POSA would have expected these mutations due to the inherited nature of breast or ovarian cancer. *Id.*, 96, 110. 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. *Id.*, 96-105, 110; GDX1007, 1:1; GDX1028, Abstract. Also, a finite number of conventional and routine methods (*e.g.*, PCR amplification and sequencing) to screen alterations were available, noted under claim 8. *See also*, GDX1006, 11:3-12:1; GDX1002, 103, 110. So, a POSA would have been motivated to identify the additional alterations, *e.g.*, alterations in Tables 11 and 12 of the '441 patent (and recited in claim 23), using techniques well within a POSA's technical grasp and were selected from a finite number of available options. GDX1002, 110-112. 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; GDX1002, 91-110.

Any potential counterargument that this combination presents the type of "obvious to try" that does not rise to the level of *prima facie* obviousness, must fail. As discussed above under claim 8 discussion, courts have cited to the two exceptions when something that is "obvious to try" would *not* be considered obvious under 35 U.S.C. § 103. Neither of those two exceptions applies here.

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 breast or ovarian cancer patients or patients with family history of breast or ovarian cancer to identify any additional alterations. GDX1002, Abstract; GDX1006, Abstract, 13:3; GDX1002, 96, 110-111. As discussed for claim 8, a finite number of conventional methods for screening alterations were known. *See also*, GDX1006, 11:3-12:1; *id.*, 103, 110. 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. *Id.*, 111. 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.

So, a POSA would have had a reasonable expectation of successfully arriving at a method for detecting the germline BRCA1 gene alterations by *analyzing* the BRCA1 gene sequence from a 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 in Table 11 and 12 of the '441 patent. *Id.*, 108-113. So, claim 23 would have been obvious over Bowcock in view of Kelsell, even in light of any allegation of objective indicia of non-obviousness, which are addressed with respect to all the claims in Section VIII.6., below.

5. Ground 3: Claims 7 and 12 Would Have Been Obvious Over Bowcock, Kelsell, and Cotton

As discussed above, Bowcock and Kelsell qualify as § 102(b) art to the June 7, 1995 filing and as § 102(a) art to the August 12, 1994 filing. Cotton qualifies as a § 102(b) art to the August 12, 1994 filing date. As discussed under Ground 2, a POSA would have had a reason to combine the teachings of Bowcock and Kelsell. GDX1002, 87-88. 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 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 gene alterations using conventional techniques disclosed in the references. *See also* GDX 1002, 86-106. Cotton discloses commonly-used techniques for detecting mutations before August 12, 1994, particularly ASO hybridization. GDX1020, Abstract, 11:9-12:1. So, a POSA looking to detect alterations in the BRCA1 gene would have had a reason to use ASO hybridization of Cotton in a method for screening the germline alterations in the BRCA1 gene disclosed in the combined teaching of Bowcock and Kelsell. GDX1002, 86-106, 115. As discussed below, and explained by Dr. Hegde, a POSA would have had a reasonable expectation of successfully arriving at the claims.

Claim 7: Claim 7 depends from claim 1 and contains every element of claim 1. Claim 1 elements are discussed above under claim 8. 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, with a reasonable expectation of success. GDX1002, 86-106, 117. That is, based on Bowcock and Kelsell, a POSA would have arrived at the claim 1 and 8 methods for screening the germline of a subject for alterations in the BRCA1 gene with a reasonable expectation of success. *Id.*

Cotton discloses using allele-specific oligonucleotide (ASO) probe hybridization as a conventional technique to detect specific mutations in genomic DNA. GDX1020, Abstract, 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. So, a POSA looking to screen for the BRCA1 gene alterations 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). GDX1002, 86-106, 117-118.

ASO probes are probes that specifically hybridize to a particular allele of a gene. *Id.*, 119-120. As Dr. Hegde explained, screening mutations by ASO probes encompasses *hybridizing* the probes to the subject's and wild-type genomic DNA, *detecting* the hybridization product from the two hybridizations, and *comparing* their hybridization patterns. *Id.* And, a POSA would have understood that a *difference* in the hybridization patterns indicates hybridization to *different alleles*, *i.e.*, different gene sequences. *Id.* A POSA would have also understood that a difference in the two sequences correlates to an *alteration*. *Id.*

Thus, a POSA would have been motivated to *screen* the germline of a subject for the BRCA1 gene alterations by *comparing* the germline BRCA1 gene sequence of a subject with the wild-type sequence. *Id.*, 118-120. A POSA would have done so by *hybridizing* an allele-specific BRCA1 gene probe to the genomic DNA of the subject and *detecting* the presence of a hybridization product, such that the presence of the product indicates the *presence* of the allele, which in turn indicates an alteration in the BRCA1 gene sequence. *Id.* So, based on the teachings of Kelsell, Bowcock, and Cotton, a POSA would have arrived at claim 7. *Id.*

Further, as discussed in this section above, before August 12, 1994, hybridization methods using ASO 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 of claim 7. GDX1002, 85-122. In sum, claim 7 would have been obvious over Bowcock, Kelsell and Cotton, even in light of any allegation of objective indicia of non-obviousness. Objective indicia of non-obviousness are addressed with respect to all the claims in Section VIII.6., below.

Claim 12: Claim 12 depends from claim 1 and contains every element of claim 1. The elements of claim 1 are discussed above under claim 8. As discussed under claim 8, based on Bowcock and Kelsell teachings, a POSA would have arrived at the methods of claims 1 and 8 for screening the germline for alterations in the BRCA1 gene by *amplifying* the BRCA1 gene and *sequencing* the amplified nucleic acids, with a reasonable expectation of success. GDX1002, 86-106.

Cotton discloses using ASO probe hybridization as one of the conventional techniques to detect specific mutations in amplified DNA. GDX1020, Abstract, 11:9-12:4; *see also* GDX1019, 99. 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 to screen for alterations in the BRCA1 gene. GDX1002, 125. And, as such, a POSA would have been motivated to use ASO probe hybridization after amplification, as suggested in Cotton. *Id.*; GDX1020, 11:9-12:1.

As discussed above under claim 7, and explained by Dr. Hegde, *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. GDX1002, 119, 126. 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. *Id.* A POSA would have also understood that a difference in the two sequences correlates to an *alteration*. *Id.* As such, based on the combined teachings of Kelsell, Bowcock, and Cotton, a POSA would have arrived at the method of claim 12. *Id.*, 125-127.

Before August 12, 1994, hybridization methods using allele-specific oligonucleotide probes were conventional and routinely used. GDX1020, Abstract, 11:9-12:1; GDX1002, 128. Therefore, because of the reasons discussed for claims 8 and 23 above 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. GDX1002, 124-129. In sum, claim 12 would have been obvious over Kelsell in view of Bowcock, even in light of any allegation of objective indicia of non-obviousness. Objective indicia of non-obviousness are address with respect to all the claims in Section VIII.6., below.

6. Objective Indicia of Non-Obviousness

Myriad's publicly-available objective-indicia arguments do not support patentability of the challenged claims. When there is strong evidence of obviousness showing, even substantial objective evidence may not dislodge it. *See, e.g., Leapfrog Enterprises Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). And, there must be a nexus between the evidence and the merits of the claimed invention. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983). Myriad may attempt to avoid obviousness by asserting objective indicia evidence, but GeneDx requests an opportunity to rebut it and develop a full record (e.g., via cross-examination) before the Board conducts a detailed analysis.

a) No Commercial Success that Favors Patentability

Myriad's commercialized BRACAnalysis[®] genetic testing does not evince commercial success favoring patentability of the challenged claims. While Myriad has made generalized allegations, pointing to the BRACAnalysis testing as purportedly showing commercial success of Myriad's collection of patents-in-suit, Myriad has not demonstrated that its commercial method is an embodiment of the claims challenged here. GDX1002, 133-134. And Myriad has not met its burden to prove any nexus between its commercial method and the merits of the claims. *Id.*

The BRACAnalysis[®]'s sales also lack the requisite nexus with the merits of the claimed invention. Myriad admits 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. Such 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 genetic testing. GDX1014, 25-31. Thus, any alleged commercial success of BRACAnalysis[®] is attributable to factors unrelated to the claims. So, Myriad has not shown a nexus with the claims.

Myriad also alleges it owns or has exclusive rights to 24 U.S. patents covering BRACAnalysis[®]. GDX1013, 5. These patents have created a hurdle to market entry by competitors. Thus, BRACAnalysis[®]'s sales data is insufficient evidence of nonobviousness. *See Merck & Co. v. Teva Pharm. USA*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (commercial success evidence is insufficient to show nonobviousness where competitors' market entry is barred by patents).

b) No Long-Felt, Unmet Need or Failure of Others

Myriad did not identify any evidence in the prosecution history or litigations that establishes a long-felt, unmet need or failure of others that has any nexus to

the challenged claims. GDX1002, 136-137. While Myriad asserts that *BRCAAnalysis*® filled a long-felt unmet need for a test that accurately evaluates a patient's risk of breast and ovarian cancers, it has not identified any particular prior art that articulates such a need. *Id.*, GDX1015, 42. Although Myriad bears the burden to establish a nexus between objective indicia and the claims, it only generally alleged a long-felt, unmet need for its testing services, without tying the need to the merits of the challenged claims. *Id.* And, although Myriad carries the burden of production, it has not provided evidence showing that the subject matter of the challenged claims meets any long-felt, unmet need. *Id.* Similarly, Myriad has provided no evidence that there was a lack of know-how for solving any technical problem related to the challenged claims. GDX1002, 137; GDX1015, 42. Rather, Myriad seems to allege that because it was first to determine the BRCA1 gene sequence, other researchers failed to arrive at the claimed invention. But Myriad does not show that 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 methods. 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. GDX1002, 31-37, 96-105, 137. Thus, Myriad has not shown any long-felt, unmet need or

failure of others that has a nexus to the merits of the challenged claims.

c) No Industry Praise that Favors Patentability

Myriad has not identified evidence in the prosecution history or litigations that establishes a nexus between any praise in the industry and the merits of the challenged claims. Though Myriad bears the burden, it has only generally asserted praise for its patents-in-suit, without tying such praise to claimed features. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363-64 (2012).

If Myriad were to assert that there had been praise for the original BRCA1 sequencing work, such praise lacks a nexus to the challenged claims. The claims are not directed to sequencing the BRCA1 gene, but are directed to screening or detecting BRCA1 gene alterations. GDX1002, 139. Even if Myriad were to assert that its *BRACAnalysis*[®] test has been praised, Myriad has not shown that praise for *BRACAnalysis*[®] is due to features of the challenged claims. *Id.*; GDX1015, 42; GDX1014, 18. And, even though Myriad has asserted that its *BRACAnalysis*[®] test is a "gold standard" (see GDX1014, 18, *citing* Eng Statement, GDX1016), Myriad has not established a nexus to the claim merits. Eng's statement was not directed to the claimed methods for screening or detecting alterations in the BRCA1 gene. GDX1002, 140. Eng's statement refers to a broad category of methods for direct nucleotide sequence analysis, not just *BRACAnalysis*[®]. *Id.* Eng stated, "[d]irect nucleotide sequence analysis is considered the gold standard for mutation detection

for genes such as *BRCA1* and *BRCA2*." *Id.*; GDX1016, 1:2. But direct nucleotide sequence analysis is not limited to BRACAnalysis[®]. It can be accomplished, *e.g.*, by using conventional techniques such as DNA sequencing, hybridization, or amplification. GDX1002, 145. Thus, Myriad has not established the requisite nexus between the alleged praise (for direct nucleotide sequence analysis) and the challenged claims. *Id.* Thus, all of Myriad's "praise" arguments must fail.

The prosecution history and litigations are devoid of any other objective indicia of nonobviousness.

IX. CONCLUSION

This Petition demonstrates the unpatentability of claims 7, 8, 12, and 23 of the '441 patent. Accordingly, Petitioner has established a reasonable likelihood of prevailing on each of the three non-cumulative Grounds set forth herein. Petitioner requests IPR of the '441 patent and cancellation of claims 7, 8, 12, and 23.

Respectfully submitted,
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CERTIFICATION OF SERVICE (37.C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the above-captioned "Petition for *Inter Partes* Review of U.S. Patent No. 5,753,441 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123" was served in its entirety on August 18, 2014, upon the following party via FEDEX®:

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