



Transforming Healthcare with Evidence

Hayes Guide to Genetic Testing for *BRCA1* and *BRCA2* Changes

Terms & Conditions: Hayes reports are proprietary, protected by copyright, and available only by purchase. By agreeing to purchase, the purchaser understands that the Hayes report(s) are for internal use only and that they may only be utilized in the facility of the purchaser and may not be transmitted to, or circulated in any other office or facility. Use of the Hayes report(s) for advertising, product support or endorsement of the technology by Hayes, either orally or in writing, in materials prepared and/or distributed by the manufacturer or its employees, agents, consultants, subsidiaries, distributors or other third party affiliates is prohibited.

Copyright © 2010 Winifred S. Hayes, Inc.



Transforming Healthcare with Evidence

Table of Contents

| | |
|--|----|
| <u>Hayes</u> | 3 |
| <u>Hayes Rating for Genetic Test Evaluation</u> | 4 |
| <u>GTE Report Sections</u> | 5 |
| <u>Breast Cancer Susceptibility 1 and 2 (BRCA1/2) Sequence Variant Testing for Susceptibility to Hereditary Breast Cancer (1.5.2009)</u> | 6 |
| <u>Update Literature Search (2.3.2010)</u> | 22 |
| <u>Comprehensive Screening for Large Rearrangements in BRCA1/2 for Assessment of Breast Cancer Risk (3.31.2008)</u> | 41 |
| <u>Update Literature Search (3.30.2009)</u> | 63 |
| <u>Update Literature Search (3.26.2010)</u> | 68 |
| <u>BRCA1 and BRCA2 Sequence Variant Analysis for Susceptibility to Hereditary Ovarian Cancer (12.16.2009)</u> | 72 |



Transforming Healthcare with Evidence

Hayes, Inc. is an independent health technology research and consulting company dedicated to promoting better health outcomes through the use of evidence. Hayes performs unbiased, evidence-based health technology assessments of the safety and efficacy of new, emerging, and controversial health technologies and evaluates the impact of these technologies on healthcare quality, utilization, and cost. In addition, Hayes provides comparative effectiveness reports, horizon scanning for new technologies, health technology trends by clinical specialty area, and evaluates the potential operational and financial impact of technologies on facilities, staffing, credentialing, and other resources. Hayes' worldwide clients include hospitals, healthcare systems, government agencies, employers, and managed care organizations.

The **Hayes Genetic Test Evaluation (GTE) program** cuts through the “genohype” to the scientific evidence concerning the appropriate use of genetic and genomic tests in clinical practice. Currently, there are more than 2,000 genetic and genomic tests for inherited and acquired disorders on the market in the United States. With an annual growth rate of 25%, this rapidly growing field has created challenges for healthcare professionals, such as how to respond quickly and appropriately to issues related to these tests.

The **Hayes Rating** is a proprietary evidence scoring system that reflects the strength and direction of the relevant research regarding the safety and efficacy of the health technology under review. With a scale of A (established benefit) through D (no proven benefit and/or not safe), the Hayes Rating distills the available information about a specific medical device, drug, biologic, procedure, diagnostic test, surgical implant, or imaging technology into a concise conclusion. Clients use the Rating to compare technology options, make decisions on technology acquisition, and address healthcare quality initiatives. The Hayes GTE Ratings share some similarities with the Hayes Ratings for other technologies, but focus specifically on the strength and direction of the evidence regarding the validity and utility of a genetic or genomic test for specific applications.

www.hayesinc.com

Copyright 2010 Winifred S. Hayes, Inc.

[Back to Table of Contents](#)



Transforming Healthcare with Evidence

Hayes GTE Rating

The Hayes GTE Rating system, developed by Winifred S. Hayes, Inc., reflects the strength and direction of the evidence regarding a genetic test, including safety and efficacy, impact on health outcomes, indications for use, patient selection criteria, and comparison with other technologies. The ratings are scaled A through D and are defined as follows:

| Rating | Description |
|----------------|--|
| A | Established benefit. A high level of positive published evidence regarding analytical validity, clinical validity, and clinical utility for the application(s) supports use of the test. |
| B | Some proven benefit. A moderate level of positive published evidence regarding analytical validity, clinical validity, and clinical utility for the application(s) supports use of the test. Further research is required. |
| C | Potential but unproven benefit. Some positive published evidence regarding analytical validity and/or clinical validity for the application(s) supports use of the test, but clinical utility has not been demonstrated because data are sparse and the level of evidence is low, or data are inconsistent or conflicting. |
| D ₁ | No proven benefit – health outcomes. The test has been shown to lack analytical validity, clinical validity, and/or clinical utility for the cited application(s). |
| D ₂ | No proven benefit – insufficient evidence. Evidence is insufficient to assess the analytical and/or clinical validity of the test for the cited application(s). |

Definitions:

- **Analytic Validity:** The ability of a genetic test to accurately and reliably measure the genotype of interest.
- **Clinical Validity:** The ability of a genetic test to detect or predict the associated disorder (phenotype).
- **Clinical Utility:** The elements that need to be considered when evaluating the risks and benefits associated with the introduction of a genetic test into routine practice.
- **Holding:** Insufficient published data are available to assess this genetic technology (<3 published studies that clearly establish the phenotype/genotype relationship of the condition, and/or there are no published clinical validity data available). Hayes will periodically search for newly available data for this technology.



Transforming Healthcare with Evidence

Hayes GTE Reports include the following sections:

- Executive Summary, called **At A Glance**, which provides a high-level review of the primary findings and conclusions of the report, including Key Questions with answers and the Hayes GTE Ratings for each patient population or application reviewed. This section is written at a level appropriate for someone without specialized knowledge of genetics.
- **Background** section, which provides an in-depth review of the disorder the test addresses. Custom figures are used whenever possible to illustrate complex ideas such as pathways or structures affected by genetic variants discussed in the report. Key Questions to be addressed in the report are listed at the end of the Background section.
- Detailed **Test Description**.
- **Patient Population(s)** that the test may be considered for.
- **Clinical Alternatives** that do not include the genetic or genomic test.
- **Current Research Evidence**, which includes a description of the review model used and defines the search strategy, as well as summarizes the evidence associated with analytical validity, clinical validity, clinical utility, and ethical, legal, and social implications.
- **Summary** of the key evidence, including Key Questions with answers. The justification for the Hayes GTE Rating assigned is also provided in this section.
- Other relevant information, including **Regulatory Information**, **Payer Coverage Policies** for several major payers, **Position and Policy Statements** from major professional organizations, and **Cost**.
- **Role of Genetic Counseling** as appropriate for the topic.
- **Evidence-Based Projections**, which is a forward-looking section regarding the future of the test and other similar tests under development.
- **Hayes GTE Ratings** for each patient population or application reviewed.
- **Ongoing Studies**, which lists the ongoing clinical trials relevant to the test and/or disorder reviewed.

January 5, 2009

Breast Cancer Susceptibility 1 and 2 (BRCA1/2) Sequence Variant Testing for Susceptibility to Hereditary Breast Cancer

AT A GLANCE

Product Names: BRACAnalysis® (Myriad Genetic Laboratories Inc.)

Background: In the United States, an estimated 182,460 women and 1990 males will be diagnosed with breast cancer in 2008. Breast cancer, the second leading cause of cancer-related deaths among women, is expected to contribute to 40,930 deaths overall in 2008. In 5% to 10% of breast cancer cases, multiple affected family members, multiple primary breast cancers in the same individual, or prevalence of both breast and ovarian cancer in the same individual or family indicate a strong family history. For those with a strong family history of breast/ovarian cancers, genetic alterations in the breast cancer susceptibility 1 (BRCA1) and/or breast cancer susceptibility 2 (BRCA2) genes are thought to account for 45% to 90% of BRCA1-related cases and 35% of BRCA2-related cases. Ethnic-specific common variants include founder effects for a few populations, especially Ashkenazi Jewish and Dutch, for which assays are variant-specific and the test population is more clearly defined. The penetrance of breast cancer by 70 years of age has been estimated as 65% to 87% for BRCA1 and 82% for BRCA2. Myriad Genetic Laboratories holds patents for genetic testing of BRCA1/2 in the United States and, therefore, this company has performed almost all testing of these genes in the United States since the introduction of clinical testing in October 1996.

Description of the Technology/Patient Population: Myriad Genetic Laboratories Inc. (Salt Lake City, UT) provides testing for BRCA1/2 sequence variants by full sequencing to identify sequence variants and ethnic-specific sequence variant testing for individuals of Ashkenazi Jewish ancestry. Genetic testing may be considered for breast cancer patients and asymptomatic individuals from high-risk families with or without a known familial BRCA1/2 deleterious variant.

Synopsis of the Clinical Evidence: Clinical testing for BRCA1/2 sequence variants is primarily performed using full sequencing with a reported analytical sensitivity of greater than 99%. Analysis of 1433 BRCA1/2 variants of unclassified clinical significance suggests 43 in favor of being deleterious and 133 in favor of being neutral.

HAYES RATING FOR GENETIC TEST

Order now!

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.
© 2009 Winifred S. Hayes, Inc.

PUBLICATION HISTORY

REFERENCES (key references are in bold)

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58(2):71-96.
2. Rosman DS, Kaklamani V, Pasche B. New insights into breast cancer genetics and impact on patient management. *Curr Treat Options Oncol*. 2007;8(1):61-73.
3. Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1993;52(4):678-701.
4. National Cancer Institute (NCI) [website]. Genetics of Breast and Ovarian Cancer (PDQ®). Updated October 17, 2008. Available at: http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/healthprofessional/allpages#Section_95. Accessed December 15, 2008.
5. Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science*. 1994;265(5181):2088-2090.
6. Gayther SA, Mangion J, Russell P, et al. Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. *Nat Genet*. 1997;15(1):103-105.
7. Kirchhoff T, Kauff ND, Mitra N, et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. *Clin Cancer Res*. 2004;10(9):2918-2921.
8. Antoniou AC, Sinilnikova OM, Simard J, et al.; Consortium of Investigators of Modifiers of BRCA 1/2 (CIMBA). RAD51 135G-->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. *Am J Hum Genet*. 2007;81(6):1186-1200.
9. Begg CB, Haile RW, Borg A, et al. Variation of breast cancer risk among BRCA1/2 carriers. *JAMA*. 2008;299(2):194-201.
10. U.S. Preventive Services Task Force (USPSTF). Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility [correction appears in *Ann Intern Med*. 2005;143(5):355-361]. *Ann Intern Med*. 2005;143(5):355-361.
11. National Comprehensive Cancer Network (NCCN) [website]. NCCN Clinical Practice Guidelines in Oncology™. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V.1.2008. Updated May 16, 2008. Available at: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. Accessed December 15, 2008.
12. Frank TS, Manley SA, Olopade OI, et al. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. *J Clin Oncol*. 1998;16(7):2417-2425.
13. Couch FJ, DeShano ML, Blackwood MA, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med*. 1997;336(20):1409-1415.
14. Berry DA, Parmigiani G, Sanchez J, et al. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. *J Natl Cancer Inst*. 1997;89(3):227-238.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

Hayes

Transforming Healthcare with Evidence

4/6/2010

Page 14 of 16

[Back to Table of Contents](#)

15. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet.* 1998;62(1):145-158.
16. Shannon KM, Muzikansky A, Chan-Smutko G, et al. Uptake of BRCA1 rearrangement panel testing: in individuals previously tested for BRCA1/2 mutations. *Genet Med.* 2006;8(12):740-745.
17. Von der Ropp A, Taubman T. Bioethics and Patent Law: The Case of Myriad. World Intellectual Property Organization (WIPO) [website]. August 2006. Available at: http://www.wipo.int/wipo_magazine/en/2006/04/article_0003.html. Accessed December 15, 2008.
18. Myriad Genetic Laboratories Inc. [website]. BRACAnalysis® Technical Specifications. Updated August 4, 2006. Available at: <http://www.myriadtests.com/provider/doc/BRACAnalysis-Technical-Specifications.pdf>. Accessed December 15, 2008.
19. Centers for Disease Control and Prevention (CDC) [website]. Evaluation of Genetic Testing. ACCE: A CDC-Sponsored Project Carried Out by the Foundation of Blood Research. Updated December 11, 2007. Available at: <http://www.cdc.gov/genomics/gtesting/ACCE.htm>. Accessed December 15, 2008.
20. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) [website]. About EGAPP. 2008. Available at: <http://www.egapreviews.org/about.htm>. Accessed December 15, 2008.
21. Gudgeon JM, McClain MR, Palomaki GE, Williams MS. Rapid ACCE: experience with a rapid and structured approach for evaluating gene-based testing. *Genet Med.* 2007;9(7):473-478.
22. **Easton DF, Deffenbaugh AM, Pruss D, et al. A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the BRCA1 and BRCA2 breast cancer-predisposition genes. *Am J Hum Genet.* 2007;81(5):873-883.**
23. **Whittemore AS, Gong G, John EM, et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. *Cancer Epidemiol Biomarkers Prev.* 2004;13(12):2078-2083.**
24. **Chen S, Iversen ES, Friebel T, et al. Characterization of BRCA1 and BRCA2 mutations in a large United States sample. *J Clin Oncol.* 2006;24(6):863-871.**
25. Milne RL, Knight JA, John EM, et al. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev.* 2005;14(2):350-356.
26. Antoniou AC, Shenton A, Maher ER, et al. Parity and breast cancer risk among BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res.* 2006;8(6):R72.
27. Jernström H, Lubinski J, Lynch HT, et al. Breast-feeding and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst.* 2004;96(14):1094-1098.
28. **Schwartz MD, Lerman C, Brogan B, et al. Utilization of BRCA1/BRCA2 mutation testing in newly diagnosed breast cancer patients. *Cancer Epidemiol Biomarkers Prev.* 2005;14(4):1003-1007.**
29. Meijers-Heijboer H, Brekelmans CT, Menke-Pluymers M, et al. Use of genetic testing and prophylactic mastectomy and oophorectomy in women with breast or ovarian cancer from families with a BRCA1 or BRCA2 mutation. *J Clin Oncol.* 2003;21(9):1675-1681.
30. van Sprundel TC, Schmidt MK, Rookus MA, et al. Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. *Br J Cancer.* 2005;93(3):287-292.
31. DiGianni LM, Rue M, Emmons K, Garber JE. Complementary medicine use before and 1 year following genetic testing for BRCA1/2 mutations. *Cancer Epidemiol Biomarkers Prev.* 2006;15(1):70-75.
32. **Phillips KA, Jenkins MA, Lindeman GJ, et al. Risk-reducing surgery, screening and chemoprevention practices of BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Clin Genet.* 2006;70(3):198-206.**
33. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol.* 2004;22(6):1055-1062.
34. Food and Drug Administration (FDA) [website]. Center for Devices and Radiological Health (CDRH). CLIA - Clinical Laboratory Improvement Amendments. Updated November 18, 2005. Available at: <http://www.fda.gov/cdrh/clia>. Accessed October 24, 2008.
35. Myriad Genetic Laboratories Inc. [website]. CLIA Certificate of Accreditation. 2007. Available at: http://www.myriadtests.com/doc/Myriad_CLIA_Certification.pdf. Accessed December 21, 2008.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.



Transforming Healthcare with Evidence

4/6/2010

Page 15 of 16

[Back to Table of Contents](#)

36. Centers for Medicare & Medicaid Services (CMS) [website]. Medicare Coverage Database [search: *BRCA1/2*]. December 21, 2008. Available at: <http://www.cms.hhs.gov/mcd/search.asp>. Accessed December 21, 2008.
37. Coalition of State Genetics Coordinators (CSGC) [website]. State Genetics websites. 2007. Available at: <http://www.stategeneticscoordinators.org/statesites.htm>. Accessed December 15, 2008.
38. National Newborn Screening and Genetics Resource Center (NNSGRC) [website]. National Newborn Screening Status Report. Updated December 8, 2008. Available at: <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf>. Accessed December 21, 2008.
39. Aetna [website]. Clinical Policy Bulletin: BRCA Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy. No. 0227. Updated November 7, 2008. Available at: http://www.aetna.com/cpb/medical/data/200_299/0227.html. Accessed December 15, 2008.
40. Anthem Blue Cross [website]. Genetic Testing for Cancer Susceptibility. GENE.00001. Updated May 15, 2008. Available at: http://www.anthem.com/ca/medicalpolicies/policies/mp_pw_a050303.htm. Accessed December 15, 2008.
41. CIGNA HealthCare [website]. Genetic Testing for Susceptibility to Breast and Ovarian Cancer (BRCA1 & BRCA2). Coverage Policy No. 0001. 2008. Available at: http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0001_coveragepositioncriteria_genetic_testing_for_breast_and_ovarian_cancer.pdf. Accessed December 15, 2008.
42. Humana [website]. Genetic Testing and Counseling for Disease Risk. Updated November 20, 2008. Available at: http://apps.humana.com/TAD/TAD_New/issuedetail.asp?issue=983. Accessed December 15, 2008.
43. Regence Group [website]. Laboratory Section – Genetic Testing for Inherited BRCA1 or BRCA2 Mutations. Policy No. 10. 2006. Available at: <http://blue.regence.com/trgmedpol/lab/lab10.html>. Accessed December 15, 2008.
44. United Healthcare (UHC) [website]. Genetic Testing for Breast Cancer: HER2, BRCA1, BRCA2. Policy No. 2008T0009F. 2008. Available at: <http://www.unitedhealthcareonline.com>. Accessed December 15, 2008.
45. Wellmark Blue Cross/Blue Shield (BC/BS) [website]. Genetic Molecular Testing for Oncologic Indications. Medical Policy No. 02.04.07. Reviewed August 2008. Available at: http://www.wellmark.com/e_business/provider/medical_policies/policies/Genetic_Molecular_Testing_Oncologic.htm. Accessed December 15, 2008.
46. Berliner JL, Fay AM; Practice Issues Subcommittee of the National Society of Genetic Counselors' Familial Cancer Risk Counseling Special Interest Group. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *J Genet Couns.* 2007;16(3):241-260.
47. van Oostrom I, Meijers-Heijboer H, Lodder LN, et al. Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. *J Clin Oncol.* 2003;21(20):3867-3874.
48. **van Dijk S, Otten W, Tollenaar RA, et al. Putting it all behind: long-term psychological impact of an inconclusive DNA test result for breast cancer. *Genet Med.* 2008;10(10):745-750.**
49. Keating NL, Stoeckert KA, Regan MM, et al. Physicians' experiences with BRCA1/2 testing in community settings. *J Clin Oncol.* 2008;26(35):5789-5796.
50. White DB, Bonham VL, Jenkins J, et al. Too many referrals of low-risk women for BRCA1/2 genetic services by family physicians. *Cancer Epidemiol Biomarkers Prev.* 2008;17(11):2980-2986.
51. ClinicalTrials.gov [website]. Searched for *BRCA1*; *BRCA2*. 2008. Available at: <http://www.clinicaltrials.gov/>. Accessed December 15, 2008.
52. Computer Retrieval of Information on Scientific Projects (CRISP) [website]. Current and Historical Awards (1972-2008) Query Form. Searched for *BRCA1* AND *BRCA2*. 2008. Available at: <http://crisp.cit.nih.gov/>. Accessed December 15, 2008.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 16 of 16

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)

Update Search

This **Update Search** summary is based only on the published abstracts; any coverage decisions or changes in policy should be based on review and analysis of complete study results. Predictions related to impact on **Hayes Ratings** are based on the data presented in the abstracts retrieved and do not constitute a guarantee of update of this report. Changes in **Hayes Ratings** for this technology will be made only after this report has been reviewed and updated.

Title: BRCA1/BRCA2 Sequence Variant Analysis for Susceptibility to Hereditary Breast Cancer (Myriad Genetics Inc.) , usgte.gte.brca12.2010

Date: February 3, 2010

Summary:

Search strategy:

Search was performed using Medline with keywords



This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2010 Winifred S. Hayes, Inc.

4/23/2010

Page 1 of

Comprehensive Screening for Large Rearrangements in *BRCA1/2* for Assessment of Breast Cancer Risk

AT A GLANCE

Product Names: BRCA*Analysis*® Rearrangement Test (BART) (Myriad Genetic Laboratories Inc.)

Background: In the United States, over 200,000 women and 1500 men are diagnosed with breast cancer each year. Breast cancer is the second leading cause of cancer-related deaths among women. For 5% to 10% of breast cancer, a strong family history is indicated by multiple site-specific cases or prevalence of both breast and ovarian cancer. Genetic alterations in *BRCA1* and/or *BRCA2* (*BRCA1/2*) are thought to account for 45% to 90% of *BRCA1*-related and 35% of *BRCA2*-related cases with a strong family history of breast/ovarian cancers. Ethnic-specific common sequence variants include founder effects for a few populations, especially Ashkenazi Jewish and Dutch, for which assays are variant-specific and the test population is more clearly defined. The penetrance for carriers of *BRCA1* and *BRCA2* sequence variants to develop breast cancer by 70 years of age has been estimated at 65% and 39%, respectively. Rare genomic rearrangements in *BRCA1/2* cannot be detected by usual methods for detecting *BRCA1/2* sequence variants. Recently screening for large rearrangements has become possible through increased throughput, dosage-sensitive, polymerase chain reaction (PCR)-based methods. Currently the most popular research-based technology used to detect *BRCA1/2* large rearrangements is multiplex ligation-dependent probe amplification (MLPA). Myriad Genetic Laboratories Inc. recently made the BRCA*Analysis* Rearrangement Test (BART) available for clinical comprehensive screening for large rearrangements in *BRCA1/2*.

Description of the Technology/Patient Population: Comprehensive screening for *BRCA1/2* rearrangements may be most effectively performed by dosage-based PCR methods, for which normal gene copies, deletions, or duplications are detected by comparative fluorescence analysis. Patients must be carefully selected for comprehensive rearrangement screening based on high-risk family history criteria and must first test negative for *BRCA1/2* sequence variants by conventional clinical methods. When available, an affected family member should be screened prior to one who is not affected.

Synopsis of the Clinical Evidence: Large rearrangements in *BRCA1/2* have previously gone undetected by conventional methods, such as full sequencing and testing to detect specific variants. When screening for large rearrangements is performed among highly selected patients who have previously tested negative for *BRCA1/2* sequence variants, 3% to 12% of patients were found to carry large rearrangements in *BRCA1/2*.

HAYES RATING FOR GENETIC TEST

Order now!

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

HAYES RATING FOR GENETIC TEST

ONGOING STUDIES

PUBLICATION HISTORY

REFERENCES (key references are in bold)

1. National Cancer Institute (NCI) [website]. Genetics of Breast and Ovarian Cancer (PDQ®). Updated December 18, 2007. Available at: http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/healthprofessional/allpages#Section_95. Accessed February 12, 2008.
2. Rosman DS, Kaklamani V, Pasche B. New insights into breast cancer genetics and impact on patient management. *Curr Treat Options Oncol*. 2007;8(1):61-73.
3. Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1993;52(4):678-701.
4. Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, *BRCA2*, to chromosome 13q12-13. *Science*. 1994;265(5181):2088-2090.
5. Gayther SA, Mangion J, Russell P, et al. Variation of risks of breast and ovarian cancer associated with different germline mutations of the *BRCA2* gene. *Nat Genet*. 1997;15(1):103-105.
6. Kirchhoff T, Kauff ND, Mitra N, et al. *BRCA* mutations and risk of prostate cancer in Ashkenazi Jews. *Clin Cancer Res*. 2004;10(9):2918-2921.
7. National Comprehensive Cancer Network (NCCN) [website]. NCCN Clinical Practice Guidelines in Oncology™ - Genetic/Familial High-Risk Assessment: Breast and Ovarian – v.1.2007. Updated March 22, 2007. Available at: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. Accessed February 12, 2008.
8. Frank TS, Manley SA, Olopade OI, et al. Sequence analysis of *BRCA1* and *BRCA2*: correlation of mutations with family history and ovarian cancer risk. *J Clin Oncol*. 1998;16(7):2417-2425.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2008 Winifred S. Hayes, Inc.

4/6/2010

Page 19 of 22

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)

9. Couch FJ, DeShano ML, Blackwood MA, et al. *BRCA1* mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med.* 1997;336(20):1409-1415.
10. Berry DA, Parmigiani G, Sanchez J, et al. Probability of carrying a mutation of breast-ovarian cancer gene *BRCA1* based on family history. *J Natl Cancer Inst.* 1997;89(3):227-238.
11. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes *BRCA1* and *BRCA2*. *Am J Hum Genet.* 1998;62(1):145-158.
12. Antoniou AC, Sinilnikova OM, Simard J, et al.; Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). *RAD51* 135G=C modifies breast cancer risk among *BRCA2* mutation carriers: results from a combined analysis of 19 studies. *Am J Hum Genet.* 2007;81(6):1186-1200.
13. Begg CB, Haile RW, Borg A, et al. Variation of breast cancer risk among *BRCA1/2* carriers. *JAMA.* 2008;299(2):194-201.
14. U.S. Preventive Services Task Force (USPSTF). Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility: recommendation statement [correction appears in *Ann Intern Med.* 2005;143(7):547]. *Ann Intern Med.* 2005;143(5):355-361.
15. Vasickova P, Machackova E, Lukesova M, et al. High occurrence of *BRCA1* intragenic rearrangements in hereditary breast and ovarian cancer syndrome in the Czech Republic. *BMC Med Genet.* 2007;8:32.
16. **Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in *BRCA1*, *BRCA2*, *CHEK2*, and *TP53* in families at high risk of breast cancer. *JAMA.* 2006;295(12):1379-1388.**
17. Fackenthal JD, Olopade OI. Breast cancer risk associated with *BRCA1* and *BRCA2* in diverse populations. *Nat Rev Cancer.* 2007;7(12):937-948.
18. Myriad Genetic Laboratories Inc. (MGL) [website]. BRACAnalysis® Technical Specifications. Updated August 4, 2006. Available at: <http://www.myriadtests.com/provider/doc/BRACAnalysis-Technical-Specifications.pdf>. Accessed February 12, 2008.
19. Schouten JP, McElgunn CJ, Waaijer R, et al. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. *Nucleic Acids Res.* 2002;30(12):e57.
20. De Lellis L, Curia MC, Aceto GM, et al. Analysis of extended genomic rearrangements in oncological research. *Ann Oncol.* 2007;18(Suppl 6):vi173-vi178.
21. Shannon KM, Muzikansky A, Chan-Smutko G, et al. Uptake of *BRCA1* rearrangement panel testing: in individuals previously tested for *BRCA1/2* mutations. *Genet Med.* 2006;8(12):740-745.
22. von der Ropp A, Taubman T. Bioethics and Patent Law: The Case of Myriad. August 2006. World Intellectual Property Organization (WIPO) [website]. Available at: http://www.wipo.int/wipo_magazine/en/2006/04/article_0003.html. Accessed February 12, 2008.
23. Myriad Genetics Inc. [website]. Myriad Introduces Enhanced BRACAnalysis® Test for Exceptionally High-Risk Breast Cancer Patients. August 1, 2006. Available at: <http://www.myriad.com/news/release/890018>. Accessed February 12, 2008.
24. **Wenstrup R, Judkins T, Eliason K, et al. Molecular genetic testing for large genomic deletion and duplication mutations in the *BRCA1* and *BRCA2* genes for hereditary breast and ovarian cancer. *J Clin Oncol.* 2007;25(18S):10513. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting Proceedings; June 1-5, 2007; Chicago, IL. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/10513. Accessed February 12, 2008.**
25. Myriad Genetic Laboratories Inc. (MGL) [website]. BRACAnalysis Rearrangement Test Criteria. May 2007. Available at: <http://www.myriadresourceguide.com/pdfs/Myriad-Resource-Guide-BART-Criteria.pdf>. Accessed February 12, 2008.
26. Casilli F, Di Rocco ZC, Gad S, et al. Rapid detection of novel *BRCA1* rearrangements in high-risk breast-ovarian cancer families using multiplex PCR of short fluorescent fragments. *Hum Mutat.* 2002;20(3):218-226.
27. Tournier I, Paillerets BB, Sobol H, et al. Significant contribution of germline *BRCA2* rearrangements in male breast cancer families. *Cancer Res.* 2004;64(22):8143-8147.
28. Weitzel JN, Lagos VI, Herzog JS, et al. Evidence for common ancestral origin of a recurring *BRCA1* genomic rearrangement identified in high-risk Hispanic families. *Cancer Epidemiol Biomarkers Prev.* 2007;16(8):1615-1620.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2008 Winifred S. Hayes, Inc.



Transforming Healthcare with Evidence

4/6/2010

Page 20 of 22

[Back to Table of Contents](#)

29. MRC-Holland [website]. MRC-Holland. 2005. Available at: <http://www.mlpa.com/pages/indexpag.html>. Accessed February 12, 2008.
30. Parmigiani G, Chen S, Iversen ES Jr, et al. Validity of models for predicting *BRCA1* and *BRCA2* mutations. *Ann Intern Med*. 2007;147(7):441-450.
31. Centers for Disease Control and Prevention (CDC) [website]. Evaluation of Genetic Testing. Updated December 11, 2007. Available at: <http://www.cdc.gov/genomics/gtesting/ACCE.htm>. Accessed February 12, 2008.
32. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) [website]. About EGAPP. 2007. Available at: <http://www.egapreviews.org/about.htm>. Accessed February 12, 2008.
33. Gudgeon JM, McClain MR, Palomaki GE, Williams MS. Rapid ACCE: experience with a rapid and structured approach for evaluating gene-based testing. *Genet Med*. 2007;9(7):473-478.
34. Hendrickson BC, Judkins T, Ward BD, et al. Prevalence of five previously reported and recurrent *BRCA1* genetic rearrangement mutations in 20,000 patients from hereditary breast/ovarian cancer families. *Genes Chromosomes Cancer*. 2005;43(3):309-313.
35. **Unger MA, Nathanson KL, Calzone K, et al. Screening for genomic rearrangements in families with breast and ovarian cancer identifies *BRCA1* mutations previously missed by conformation-sensitive gel electrophoresis or sequencing. *Am J Hum Genet*. 2000;67(4):841-850.**
36. Casilli F, Tournier I, Sinilnikova OM, et al. The contribution of germline rearrangements to the spectrum of *BRCA2* mutations. *J Med Genet*. 2006;43(9):e49.
37. **Montagna M, Dalla Palma M, Menin C, et al. Genomic rearrangements account for more than one-third of the *BRCA1* mutations in northern Italian breast/ovarian cancer families. *Hum Mol Genet*. 2003;12(9):1055-1061.**
38. Agata S, Viel A, Della Puppa L, et al. Prevalence of *BRCA1* genomic rearrangements in a large cohort of Italian breast and breast/ovarian cancer families without detectable *BRCA1* and *BRCA2* point mutations. *Genes Chromosomes Cancer*. 2006;45(9):791-797.
39. Santarosa M, Viel A, Dolcetti R, et al. Low incidence of *BRCA1* mutations among Italian families with breast and ovarian cancer. *Int J Cancer*. 1998;78(5):581-586.
40. Agata S, Dalla Palma M, Callegaro M, et al. Large genomic deletions inactivate the *BRCA2* gene in breast cancer families. *J Med Genet*. 2005;42(10):e64.
41. Veschi S, Aceto G, Scioletti AP, et al. High prevalence of *BRCA1* deletions in BRCAPRO-positive patients with high carrier probability. *Ann Oncol*. 2007;18(Suppl 6):vi86-vi92.
42. **Woodward AM, Davis TA, Silva AG, et al.; kConFab Investigators. Large genomic rearrangements of both *BRCA2* and *BRCA1* are a feature of the inherited breast/ovarian cancer phenotype in selected families. *J Med Genet*. 2005;42(5):e31.**
43. de la Hoya M, Gutiérrez-Enriquez S, Velasco E, et al. Genomic rearrangements at the *BRCA1* locus in Spanish families with breast/ovarian cancer. *Clin Chem*. 2006;52(8):1480-1485.
44. Gutiérrez-Enriquez S, de la Hoya M, Martínez-Bouzas C, et al. Screening for large rearrangements of the *BRCA2* gene in Spanish families with breast/ovarian cancer. *Breast Cancer Res Treat*. 2007;103(1):103-107.
45. Syrjäkoski K, Kuukasjärvi T, Waltering K, et al. *BRCA2* mutations in 154 Finnish male breast cancer patients. *Neoplasia*. 2004;6(5):541-545.
46. Karhu R, Laurila E, Kallioniemi A, Syrjäkoski K. Large genomic *BRCA2* rearrangements and male breast cancer. *Cancer Detect Prev*. 2006;30(6):530-534.
47. Tchou J, Ward MR, Volpe P, et al. Large genomic rearrangement in *BRCA1* and *BRCA2* and clinical characteristics of men with breast cancer in the United States. *Clin Breast Cancer*. 2007;7(8):627-633.
48. Hogervorst FB, Nederlof PM, Gille JJ, et al. Large genomic deletions and duplications in the *BRCA1* gene identified by a novel quantitative method. *Cancer Res*. 2003;63(7):1449-1453.
49. Shattuck-Eidens D, McClure M, Simard J, et al. A collaborative survey of 80 mutations in the *BRCA1* breast and ovarian cancer susceptibility gene. Implications for presymptomatic testing and screening. *JAMA*. 1995;273(7):535-541.
50. Thomassen M, Gerdes AM, Cruger D, et al. Low frequency of large genomic rearrangements of *BRCA1* and *BRCA2* in western Denmark. *Cancer Genet Cytogenet*. 2006;168(2):168-171.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2008 Winifred S. Hayes, Inc.

Hayes

Transforming Healthcare with Evidence

4/6/2010

Page 21 of 22

[Back to Table of Contents](#)

51. Nelson HD, Huffman LH, Fu R, Harris EL; U.S. Preventive Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force [correction in *Ann Intern Med.* 2005;143(7):547]. *Ann Intern Med.* 2005;143(5):362-379.
52. Karlan BY, Berchuck A, Mutch D. The role of genetic testing for cancer susceptibility in gynecologic practice. *Obstet Gynecol.* 2007;110(1):155-167.
53. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in *BRCA1* and *BRCA2* mutation carriers: the PROSE Study Group. *J Clin Oncol.* 2004;22(6):1055-1062.
54. Uyei A, Peterson SK, Erlichman J, et al. Association between clinical characteristics and risk-reduction interventions in women who underwent *BRCA1* and *BRCA2* testing: a single-institution study. *Cancer.* 2006;107(12):2745-2751.
55. Friebel TM, Domchek SM, Neuhausen SL, et al. Bilateral prophylactic oophorectomy and bilateral prophylactic mastectomy in a prospective cohort of unaffected *BRCA1* and *BRCA2* mutation carriers. *Clin Breast Cancer.* 2007;7(11):875-882.
56. Heemskerk-Gerritsen BA, Brekelmans CT, Menke-Pluymers MB, et al. Prophylactic mastectomy in *BRCA1/2* mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. *Ann Surg Oncol.* 2007;14(12):3335-3344.
57. Myriad Genetic Laboratories Inc. (MGL) [website]. Centers for Medicare & Medicaid Services Clinical Laboratory Improvement Amendments – Certificate of Accreditation. April 27, 2007. Available at: http://www.myriadtests.com/doc/Myriad_CLIA_Certification.pdf. Accessed February 12, 2008.
58. Centers for Medicare & Medicaid Services (CMS) [website]. Medicare Coverage Database. Updated February 13, 2008. Available at: <http://www.cms.hhs.gov/mcd/search.asp>. Accessed February 13, 2008.
59. Aetna [website]. BRCA Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy. Clinical Policy Bulletin No. 0227. Reviewed December 21, 2007. Available at: http://www.aetna.com/cpb/medical/data/200_299/0227.html. Accessed February 12, 2008.
60. Blue Cross of CA [website]. Genetic Testing for Cancer Susceptibility and Inherited Disorders. Policy No. GENE.00001. Updated November 29, 2007. Available at http://www.bluecrossca.com/medicalpolicies/policies/mp_pw_a050303.htm. Accessed February 12, 2008.
61. CIGNA HealthCare [website]. Genetic Testing for Susceptibility to Breast and Ovarian Cancer (*BRCA1* & *BRCA2*). Coverage Position No. 0001. Updated June 15, 2007. Available at: http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0001_coveragepositioncriteria_genetic_testing_for_breast_and_ovarian_cancer.pdf. Accessed February 12, 2008.
62. Humana [website]. Genetic Testing/Genetic Counseling/Pharmacogenetic Testing. Medical Coverage Policy. Updated June 28, 2007. Available at: http://apps.humana.com/TAD/TAD_New/returnContent.asp?mime=application/pdf&id=5298&issue=608. Accessed February 12, 2008.
63. Regence Group [website]. Genetic Testing for Inherited *BRCA1* or *BRCA2* Mutations. Policy No. 10. December 5, 2006. Available at: <http://www.regence.com/trgmedpol/lab/lab10.html>. Accessed February 12, 2008.
64. United Healthcare (UHC) [website]. Genetic Testing for Breast Cancer: *HER2*, *BRCA1*, *BRCA2*. Policy No. 2007T0009E. December 6, 2007. Available at: <http://www.unitedhealthcareonline.com>. Accessed February 12, 2008.
65. Wellmark Blue Cross/Blue Shield (BC/BS) [website]. Genetic Molecular Testing for Oncologic Indications. Medical Policy No. 02.04.07. Reviewed October 2006. Available at: http://www.wellmark.com/e_business/provider/medical_policies/policies/Genetic_Molecular_Testing_Oncologic.htm. Accessed February 12, 2008.
66. Rubinstein WS. Roles and responsibilities of a medical geneticist. *Fam Cancer.* 2007 Jul 12 [Epub ahead of print].

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2008 Winifred S. Hayes, Inc.

4/6/2010

Page 22 of 22

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)

Update Search

This **Update Search** summary is based only on the published abstracts; any coverage decisions or changes in policy should be based on review and analysis of complete study results. Predictions related to impact on **Hayes Ratings** are based on the data presented in the abstracts retrieved and do not constitute a guarantee of update of this report. Changes in **Hayes Ratings** for this technology will be made only after this report has been reviewed and updated.

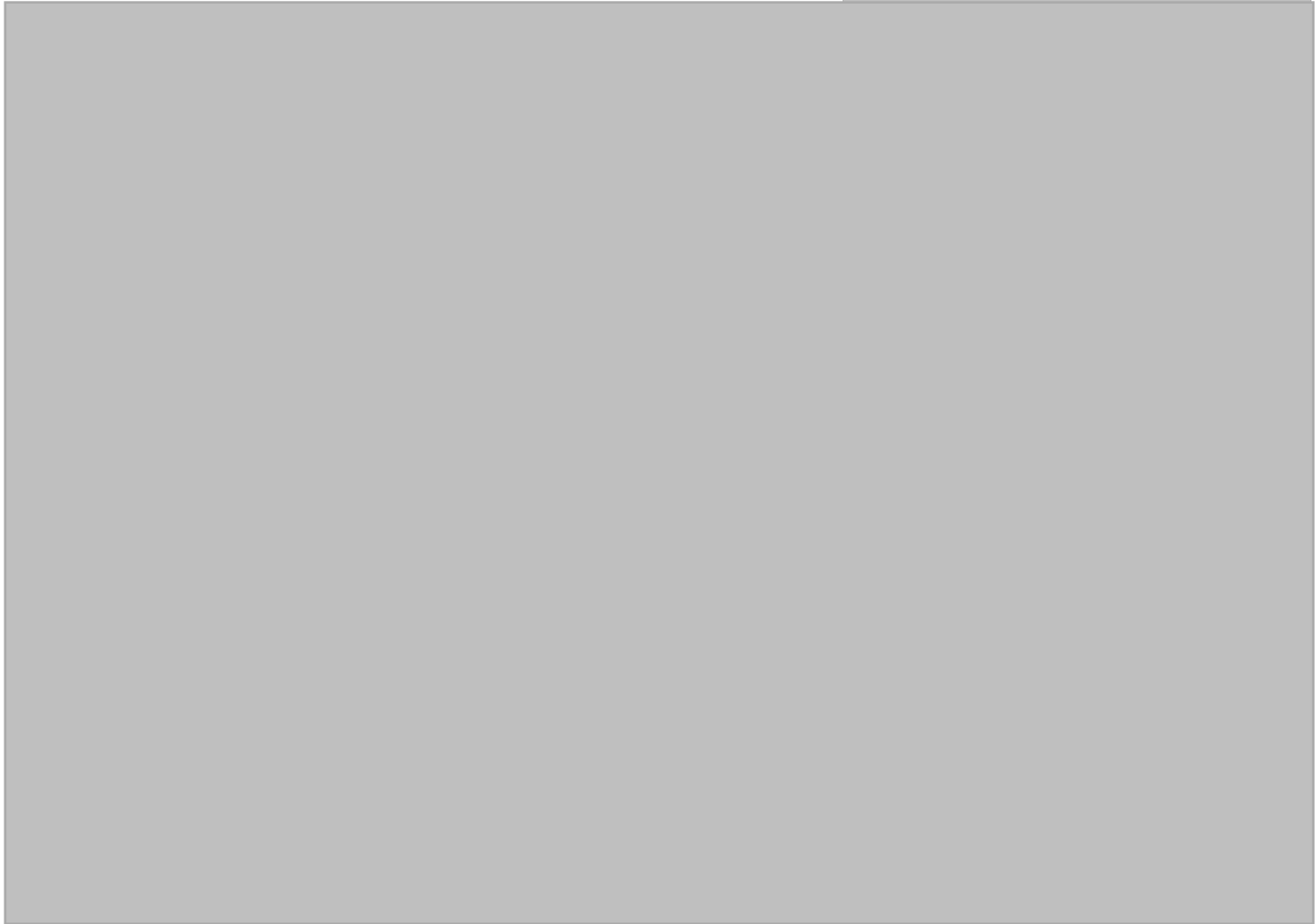
Title: Comprehensive Screening for Large Rearrangements in BRCA1/2 for Assessment of Breast Cancer Risk, usgts.3.2009

Date: March 30, 2009

Summary:

Search strategy:

Search was performed using Medline and Embase with keywords



This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/23/2010

Page 1 of



Transforming Healthcare with Evidence

[Back to Table of Contents](#)

Update Search

This **Update Search** summary is based only on the published abstracts; any coverage decisions or changes in policy should be based on review and analysis of complete study results. Predictions related to impact on **Hayes Ratings** are based on the data presented in the abstracts retrieved and do not constitute a guarantee of update of this report. Changes in **Hayes Ratings** for this technology will be made only after this report has been reviewed and updated.

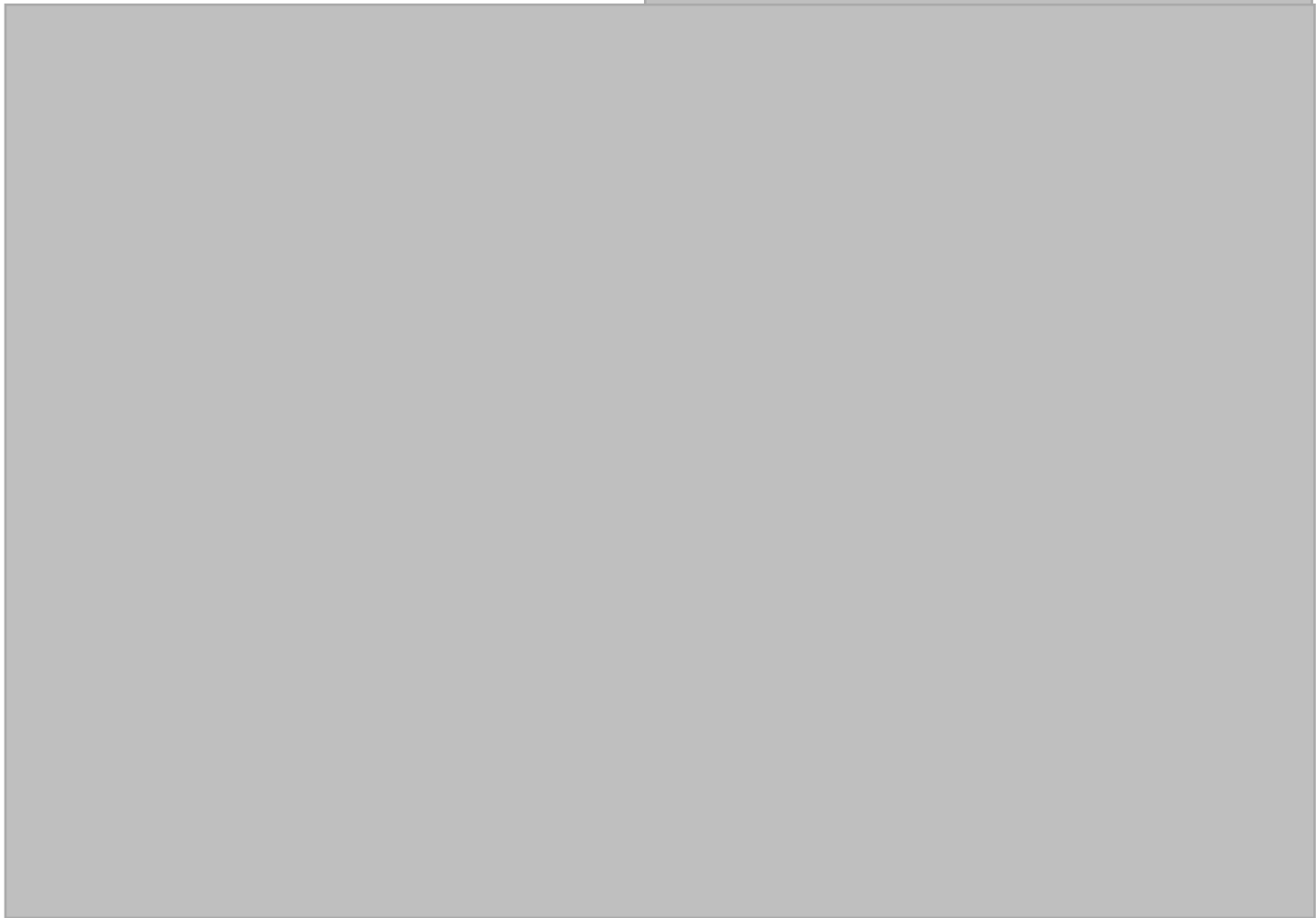
Title: Comprehensive Screening for Large Rearrangements in BRCA1/2 for Assessment of Breast Cancer Risk, usgte.brca.2010

Date: March 26, 2010

Summary:

Search strategy:

Search was performed using Medline with keywords



This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2010 Winifred S. Hayes, Inc.

4/23/2010

Page 1 of

December 16, 2009

BRCA1 and BRCA2 Sequence Variant Analysis for Susceptibility to Hereditary Ovarian Cancer

AT A GLANCE

Product Names: BRACAnalysis®, BRCA1 Analysis, BRCA2 Analysis, and BRACAnalysis® Rearrangement Test (BART™) (Myriad Genetic Laboratories Inc.);

Background: It is estimated that more than 21,000 women will be diagnosed with ovarian cancer in the United States in 2009, and more than 14,000 women will die from the disease. It has also been estimated that approximately 10% of patients with ovarian cancer, the vast majority of who have epithelial tumors, carry germline variants in 1 of 2 hereditary breast and ovarian cancer genes: *BRCA1* and *BRCA2*. *BRCA1* (breast cancer gene 1, located on chromosome 17 at band q21) and *BRCA2* (breast cancer gene 2, located on chromosome 13 at band q12.3) encode proteins that function in the double-strand DNA break repair pathway and behave as tumor suppressor genes. Most alterations in the *BRCA1* and *BRCA2* genes are frameshift, nonsense, or splice-site variants that lead to premature truncation of the protein during translation. While many of these are considered “private” variants, having been found in only 1 or a few families, common ethnic-specific variants have also been identified for some populations. Individuals carrying deleterious variants in either *BRCA1* or *BRCA2* are known to have an increased risk for both breast and ovarian cancer. In comparison with a lifetime risk of 1.8% for a woman in the general population, the lifetime risk of ovarian cancer is approximately 30% to 60% for *BRCA1* carriers and 10% to 30% for *BRCA2* carriers.

Description of the Technology/Patient Population: *BRCA1* and *BRCA2* gene testing for hereditary ovarian cancer is performed by direct sequencing. Myriad Genetics Inc. provides a comprehensive analysis of both genes that looks for pathogenic variants in the coding regions and flanking intron sequences. This test, known as BRACAnalysis, also includes testing for the 5 most common large rearrangements in *BRCA1*. A targeted analysis that tests for 3 specific variants common among individuals of Ashkenazi Jewish descent may also be performed. High-risk patients who test negative with the traditional BRACAnalysis may undergo a comprehensive screening for large genomic rearrangements using the BRACAnalysis Rearrangement Test (BART). Initial *BRCA1/2* gene testing may be considered in patients with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. It may also be performed in patients with a personal or family history consistent with hereditary breast and ovarian cancer, or in relatives of individuals who carry *BRCA1* or *BRCA2* sequence variants known to be pathogenic.

Synopsis of the Clinical Evidence: While studies of the analytical validity of *BRCA1/2* gene sequencing were not located, sequence analysis is considered the most sensitive technique for identifying pathogenic sequence variants. However, direct gene sequencing is unable to detect large deletions and duplications. As such, testing for large rearrangements in the *BRCA1* and *BRCA2* genes may be indicated in individuals with a family history strongly suggestive of a familial form of ovarian cancer, who have tested negative by gene sequencing. Direct sequencing may also identify variants of unknown clinical significance.

Order now!

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 1 of 34

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)

PUBLICATION HISTORY

REFERENCES (key references are in bold)

1. National Comprehensive Cancer Network (NCCN) [website]. NCCN Clinical Practice Guidelines in Oncology™. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. v.2.2009. Updated May 21, 2009. Available at: http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf. Accessed December 7, 2009.
2. American College of Obstetricians and Gynecologists (ACOG); ACOG Committee on Practice Bulletins--Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol.* 2009;113(4):957-966.
3. United States Preventive Services Task Force (USPSTF). Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement [correction appears in *Ann Intern Med.* 2005;143(7):547]. *Ann Intern Med.* 2005;143(5):355-361.
4. **Ramus SJ, Gayther SA. The contribution of BRCA1 and BRCA2 to ovarian cancer. *Mol Oncol.* 2009;3(2):138-150.**
5. Evans DG, Young K, Bulman M, Shenton A, Wallace A, Laloo F. Probability of BRCA1/2 mutation varies with ovarian histology: results from screening 442 ovarian cancer families. *Clin Genet.* 2008;73(4):338-345.
6. Palma M, Ristori E, Ricevuto E, Giannini G, Gulino A. BRCA1 and BRCA2: the genetic testing and the current management options for mutation carriers. *Crit Rev Oncol Hematol.* 2006;57(1):1-23.
7. Søggaard M, Kjaer SK, Gayther S. Ovarian cancer and genetic susceptibility in relation to the BRCA1 and BRCA2 genes. Occurrence, clinical importance and intervention. *Acta Obstet Gynecol Scand.* 2006;85(1):93-105.
8. Metcalfe KA, Lynch HT, Ghadirian P, et al. The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers. *Gynecol Oncol.* 2005;96(1):222-226.
9. National Comprehensive Cancer Network (NCCN) [website]. NCCN Clinical Practice Guidelines in Oncology™. Genetic/Familial High-Risk Assessment: Breast and Ovarian. v.1.2009.Updated May 4, 2009. Available at: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. Accessed December 9, 2009.
10. Swisher E. Prophylactic surgery and other strategies for reducing the risk of familial ovarian cancer. *Curr Treat Options Oncol.* 2003;4(2):105-110.
11. Guillem JG, Wood WC, Moley JF, et al.; ASCO; SSO. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. *J Clin Oncol.* 2006;24(28):4642-4660.
12. **Nelson HD, Huffman LH, Fu R, Harris EL.; U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005;143(5):362-379.**
13. Verheijen RH, Hermesen B. The clinical implications of genetics. BRCA1- and BRCA2-positive: how do I proceed? Implications for ovarian cancer prevention. *Ann Oncol.* 2008;19(SUPPL. 5):v84-v86.
14. Olopade OI, Artioli G. Efficacy of risk-reducing salpingo-oophorectomy in women with BRCA-1 and BRCA-2 mutations. *Breast J.* 2004;(10 Suppl 1):S5-S9.
15. **Rosen B, Kwon J, Fung Kee Fung M, Gagliardi A, Chambers A; Cancer Care Ontario's Practice Guidelines Initiative Gynecology Cancer Disease Site Group. Systematic review of management options for women with a hereditary predisposition to ovarian cancer. *Gynecol Oncol.* 2004;93(2):280-286.**
16. Casey MJ, Synder C, Bewtra C, Narod SA, Watson P, Lynch HT. Intra-abdominal carcinomatosis after prophylactic oophorectomy in women of hereditary breast ovarian cancer syndrome kindreds associated with *BRCA1* and *BRCA2* mutations. *Gynecol Oncol.* 2005;97(2):457-467.
17. Myriad Genetic Laboratories Inc. [website]. BRACAnalysis® Technical Specifications. February 2009. Available at: <http://www.myriadtests.com/provider/doc/BRACAnalysis-Technical-Specifications.pdf>. Accessed December 7, 2009.
18. Bodmer D, Ligtenberg M, van der Hout A, et al. Optimal selection for BRCA1 and BRCA2 mutation testing using a combination of 'easy to apply' probability models. *Br J Cancer.* 2006;95(6):757-762.
19. James PA, Doherty R, Harris M, et al. Optimal selection of individuals for BRCA mutation testing: a comparison of available methods. *J Clin Oncol.* 2006;24(4):707-715.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 28 of 34

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)

20. Palomaki GE, McClain MR, Steinort K, Sifri R, LoPresti L, Haddow JE. Screen-positive rates and agreement among six family history screening protocols for breast/ovarian cancer in a population-based cohort of 21- to 55-year-old women. *Genet Med*. 2006;8(3):161-168.
21. Parmigiani G, Chen S, Iversen ES Jr, et al. Validity of models for predicting BRCA1 and BRCA2 mutations. *Ann Intern Med*. 2007;147(7):441-450.
22. McClain MR, Palomaki GE, Hampel H, Westman JA, Haddow JE. Screen positive rates among six family history screening protocols for breast/ovarian cancer in four cohorts of women. *Fam Cancer*. 2008;7(4):341-345.
23. Bast RC Jr, Brewer M, Zou C, et al. Prevention and early detection of ovarian cancer: mission impossible? *Recent Results Cancer Res*. 2007;174:91-100.
24. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet*. 1994;343(8899):692-695.
25. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1995;56:265(1)-271.
26. Abeliovich D, Kaduri L, Lerer I, et al. The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. *Am J Hum Genet*. 1997;60(3):505-514.
27. Levy-Lahad E, Catane R, Eisenberg S, et al. Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. *Am J Hum Genet*. 1997;60(5):1059-1067.
28. Frank TS, Manley SA, Olopade OI, et al. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. *J Clin Oncol*. 1998;16(7):2417-2425.
29. Lu KH, Cramer DW, Muto MG, Li EY, Niloff J, Mok SC. A population-based study of BRCA1 and BRCA2 mutations in Jewish women with epithelial ovarian cancer. *Obstet Gynecol*. 1999;93(1):34-37.
30. Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet*. 2001;68(3):700-710.
31. Reedy M, Gallion H, Fowler JM, Kryscio R, Smith SA. Contribution of BRCA1 and BRCA2 to familial ovarian cancer: a gynecologic oncology group study. *Gynecol Oncol*. 2002;85(2):255-259.
32. Lux M, Ackermann S, Nestle-Krämling C, et al. Use of intensified early cancer detection in high-risk patients with familial breast and ovarian cancer. *Eur J Cancer Prev*. 2005;14(4):399-411.
33. Kinney AY, Simonsen SE, Baty BJ, et al. Risk reduction behaviors and provider communication following genetic counseling and BRCA1 mutation testing in an African American kindred. *J Genet Couns*. 2006;15(4):293-305.
34. Leunen K, Legius E, Moerman P, Amant F, Neven P, Vergote I. Prophylactic salpingo-oophorectomy in 51 women with familial breast-ovarian cancer: importance of fallopian tube dysplasia. *Int J Gynecol Cancer*. 2006;16(1):183-188.
35. Mæhle L, Apold J, Paulsen T, et al. High risk for ovarian cancer in a prospective series is restricted to BRCA1/2 mutation carriers. *Clin Cancer Res*. 2008;14(2):7569-7573.
36. Grann VR, Panageas KS, Whang W, Antman KH, Neugut AI. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. *J Clin Oncol*. 1998;16(3):979-985.
37. Grann VR, Whang W, Jacobson JS, Heitjan DF, Antman KH, Neugut AI. Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2. *J Clin Oncol*. 1999;17(2):494-500.
38. Grann VR, Jacobson JS, Whang W, et al. Prevention with tamoxifen or other hormones versus prophylactic surgery in BRCA1/2-positive women: a decision analysis. *Cancer J Sci Am*. 2000;6(1):13-20.
39. Schrag D, Kuntz KM, Garber JE, Weeks JC. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. *JAMA*. 2000;283(5):617-624.
40. Grann VR, Jacobson JS, Thomason D, Hershman D, Heitjan DF, Neugut AI.. Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis. *J Clin Oncol*. 2002;20(10):2520-2529.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 29 of 34



Transforming Healthcare with Evidence

[Back to Table of Contents](#)

41. Armstrong K, Schwartz JS, Randall T, Rubin SC, Weber B. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. *J Clin Oncol.* 2004;22(6):1045-1054.
42. Eng C, Brody LC, Wagner TMU, et al.; Steering Committee of the Breast Cancer Information Core (BIC) Consortium. Interpreting epidemiological research: blinded comparison of methods used to estimate the prevalence of inherited mutations in BRCA1. *J Med Genet.* 2001;38(12):824-833.
43. Andrulis IL, Anton-Culver H, Beck J, et al.; Cooperative Family Registry for Breast Cancer studies. Comparison of DNA- and RNA-based methods for detection of truncating BRCA1 mutations. *Hum Mutat.* 2002;20(1):65-73.
44. Centers for Disease Control and Prevention (CDC) [website]. Genomic Translation. ACCE Model for Process for Evaluating Genetic Tests. Reviewed July 21, 2009. Available at: <http://www.cdc.gov/genomics/gtesting/ACCE/index.htm>. Accessed December 7, 2009.
45. Teutsch SM, Bradley LA, Palomaki GE, et al.; EGAPP Working Group. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med.* 2009;11(1):3-14.
46. **Hall MJ, Reid JE, Burbidge LA, et al. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. *Cancer.* 2009;115(10):2222-2233.**
47. Meindl A; German Consortium for Hereditary Breast and Ovarian Cancer. Comprehensive analysis of 989 patients with breast or ovarian cancer provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. *Int J Cancer.* 2002;97(4):472-480.
48. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol.* 2002;20(6):1480-1490.
49. Jacobi CE, Van Ierland Y, van Asperen CJ, et al. Prediction of BRCA1/2 mutation status in patients with ovarian cancer from a hospital-based cohort. *Genet Med.* 2007;9(3):173-179.
50. Hogervorst FB, Nederlof PM, Gille JJ, et al. Large genomic deletions and duplications in the BRCA1 gene identified by a novel quantitative method. *Cancer Res.* 2003;63(7):1449-1453.
51. Woodward AM, Davis TA, Silva AG, Kirk JA, Leary JA; kConFab Investigators. Large genomic rearrangements of both BRCA2 and BRCA1 are a feature of the inherited breast/ovarian cancer phenotype in selected families. *J Med Genet.* 2005;42(5):e31.
52. Agata S, Viel A, Della Puppa L, et al. Prevalence of BRCA1 genomic rearrangements in a large cohort of Italian breast and breast/ovarian cancer families without detectable BRCA1 and BRCA2 point mutations. *Genes Chromosomes Cancer.* 2006;45(9):791-797.
53. de la Hoya M, Gutiérrez-Enríquez S, Velasco E, et al. Genomic rearrangements at the BRCA1 locus in Spanish families with breast/ovarian cancer. *Clin Chem.* 2006;52(8):1480-1485.
54. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *JAMA.* 2006;295(12):1379-1388.
55. Gutiérrez-Enríquez S, de la Hoya M, Martínez-Bouzas C, et al. Screening for large rearrangements of the BRCA2 gene in Spanish families with breast/ovarian cancer. *Breast Cancer Res Treat.* 2007;103(1):103-107.
56. Weitzel JN, Lagos VI, Herzog JS, et al. Evidence for common ancestral origin of a recurring BRCA1 genomic rearrangement identified in high-risk Hispanic families. *Cancer Epidemiol Biomarkers Prev.* 2007;16(8):1615-1620.
57. Wenstrup R, Judkins T, Eliason K, et al. Molecular genetic testing for large genomic deletion and duplication mutations in the BRCA1 and BRCA2 genes for hereditary breast and ovarian cancer. *J Clin Oncol.* 2007;25(18S):10513.
58. Palma MD, Domchek SM, Stopfer J, et al. The relative contribution of point mutations and genomic rearrangements in BRCA1 and BRCA2 in high-risk breast cancer families. *Cancer Res.* 2008;68(17):7006-7014.
59. Ratajska M, Brozek I, Senkus-Konefka E, et al. BRCA1 and BRCA2 point mutations and large rearrangements in breast and ovarian cancer families in Northern Poland. *Oncol Rep.* 2008;19(1):263-268.
60. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med.* 1997;336(20):1401-1408.
61. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *J Natl Cancer Inst.* 2002;94(18):1365-1372.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 30 of 34

62. Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Clin Cancer Res.* 2002;8(12):3776-3781.
63. Heimdal K, Maehle L, Apold J, Pedersen JC, Møller P. The Norwegian founder mutations in BRCA1: high penetrance confirmed in an incident cancer series and differences observed in the risk of ovarian cancer. *Eur J Cancer.* 2003;39(15):2205-2213.
64. King MC, Marks JH, Mandell JB; New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science.* 2003;302(5645):643-646.
65. Marroni F, Aretini P, D'Andrea E, et al. Penetrances of breast and ovarian cancer in a large series of families tested for BRCA1/2 mutations. *Eur J Hum Genet.* 2004;12(11):899-906.
66. **Chen S, Iversen ES, Friebel T, et al. Characterization of BRCA1 and BRCA2 mutations in a large United States sample. *J Clin Oncol.* 2006;24(6):863-871.**
67. Risch HA, McLaughlin JR, Cole DE, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. *J Natl Cancer Inst.* 2006;98(23):1694-1706.
68. Evans D, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer.* 2008a;8:155.
69. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected from family history: a combined analysis of 22 studies [correction appears in *Am J Hum Genet.* 2003;73(3):709]. *Am J Hum Genet.* 2003;72(5):1117-1130.
70. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol.* 2007;25(11):1329-1333.
71. Gayther SA, Warren W, Mazoyer S, et al. Germline of the BRCA1 gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. *Nat Genet.* 1995;11(4):428-433.
72. Thompson D, Easton D; Breast Cancer Linkage Consortium. Variation in BRCA1 cancer risks by mutation position. *Cancer Epidemiol Biomarkers Prev.* 2002;11(4):329-336.
73. Gayther SA, Mangion J, Russell P, et al. Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. *Nat Genet.* 1997;15(1):103-105.
74. Thompson D, Easton D; Breast Cancer Linkage Consortium. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. *Am J Hum Genet.* 2001;68(2):410-419.
75. Easton DF, Deffenbaugh AM, Pruss D, et al. A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the BRCA1 and BRCA2 breast cancer-predisposition genes. *Am J Hum Genet.* 2007;81(5):873-883.
76. Spearman AD, Sweet K, Zhou XP, McLennan J, Couch FJ, Toland AE. Clinically applicable models to characterize BRCA1 and BRCA2 variants of uncertain significance. *J Clin Oncol.* 2008;26(33):5393-5400.
77. Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. *J Clin Oncol.* 2002;20(5):1260-1268.
78. Claes E, Evers-Kiebooms G, Decruyenaere M, et al. Surveillance behavior and prophylactic surgery after predictive testing for hereditary breast/ovarian cancer. *Behav Med.* 2005;31(3):93-105.
79. Metcalfe KA, Snyder C, Seidel J, Hanna D, Lynch HT, Narod S. The use of preventive measures among healthy women who carry a BRCA1 or BRCA2 mutation. *Fam Cancer.* 2005;4(2):97-103.
80. Schmeler KM, Sun CC, Bodurka DC, et al. Prophylactic bilateral salpingo-oophorectomy compared with surveillance in women with BRCA mutations. *Obstet Gynecol.* 2006;108(3 Pt 1):515-520.
81. Foster C, Watson M, Eeles R, et al.; Psychosocial Study Collaborators. Predictive genetic testing for BRCA1/2 in a UK clinical cohort: three-year follow-up. *Br J Cancer.* 2007;96(5):718-724.
82. Gaarenstroom KN, van der Hiel B, Tollenaar R, et al. Efficacy of screening women at high risk of hereditary ovarian cancer: results of an 11-year cohort study. *Int J Gynecol Cancer.* 2006;16(Suppl 1):54-59.
83. Oei AL, Massuger LF, Bulten J, et al. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. *Br J Cancer.* 2006;94(6):814-819.
84. Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. *Gynecol Oncol.* 2006;100(1):20-26.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 31 of 34

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)

85. van der Velde NM, Mourits MJ, Arts HJ, et al. Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? *Int J Cancer*. 2009;124(4):919-923.
86. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2002;346(21):1609-1615.
87. Rebbeck TR, Lynch HT, Neuhausen SL, et al.; Prevention and Observation of Surgical End Points Study Group. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med*. 2002;346(21):1616-1622.
88. Rutter JL, Wacholder S, Chetrit A, et al. Gynecologic surgeries and risk of ovarian cancer in women with BRCA1 and BRCA2 Ashkenazi founder mutations: an Israeli population-based case-control study. *J Natl Cancer Inst*. 2003;95(14):1072-1078.
89. Olivier RI, van Beurden M, Lubsen MA, et al. Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. *Br J Cancer*. 2004;90(8):1492-1497.
90. Narod SA, Sun P, Ghadirian P, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. *Lancet*. 2001;357(9267):1467-1470.
91. Cass I, Baldwin RL, Varkey T, Moslehi R, Narod SA, Karlan BY. Improved survival in women with BRCA-associated ovarian carcinoma. *Cancer*. 2003;97(9):2187-2195.
92. Whittemore AS, Balise RR, Pharoah PD, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. *Br J Cancer*. 2004;91(11):1911-1915.
93. Baty BJ, Dudley WN, Musters A, Kinney AY. Uncertainty in BRCA1 cancer susceptibility testing. *Am J Med Genet C Semin Med Genet*. 2006;142C(4):241-250.
94. Fortuny D, Balmaña J, Graña B, et al. Opinion about reproductive decision making among individuals undergoing BRCA1/2 genetic testing in a multicentre Spanish cohort. *Hum Reprod*. 2009;24(4):1000-1006.
95. Anderson K, Jacobson JS, Heitjan DF, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. *Ann Intern Med*. 2006;144(6):397-406.
96. Kwon JS, Daniels MS, Sun CC, Lu KH. Preventing future cancers by testing women with ovarian cancer for BRCA mutations. *J Clin Oncol*. 2009. Epub ahead of print. October 19, 2009. Available at: <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2008.21.4684>. Accessed December 7, 2009.
97. Klaren HM, van't Veer LJ, van Leeuwen FE, Rookus MA. Potential for bias in studies on efficacy of prophylactic surgery for BRCA1 and BRCA2 mutation. *J Natl Cancer Inst*. 2003;95(13):941-947.
98. Lessick M. Genetic testing for breast and ovarian cancer: ethical, legal, and psychosocial considerations. *Nurs Womens Health*. 2007;11(4):390-399.
99. Food and Drug Administration (FDA) [website]. Clinical Laboratory Improvement Amendments (CLIA). Updated July 15, 2009. Available at: <http://www.fda.gov/cdrh/clia>. Accessed December 9, 2009.
100. Myriad Genetic Laboratories Inc. [website]. CLIA Certification. 2009. Available at: http://www.myriadtests.com/doc/Myriad_CLIA_Certification.pdf. Accessed December 7, 2009.
101. Centers for Medicare & Medicaid Services (CMS) [website]. Medicare Coverage Database. National Coverage Documents [search: BRCA]. Updated December 7, 2009. Available at: <http://www.cms.hhs.gov/mcd/search.asp>. Accessed December 7, 2009.
102. Coalition of State Genetics Coordinators (CSGC) [website]. State Genetics websites. 2007. Available at: <http://www.stategeneticscoordinators.org/statesites/statesites.htm>. Accessed November 16, 2009.
103. National Newborn Screening and Genetics Resource Center (NNSGRC) [website]. National Newborn Screening Status Report. Updated December 4, 2009. Available at: <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf>. Accessed December 9, 2009.
104. Aetna [website]. Clinical Policy Bulletin: BRCA Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy. Policy No. 0227. Reviewed November 18, 2009. Available at: http://www.aetna.com/cpb/medical/data/200_299/0227.html. Accessed December 7, 2009.
105. Anthem Blue Cross [website]. Genetic testing for cancer susceptibility. Policy No. GENE.00001. Reviewed May 21, 2009. Available at: http://www.anthem.com/ca/medicalpolicies/policies/mp_pw_a050303.htm. Accessed December 7, 2009.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 32 of 34

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)

106. CIGNA HealthCare [website]. Genetic Testing for Susceptibility to Breast and Ovarian Cancer (e.g. BRCA1 & BRCA2). Policy No. 0001. Reviewed July 15, 2008. Available at: http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0001_coveragepositioncriteria_genetic_testing_for_breast_and_ovarian_cancer.pdf. Accessed December 7, 2009.
107. Humana [website]. Medical Coverage Policies. Genetic Testing and Genetic Counseling for Diagnosis and Monitoring of Cancer. Policy No. CPD-0460-006. Revised July 23, 2009. Available at: http://www.humana.com/providers/tools/provider_tools/clinical_healthcare.asp. Accessed December 7, 2009.
108. Humana [website]. Medical Coverage Policies. Genetic Testing and Genetic Counseling for Disease Risk. Policy No. CPD-0464-004. Revised September 24, 2009. Available at: http://www.humana.com/providers/tools/provider_tools/clinical_healthcare.asp. Accessed December 7, 2009.
109. Regence Group [website]. Genetic Testing. Policy No. 20. Approved June 9, 2009. Available at: <http://blue.regence.com/trgmedpol/lab/lab20.html>. Accessed December 9, 2009.
110. United Healthcare (UHC) [website]. Genetic Testing for Breast Cancer: BRCA1, BRCA2 and BRAC. No. 2009T0009G. Updated August 14, 2009. Available at: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesHtml/MedicalPolicies/Genetic_Testing_for_Breast_Cancer_BRCA1_BRCA2_and_BRAC.htm. Accessed December 9, 2009.
111. Wellmark Blue Cross/Blue Shield [website]. Genetic Molecular Testing for Oncologic Indications. Policy No. 02.04.07. Reviewed August 2008. Available at: http://www.wellmark.com/Provider/MedPoliciesAndAuthorizations/MedicalPolicies/Policies/Genetic_Molecular_Testing_Oncologic.aspx. Accessed December 9, 2009.
112. American Society of Clinical Oncology (ASCO). American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol*. 2003;21(12):2397-2406.
113. Berliner JL, Fay AM; Practice Issues Subcommittee of the National Society of Genetic Counselors' Familial Cancer Risk Counseling Special Interest Group. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2007;16(3):241-260.
114. Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol*. 2007;107(2):159-162.
115. Fries MH, Holt C, Carpenter I, et al. Guidelines for evaluation of patients at risk for inherited breast and ovarian cancer: recommendations of the Department of Defense Familial Breast/Ovarian Cancer Research Project. *Mil Med*. 2002;167(2):93-98.
116. Vadaparampil ST, Miree CA, Wilson C, Jacobsen PB. Psychosocial and behavioral impact of genetic counseling and testing. *Breast Dis*. 2006-2007;27:97-108.
117. American Medical Association (AMA). CEJA Report 4 – A-95. Testing Children for Genetic Status. 1995. Available at: http://www.ama-assn.org/ama1/pub/upload/mm/369/ceja_4a95.pdf. Accessed December 7, 2009.
118. American Society of Human Genetics (ASHG) and American College of Medical Genetics (ACMG). Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors and American College of Medical Genetics Board of Directors. *Am J Hum Genet*. 1995;57(5):1233-1241.
119. Smith A, Moran A, Boyd MC, et al. Phenocopies in BRCA1 and BRCA2 families: evidence for modifier genes and implications for screening. *J Med Genet*. 2007;44(1):10-15.
120. Phelan CM, Rebbeck TR, Weber BL, et al. Ovarian cancer risk in BRCA1 carriers is modified by the HRAS1 variable number of tandem repeat (VNTR) locus. *Nat Genet*. 1996;12(3):309-311.
121. Rebbeck TR, Mitra N, Domchek SM, et al. Modification of ovarian cancer risk by BRCA1/2-interacting genes in a multicenter cohort of BRCA1/2 mutation carriers. *Cancer Res*. 2009;69(14):5801-5810.
122. Tagliaferri P, Ventura M, Baudi F, et al. BRCA1/2 genetic background-based therapeutic tailoring of human ovarian cancer: hope or reality? *J Ovarian Res*. 2009;2:14.
123. ClinicalTrials.gov [website]. Search for Clinical Trials [search: BRCA1 AND BRCA2 AND ovarian cancer]. 2009a. Available at: <http://www.clinicaltrials.gov/>. Accessed December 7, 2009.

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 33 of 34

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)

124. National Taiwan University Hospital. Establishing the Incidences of BRCA1 and BRCA2 Mutation by Combining DHPLC and Direct Sequencing in Ovarian Cancer National Library of Medicine (NLM) Identifier: NCT00155896. Updated September 9, 2009. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00155896>. Accessed December 7, 2009.
125. Research Portfolio Online Reporting Tool Expenditures and Results (RePORTER) Database [website]. Search for National Institutes of Health (NIH) Research Activities [search: *BRCA1 AND BRCA2 AND ovarian cancer*]. 2009. Available at: <http://projectreporter.nih.gov/reporter.cfm>. Accessed December 9, 2009.
126. Tissue Genetics Inc. Molecular *BRCA2* Hereditary Ovarian Cancer Tissue Truncation Test. 2009. RePORTER Database [website]. Available at: <http://projectreporter.nih.gov/reporter.cfm>. Accessed December 7, 2009.
127. Ambergen Inc. Molecular Test for Inherited Mutations in Breast Cancer. 2009. RePORTER Database [website]. Available at: http://projectreporter.nih.gov/project_info_description.cfm. Accessed December 9, 2009.



Order now!

This report is intended to provide research assistance and general information only. It is not intended to be used as the sole basis for determining coverage, reimbursement, or technology acquisition. Any decision regarding claims eligibility or benefits, or acquisition of a health technology is solely within the discretion of your organization. Hayes, Inc. assumes no responsibility or liability for such decisions. This report is not intended to be used as the sole basis for defining treatment protocols, or medical modalities, nor should it be construed as providing medical advice regarding treatment of an individual's specific case. This report has been prepared for you by Hayes, Inc. and is for informational purposes only. This report is for internal use by the Purchaser and not intended for distribution.

© 2009 Winifred S. Hayes, Inc.

4/6/2010

Page 34 of 34

Hayes

Transforming Healthcare with Evidence

[Back to Table of Contents](#)