

MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	GENETIC TESTING FOR HEREDITARY BRCA MUTATIONS
Policy Number	2.02.06
Category	Laboratory Test
Effective Date	01/17/02
Revised Date	08/21/03, 09/16/04, 08/18/05, 06/15/06, 06/21/07, 06/19/08, 08/20/09, 01/21/10, 08/19/10, 08/18/11, 05/24/12, 02/21/13, 04/17/14, 10/15/15, 08/18/16, 08/17/17, 10/18/18
Product Disclaimer	<ul style="list-style-type: none"> • If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply. • If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit. • If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.

POLICY STATEMENT

- I. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines genetic testing for hereditary breast and/or ovarian cancer has been medically proven to be effective and therefore **medically appropriate** in the following circumstances, when performed by a qualified laboratory and offered in a setting with adequately trained health care providers to provide appropriate pre-and post-test genetic counseling that will guide decisions regarding cancer prevention, surveillance, and treatment options.

Testing should be performed in the family member with a personal history of cancer (affected) first unless an unaffected individual has a family history of a known mutation; an affected individual has the highest likelihood for a positive test result (e.g., the family member with the youngest age at diagnosis, or bilateral disease, or multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the individual being tested). Testing of unaffected individuals (an individual who does not have cancer) should only be considered when an appropriate affected family member is unavailable for testing. A negative result for an unaffected individual with only a family history of cancer is considered indeterminate (or uninformative) and does not provide the same level of information as when there is a known deleterious mutation in the family. Testing of unaffected family members in the absence of having tested affected family members significantly limits the interpretation of the test results.

A. General Coverage Criteria (81162):

1. Individual from a family with a known BRCA1/BRCA2 pathogenic / likely pathogenic variant, including such variants found on research testing irrespective of degree of relatedness; testing for the specific known mutation rather than full gene sequencing is recommended (CPT 81215 or 81217).
2. Personal history of male breast cancer.
3. Personal history of ovarian/fallopian tube/ primary peritoneal cancer.
4. Personal history of pancreatic cancer diagnosed at any age
5. Personal history of prostate cancer (Gleason score greater than or equal to 7) diagnosed at any age; AND one or more 1 st , 2 nd , or 3 rd degree relatives on the same side of the family with: <ol style="list-style-type: none"> Ashkenazi Jewish ancestry; or Breast cancer diagnosed at age 50 years or younger; or Ovarian/fallopian tube/ primary peritoneal cancer, pancreatic cancer or metastatic prostate cancer diagnosed at any age; or Two 1st, 2nd, or 3rd degree relative(s) with breast or prostate cancer any grade diagnosed at any age;

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OR

6. Personal history of metastatic prostate cancer (biopsy proven and /or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence (e.g., rising PSA after treatment with surgery or radiation)).

B. Personal history of breast cancer (includes invasive and ductal carcinoma in situ) (affected) (81162) AND:

1. Diagnosed at age less than or equal to 45 years; OR

2. Diagnosed at age 50 years or younger; AND

- a. Has one or more 1st, 2nd, or 3rd degree relative(s) on the same side of the family diagnosed with breast, cancer at any age; or
- b. With two breast primaries; includes bilateral (contralateral) disease or 2 or more clearly separate ipsilateral primary tumors that occur at the same time (synchronous) or at intervals (asynchronous); or
- c. Has limited family history (e.g., fewer than 2 first or second degree female relatives on the same side of the family or female relatives surviving beyond 45 years in either lineage); OR

3. Diagnosed at age 60 years or younger with a triple negative breast cancer (ER-/PR-/HER2-); OR

4. Diagnosed at any age, AND has

- a. One or more 1st, 2nd, or 3rd degree blood relative(s) on the same side of the family with breast cancer diagnosed at age 50 years or younger; or
- b. One or more 1st, 2nd, or 3rd degree blood relative(s) on the same side of the family with ovarian/fallopian tube/primary peritoneal cancer diagnosed at any age; or
- c. One or more 1st, 2nd, or 3rd degree male relative(s) on the same side of the family with breast cancer; or
- d. One or more 1st, 2nd, or 3rd degree blood relatives on the same side of the family with pancreatic, or prostate cancer (Gleason score greater than or equal to 7) or metastatic prostate cancer (biopsy proven and /or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence) diagnosed at any age; or
- e. Greater than or equal to two additional diagnosis of breast cancer (includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously) at any age in patient and/or in 1st, 2nd, or 3rd degree blood relatives.

5. Diagnosed at any age, AND of an ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) (CPT 81212). Testing for Ashkenazi Jewish founder-specific mutations(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other BRCA-related criteria are met.

C. Family History Only (Unaffected individual; an individual who does not have cancer) (81162):

1. Testing of unaffected (an individual who does not have cancer) family members should only be considered when no affected family member is able to be tested and then the unaffected family member with the highest probability of mutation should be tested.

2. An individual who does not have cancer but has one 1st or 2nd degree relative on the same side of the family diagnosed with:

- a. Breast cancer diagnosed at age 45 years or younger; or
- b. Ovarian/fallopian tube/primary peritoneal cancer diagnosed at any age; or
- c. Male breast cancer; or
- d. Pancreatic cancer; or
- e. Metastatic prostate cancer (biopsy proven and /or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence (e.g., rising PSA after treatment with surgery or radiation));or
- f. Breast cancer and Ashkenazi Jewish ancestry.

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<p>3. An individual who does not have cancer but has one 1st or 2nd degree relative diagnosed with breast cancer at age 50 years or younger; AND the affected relative has:</p> <ul style="list-style-type: none">a. Has one or more 1st, 2nd, or 3rd degree relative(s) on the same side of the family diagnosed with breast, cancer at any age; orb. With two breast primaries; includes bilateral (contralateral) disease or 2 or more clearly separate ipsilateral primary tumors that occur at the same time (synchronous) or at intervals (asynchronous); orc. Has limited family history (e.g., fewer than 2 first or second degree female relatives on the same side of the family or female relatives surviving beyond 45 years in either lineage); OR
<p>4. An individual who does not have cancer but has one 1st or 2nd degree relative diagnosed with breast cancer at any age AND the affected relative has:</p> <ul style="list-style-type: none">a. One or more 1st, 2nd, or 3rd degree blood relative(s) on the same side of the family with breast cancer diagnosed at age 50 years or younger; orb. One or more 1st, 2nd, or 3rd degree blood relative(s) on the same side of the family with ovarian/fallopian tube/primary peritoneal cancer diagnosed at any age; orc. One or more 1st, 2nd, or 3rd degree male relative(s) on the same side of the family with breast cancer; ord. One or more 1st, 2nd, or 3rd degree blood relatives on the same side of the family with pancreatic, or prostate cancer (Gleason score greater than or equal to 7) or metastatic prostate cancer (biopsy proven and /or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence (e.g., rising PSA after treatment with surgery or radiation) diagnosed at any age; ore. Greater than or equal to two additional diagnosis of breast cancer (includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously) at any age in patient and/or in 1st, 2nd, or 3rd degree blood relatives.
<p>5. An individual who does not have cancer but has a 1st or 2nd degree relative affected with breast cancer at age 60 years or younger with a triple negative breast cancer (ER-/PR-/HER2-); OR</p>
<p>6. An individual who does not have cancer but has a 1st or 2nd degree relative diagnosed with breast cancer at any age and the affected relative is of an ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) (CPT 81212) Testing for Ashkenazi Jewish founder-specific mutations(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other BRCA-related criteria are met; OR</p>
<p>7. An individual who does not have cancer but has one 1st or 2nd degree relative diagnosed with pancreatic cancer diagnosed at any age.</p>
<p>8. An individual who does not have cancer but has one 1st or 2nd degree relative diagnosed with aggressive prostate cancer (Gleason score greater than or equal to 7) diagnosed at any age; AND the affected relative has one or more 1st, 2nd, or 3rd degree relatives on the same side of the family with:</p> <ul style="list-style-type: none">a. Breast cancer diagnosed at age 50 years or younger; orb. Ovarian/fallopian tube/primary peritoneal cancer diagnosed at any age; orc. Pancreatic cancer; ord. Metastatic prostate cancer at any age; ore. Two or more 1st or 2nd or 3rd degree relatives with breast cancer, or prostate cancer (any grade) diagnosed at any age; and/orf. The affected relative is of Ashkenazi Jewish ancestry.

II. Based upon our criteria and assessment of the peer-reviewed literature, genetic testing for hereditary breast and/or ovarian cancer is considered **not medically necessary** for all other indications, including but not limited to:

<p>A. Unaffected family members with a known absence of BRCA1 or BRCA2 mutation in the family (e.g., the affected individuals at high risk of mutation have been tested and have been negative); or</p>
<p>B. Unaffected individuals of high-risk populations (e.g., Ashkenazi Jewish descent) in the <u>absence</u> of a positive</p>

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family history of breast and/or ovarian cancer; or
C. Unaffected minors less than 18 years of age; or
D. Genetic screening for BRCA1 or BRCA2 mutations in general population; or
E. Genetic testing for BRCA1 or BRCA2 when performed primarily for the medical management of other family members not covered by the affected member's subscriber agreement.

III. Based upon our criteria and assessment of the peer-reviewed literature, testing for BRCA gene mutations is considered **medically necessary** in women with advanced ovarian cancer when treatment with Lynparza (olaparib), Zejula (niraparib), and Rubraca (rucaparib) is being considered and who have not had previous BRCA mutation testing.

IV. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, testing for a variant of unknown significance discovered in a family member, is considered **investigational** and should be performed in a research setting.

Refer to Corporate Medical Policy #2.02.03 regarding Genetic Testing for Specific Diseases.

Refer to Corporate Medical Policy # 2.02.44 regarding Genetic Testing for Hereditary Cancer Risk (e.g., BreastNext™, CancerNext™, and OvaNext™, BRCAplus™ (Ambry Genetics), Panexia®, Melaris®, Prolaris®, MyRisk™ Hereditary Cancer test (Myriad Genetics).

POLICY GUIDELINES

I. Supporting documentation required:

The purpose of BRCA1 and BRCA2 testing is to provide information that will guide decisions regarding cancer prevention, surveillance, and treatment options. Documentation which must be submitted for review includes:

- A. Family history (pedigree) which includes first-, second-, and third-degree relatives, identifying family members affected with cancer; and
- B. Type of cancer, age at diagnosis for each affected family member and whether they are living or deceased;
- C. Genetic testing results from any other family members. If family member(s) have not been tested (and are more appropriate to be tested first), clear and distinct rationale as to why the family member(s) cannot be tested (i.e., specific reason why testing was declined); and
- D. Documentation of discussion between the physician and member of rationale for genetic testing and treatment options for the individual patient based on test results; and
- E. Documentation of discussion between the physician and unaffected member of rationale for genetic testing when the affected family member cannot be tested including that a negative result for an unaffected individual with only a family history of cancer is considered indeterminate (or uninformative) and does not provide the same level of information as when there is a known deleterious mutation in the family. Testing of unaffected family members in the absence of having tested affected family members significantly limits the interpretation of the test results.

II. Early age at diagnosis refers generally to diagnosis before age 45 or 50; an exact cutoff for testing affected individuals without known family history but with cancer diagnosis at an early age has not been established, although guidelines of the National Comprehensive Cancer Network suggest age 45 or younger. The decision to test an affected individual based on age at diagnosis when the family history is limited (e.g., fewer than 2 first or second degree female relatives or female relatives surviving beyond 45 years in either lineage) or in the absence of family history will depend on the risk estimate for the individual patient (e.g., from widely available risk assessment computer programs) and the patient tolerance for risk, and the desire to inform the risk of family members.

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- III. A first-degree relative is a blood relative with whom an individual shares approximately 50% of her/his genes (parents, full siblings, and children). A second-degree relative is a blood relative with whom an individual shares approximately 25% of her/his genes (grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings). A third-degree relative is a blood relative with whom an individual shares approximately 12.5% of her/his genes (great-grandparents, great-grandchildren, great-aunts, great-uncles, first cousin, and grand-niece or nephew.) NCCN guidelines for Hereditary Breast and/or Ovarian Cancer Syndrome defines a close blood relative as a first-, second-, or third-degree relative on the same side of the family.
- IV. For the majority of families in whom mutation status is unknown, it is best to consider testing an affected family member first, especially a family member with early-onset disease, bilateral disease, or multiple primaries, because that individual is most likely to test positive. The testing of unaffected family members may be considered when no affected member is available.
- V. For an individual with Ashkenazi Jewish ancestry, testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other hereditary breast and ovarian cancer criteria are met. Founder mutations exist in other populations.
- VI. It is recommended that unaffected individuals with a strong family history who do not meet criteria for BRCA testing or who test negative be referred to an adequately trained health care professional (genetic counselor) to provide appropriate genetic risk assessment to determine the individual's risk for developing cancer.
- VII. Genetic testing in the absence of a personal or family history of breast cancer is not medically appropriate due to the low probability of detecting a mutation and the considerable psychological impact that may be involved. Widespread screening of specific sub-populations is not endorsed.
- VIII. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.
- IX. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).
- X. If the genetic test is being done for knowledge only and that knowledge will not alter management or treatment of the patient or family member then the testing is not medically appropriate.

DESCRIPTION

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have causative mutations in BRCA genes in common. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, and ovarian cancer at any age. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early-onset breast cancer with or without male cases, but without ovarian cancer. In this policy, both are referred to collectively as hereditary breast and/or ovarian cancer.

Germline mutations in the BRCA1 and BRCA2 genes are responsible for the cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, BRCA mutations are responsible for only a proportion of affected families, and research to date has not yet identified other moderate or high-penetrance gene mutations that account for disease in these families. BRCA gene mutations are inherited in an autosomal dominant fashion through either the maternal or paternal lineage. It is possible to test for abnormalities in BRCA1 and BRCA2 genes to identify the specific mutation in cancer cases, and to identify family members with increased cancer risk. Family members without existing cancer who are found to have BRCA mutations can consider preventive interventions for reducing risk and mortality.

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The risk of being diagnosed with breast cancer in the general population is 1% for women up to age 40, and thereafter, increases to a lifetime risk of 12.5%. Inherited forms of breast cancer are estimated to account for about 5% to 10% of all breast cancer cases. A similarly small percentage of ovarian cancer, approximately 10%, is also attributed to a dominantly inherited susceptibility. Germline alterations in two genes, BRCA1 and BRCA2, are associated with an increased risk of breast and ovarian cancers with a lifetime risk of breast cancer is 60 to 85% and of ovarian cancer is 15 to 40% for women with either of these mutations. Studies are emerging which are associating BRCA mutations with other cancers such as melanoma, prostate and pancreatic cancer. The prevalence of BRCA mutations is approximately 0.1-0.2% in the general population. Prevalence of BRCA mutations may be much higher in certain ethnic groups with characterized founder mutations (e.g., 2%-3% in the Ashkenazi Jewish population).

The purpose of BRCA1 and BRCA2 testing is to provide information that will guide decisions regarding cancer prevention, surveillance, and treatment options for individuals who test positive. Women who test negative are at the same risk of developing breast or ovarian cancer as the general population, assuming that there is no history on the other side of the family that might be suggestive of a hereditary cancer syndrome and that there are no other risk factors such as atypia. Thus these women should be managed based on their family history or other risk factors.

Testing of large genomic re-arrangements (e.g., BRCA^{Analysis}® Rearrangement Test (BART test)), is performed for women who are exceptionally high risk and have tested negative for BRCA 1 and 2 mutations. Specifically the BART test (Myriad Genetics, Inc.) is an example of an enhancement to BRCA^{Analysis} testing and the test is able to detect rare, large rearrangements of the DNA in the BRCA1 and BRCA2 genes which were previously undetected by standard genetic testing. These types of mutations have similar clinical implications on breast and ovarian cancer risk as mutations found using traditional testing technology. Myriad Genetic Laboratories reports that BART testing will identify an additional approximate 10% of BRCA 1 and BRCA2 mutations in very high-risk families.

Recently BRCA testing has been added to multi-gene panels which include other genes associated with inherited breast and ovarian cancers (e.g., BreastNext™, OvaNext™ (Ambry Genetics), and MyRisk™ (Myriad Genetics, Inc.)). Mutations in these genes are addressed in 2.02.44 Genetic Testing for Hereditary Cancer Risk.

Several probability models have been developed to assist with determining the probability an individual carries the BRCA mutation. Each mutation probability model has its unique attributes determined by the methods, sample size, and population used to create it. These models include those using logistic regression, genetic risk models using Bayesian analysis, and empiric data such as the Myriad prevalence tables. Two examples of these models include the BRCAPRO (<https://www4.utsouthwestern.edu/breasthealth/cagene/>) and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) [<http://ccge.medschl.cam.ac.uk/boadicea/>]. According to the American Society of Clinical Oncology (ASCO) policy statement on genetic testing for cancer susceptibility (2003), there is no numerical threshold generated from these models that should be used in determining the appropriateness of genetic testing. The use of probability models, however, has been shown to help further discriminate which individuals are more likely to have a BRCA1 or BRCA2 mutation, even among experienced providers.

RATIONALE

The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with a high positive predictive value of the occurrence of a disease. Analytical sensitivity and specificity of a genetic test must be of such a level that the tests results can and will be used in making treatment decisions.

The American Society of Clinical Oncology (ASCO) recommends that cancer predisposition testing be offered when:

- I. the individual has personal or family history features suggestive of a genetic cancer susceptibility condition;
- II. the test can be adequately interpreted; and
- III. the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

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Information on the risks and benefits of genetic testing must be presented fully and objectively without coercion to persons contemplating genetic testing.

Families at high risk for harboring a BRCA1 or BRCA2 mutation are those in which the incidence of breast or ovarian cancer in first- or second-degree relatives suggests an autosomal dominant inheritance, e.g., about half the family members are affected. However, this criterion identifies only a subset of mutation carriers, and may not adequately cover the possibility of paternal transmission of a BRCA1 or BRCA2 mutation. Men rarely develop breast cancer and thus there may not be an affected first-degree relative, and the size of the family may not permit analysis of possible autosomal dominant inheritance.

As the majority of test results will be negative and uninformative in unaffected family members of potential BRCA mutation families, it is strongly recommended that an affected family member be tested first whenever possible to adequately interpret the test. Should a BRCA mutation be found in an affected family member(s), the DNA from the unaffected family member can be tested specifically for the same mutation of the affected family member without having to sequence the entire gene. Interpreting the test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result, but leads to difficulties in interpreting negative test results because the possibility of a BRCA mutation is not ruled out. In patients with breast or ovarian cancer who are from high-risk families without a known BRCA1 or BRCA2 gene, the entire gene must be sequenced to identify possible mutations.

Testing in eligible individuals who belong to ethnic populations in which there are well-characterized founder mutation should begin with tests specifically for these mutations. For example, founder mutations account for approximately three-quarters of the BRCA mutations found in Ashkenazi Jewish populations. When the testing for founder mutations is negative for individuals who have a positive family history for BRCA-related cancers, full gene sequencing should then be performed.

Studies published in peer-reviewed scientific literature indicate that genetic testing for BRCA1 and BRCA2 mutations is appropriate for individuals who have been identified to be at high risk for hereditary breast and ovarian cancers. Several professional organizations (National Comprehensive Cancer Network, US Preventive Services Task Force, American College of Medical Genetics, and American Society of Clinical Oncology), have issued statements regarding the role of BRCA testing in the management of high-risk individuals.

The National Comprehensive Cancer Network (2012) updated their guidelines for Genetic/familial high-risk assessment for breast and ovarian cancer to include BRCA mutation testing for patients with triple-negative breast cancer (ER-/PR-/HER2-). Studies have shown that the BRCA1 mutations have been found in 11-28% of patients with triple-negative breast cancer. These patients are diagnosed at a younger age, have smaller tumors and longer freedom from metastases compared to non-carriers. However BRCA1 mutation carriers were more likely to develop brain metastases.

The National Comprehensive Cancer Network (2012) updated their guidelines for Genetic/familial high-risk assessment for breast and ovarian cancer to include BRCA mutation testing for individuals with pancreatic cancer or unaffected individuals with a family history of breast, ovarian or pancreatic cancer in two or more close blood relatives. Analysis of samples taken from patients with familial pancreatic cancer (kindreds in which greater than or equal to 3 family members had pancreatic cancer, at least 2 of which were 1st degree relatives), BRCA2 mutations were detected in 17% of patients samples. Among the Ashkenazi Jewish population, BRCA2 mutations have been identified in about 4% of patients with pancreatic cancer.

The National Comprehensive Cancer Network (2013) updated their guidelines for Genetic/familial high-risk assessment for breast and ovarian cancer to include BRCA mutation testing for individuals with aggressive prostate cancer. In particular, BRCA2 mutations have been associated with 2- to 6-fold increase in risk of prostate cancer, while increased risks were not observed for BRCA1 mutation carriers in some studies. Prostate cancer with germline BRCA mutations

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appear to have a more aggressive phenotype (e.g., more frequently associated with Gleason score of greater than or equal to 8) than tumors from non-carrier patients. Prostate cancer in patients with BRCA2 mutations has also been associated with a higher histologic grade in some studies. In addition, analyses of data obtained from cancer registries and treatment center databases showed that BRCA2 mutation carriers with prostate cancer had more aggressive or rapidly progressive disease, and significant decreased survival compared with patients who were BRCA1 mutation carriers or non-carriers.

The risk of cancer in a BRCA mutation carrier is significant, and knowledge of mutation status in individuals at potentially increased risk of a BRCA mutation may impact healthcare decisions to reduce risk. Risk-reducing options include intensive surveillance, prophylactic mastectomy, or prophylactic oophorectomy. Studies indicate that results of genotyping significantly influence treatment choices.

In unaffected individuals with a family history only (does not have cancer), significant limitations of interpreting test results should be discussed prior to any testing. Moreover, testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing. Clinical judgment should be used to evaluate each unaffected individual for his/her likelihood of carrying the mutation based on factors such as the unaffected individual's current age and the age of the unaffected female relatives who link the individual with an affected close relative.

Unaffected individuals with a known family history but unknown family mutation may obtain interpretable results in most cases of a positive test. Most BRCA1 and BRCA2 mutations reported to date consist of frameshift deletions, insertions, or nonsense mutations leading to premature truncation of protein transcription. These are invariably deleterious and thus are informative in the absence of an established family genotype. In addition, specific missense mutations and noncoding intervening sequence mutations may be interpreted as deleterious on the basis of accumulated data or from specific functional or biochemical studies. However, some mutations may have uncertain significance in the absence of a family study, and negative results offer no useful information, e.g., the patients may still be at increased risk of a mutation.

Genetic testing in the absence of an increased risk for childhood malignancy, as is the case with breast and ovarian cancer, is not recommended for minors because of a lack of effective interventions to be applied during childhood.

The US Preventative Services Task Force (USPSTF) (2014) recently updated their recommendations on risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women. The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1 or BRCA2). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (Grade: B Recommendation). The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1 or BRCA2 genes. (Grade: D Recommendation).

On December 19, 2014, the U.S. Food and Drug Administration granted accelerated approval to Lynparza (olaparib), a new drug treatment for women with advanced ovarian cancer associated with defective BRCA genes, as detected by an FDA-approved test. Lynparza is a poly ADP-ribose polymerase (PARP) inhibitor that blocks enzymes involved in repairing damaged DNA. It is intended for women with heavily pretreated ovarian cancer that is associated with defective BRCA genes. The FDA approved Lynparza with a genetic test called BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.), a companion diagnostic that will detect the presence of mutations in the BRCA genes in blood samples from patients with ovarian cancer. The FDA's approval of the BRACAnalysis CDx was based on data from the clinical study used to support approval of Lynparza. Blood samples from clinical trial participants were tested to validate the test's use for detecting BRCA mutations in this population.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*

Proprietary Information of Univera Healthcare

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- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (includes both 81211 and 81213)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence (effective 1/1/2019)
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) (effective 1/1/2019)
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence (effective 1/1/2019)
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) (effective 1/1/2019)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) (effective 1/1/2019)
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185 del AG, 5385insC, 6174 del T variants
81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis full sequence analysis
81217	BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81406	Molecular Pathology Procedure Level 7
81479	Unlisted molecular pathology procedure

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Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
C25.0-C25.9	Malignant neoplasm of pancreas (code range)
C50.011-C50.929	Malignant neoplasm of breast (code range)
C56.1-C56.9	Malignant neoplasm of ovary (code range)

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Code	Description
C61	Malignant neoplasm of prostate
C79.60-C79.62	Secondary malignant neoplasm of ovary (code range)
C79.81	Secondary malignant neoplasm of breast
C79.82	Secondary malignant neoplasm of genital organs
D05.00-D05.02	Lobular carcinoma in situ of breast (code range)
D05.10-D05.12	Intraductal carcinoma in situ of breast (code range)
D05.80-D05.92	Carcinoma in situ of breast, specified, unspecified (code range)
D07.30-D07.39	Carcinoma in situ of other and unspecified female genital organs (code range)
D07.5	Carcinoma in situ of prostate
D40.0	Neoplasm of uncertain behavior of prostate
Z80.0	Family history of malignant neoplasm of digestive organs
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary
Z80.42	Family history of malignant neoplasm of prostate
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary
Z85.46	Personal history of malignant neoplasm of prostate

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*Key Article

KEY WORDS

Breast cancer, BRCA1, BRCA2, BART testing, Ovarian cancer, Pancreas cancer, and Prostate cancer.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=128&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AggAAAIBAAAA&

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