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# CLINICAL MEDICAL POLICY

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| **Policy Name:** | BRCA1 and BRCA2 Genetic Mutation Testing and Related Genetic Counseling |
| Policy Number: | MP-011-MD-PA |
| Approved By: | Medical Management |
| Provider Notice Date: | 06/01/16 |
| Original Effective Date: | 08/01/16 |
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| Application: | All participating hospitals and providers |
| Page Number(s): | 10 |

## Disclaimer

***Gateway Health℠ (Gateway) medical payment and prior-authorization policy is intended to serve only as a general reference resource regarding payment and coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.***

**POLICY STATEMENT**:

Gateway provides coverage under the laboratory section of the medical benefits of the Company's Medicaid products for medically necessary BRCA testing.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrants individual consideration, based upon review of applicable medical records.

(Current applicable PA HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

**DEFINITIONS:**

**Prior Authorization Review Panel –** A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

**Close relative** - for the purpose of familial assessment, includes first-, second- and third degree relatives on the same side of the family (maternal or paternal).

**First-degree relatives** - includes parents, children, and siblings.

**Second-degree relatives -** includes grandparents, aunts, uncles, nieces, nephews, grandchildren and half-siblings.

**Third-degree relatives** - includes great-grandparents, great-aunts, great-uncles, great-grandchildren and first cousins.

**Triple–negative breast cancer** - the term used to describe breast cancer cells that do not have estrogen receptors, progesterone receptors, or large of amounts of HER/neu protein. Also called ER-negative PR-negative HER2neu-negative and ER-PR-GER2/neu-.

## PROCEDURES

1. The following medical necessity criteria for unaffected/asymptomatic women (18 years of age and older) must be met:
    a. Has a biologically related individual of a family with a known BRCA1 or BRCA2 gene mutation; OR
    b. Has a first- or second-degree blood relative meeting any of the criteria outlined under the affected/symptomatic section below; OR
    c. Has a third-degree blood relative with breast cancer and/or ovarian, fallopian tube, primary peritoneal cancer with two or more close blood relatives with breast cancer (at least one with breast cancer and less than or equal to 50 years of age) and/or ovarian cancer, fallopian tube, or primary peritoneal cancer.

1. The following medical necessity criteria for affected/symptomatic women (18 years of age and older) must be met:
    a. Personal history of breast cancer (both invasive breast cancer and ductal carcinoma); AND one or more of the following:
        i. Diagnosed at age 45 years or younger, with or without family history; OR
        ii. Diagnosed at age less than 50 years with an unknown (e.g., adopted) or limited family history; OR
        iii. Diagnosed at age 50 years or younger with one or more close blood relatives with breast cancer at any age, and/or one or more close blood relatives with epithelial ovarian, fallopian tube or primary peritoneal cancer at any age
        iv. Two breast primaries when first breast cancer diagnosis occurred prior to or at age 50 year. Two breast primaries include bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.
        v. Diagnosed at age 60 years or younger with triple negative (ER-, PR-, HER2-) breast cancer
        vi. Diagnosed at any age, with at least one close blood relative with breast cancer at age 50 or less
        vii. Diagnosed at any age, with at least two close blood relatives with breast cancer diagnosed at any age
        viii. Diagnosed at any age, with at least one close blood relative with epithelial ovarian, fallopian tube or primary peritoneal cancer diagnosed at any age
        ix. Diagnosed at any age, with at least two close blood relatives with pancreatic cancer or prostate cancer diagnosed at any age
        x. Close male blood relative with breast cancer
        xi. Personal history of epithelial ovarian, fallopian tube or primary peritoneal cancer
        xii. For an individual or an ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish), no additional family history required.

2. Testing for BRCA gene mutation is eligible for men who meet the following criteria:

a. Has a first-, second- or third-degree blood relative who has a known BRCA1 or BRCA2 mutation, where the results will influence clinical utility (e.g., reproductive decision making); OR
b. Has a personal history of male breast cancer at any age; OR
c. Has a personal history of pancreatic cancer or prostate cancer (Gleason score greater than or equal to 7) diagnosed at any age with a least one close relative with breast cancer (≤ 50 years), ovarian cancer, cancer of fallopian tube, primary peritoneal cancer, pancreatic cancer or prostate (Gleason score >7) cancer at any age.

Large genomic rearrangement testing (code 81213) to identify individuals at risk for BRCA1/2 related cancers is not typically medically necessary (e.g., BART™). Therefore, requests for this service will require case-by-case physician review only when both sequencing and testing for common large rearrangements have been performed and are negative.

Note: Generally, genetic testing for a particular disease should be performed once per lifetime; however, there are rare instances in which testing may be performed more than once in a lifetime (e.g., previous testing methodology is inaccurate or a new discovery has added significant relevant mutations for a disease).

3. Genetic Counseling
Pre-test and post-test genetic counseling are considered medically necessary, and are covered as an adjunct to genetic testing.

Genetic Counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for BRCA mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for BRCA mutation requires documentation of medical necessity from one of the following providers who has evaluated the member and intends to see the person after testing has been performed for counseling:
- Board Eligible or Board Certified Genetic Counselor
- Advanced Genetics Nurse
- Genetic Clinical Nurse
- Advanced Practice Nurse in Genetics
- Board Eligible or Board Certified Clinical Geneticist
- A physician with experience in cancer genetics

4. Services are not covered for conditions other than those listed above because the scientific evidence has not been established.

Genetic testing in minors for BRCA1 or BRCA mutations **does not meet the definition of medical necessity**. There is no change in management for minors as a result of knowledge of the presence or absence of a deleterious mutation. In addition, there are potential harms related to stigmatization and discrimination.

Use of the CHEK2 is considered not medically necessary because the efficacy of this test in determining an individual's risk of cancer has not yet been prove.

5. Post-payment Audit Statement
The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Gateway at any time pursuant to the terms of your provider agreement.

6. The place of service for BRCA testing is outpatient.

7. Governing Bodies Approval
   a. FDA
      Genetic testing is regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1998. Additional information available at: Http://www.fda.gov/MedicalDevices/DeviceRegulationsandGuidance/IVDRegulatoryAssitance/ucm124105.htm. Accessed on April 12, 2016.

      Myriad Genetic Laboratories (Salt Lake City, UT) offers (1) Comprehensive BRAC Analysis® that includes complete sequencing of BRCA1/BRCA2 and gap polymerase chain reaction for 5 common rearrangements (deletions/duplications) in BRCA1; (2) BRAC Analysis® Large Rearrangement Test (BART™), which may be ordered as a reflex for patients who test negative for Comprehensive BRAC Analysis® to detect uncommon large rearrangements in BRCA1 and BRCA2; and (3) Integrated BRAC Analysis®, which includes BART as part of BRCA1/BRCA2 analysis.

      Quest Diagnostics (Madison, NJ) offers BRCAvantage™ that includes sequencing of BRCA1/BRCA2 and a multiplex ligation-dependent probe amplification assay to detect both common and uncommon gene rearrangements.

      LabCorp (Burlington, NC) offers the BRCAssureSM suite of tests which includes: targeted BRCA1/BRCA2 analysis for known BRCA1 or BRCA2 mutations; a founder mutation panel for Ashkenazi Jewish patients (3 mutations); comprehensive BRCA1/BRCA2 analysis (full gene sequencing plus analysis of common and uncommon large rearrangements); and deletion/duplication analysis of uncommon large rearrangements only (without sequencing) for use when comprehensive analysis is negative.

   b. US Preventive Services Task Force (USPSTF)
      Current USPSTF guidelines recommend screening women with any family history of breast, ovarian, tubal, or peritoneal cancer. Women with positive screening results should receive genetic counseling and, if indicated after counseling, *BRCA* testing. (Grade B Recommendation; Recommended). 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* gene. (Grade D recommendation; Not recommended).

   c. There are no National Coverage Determinations (NCD) for BRCA testing. There are two Novitas Solutions Local Coverage Determinations (LCD) related to BRCA testing. LCD 35396: Biomarkers for Oncology and L34796: Biomarkers Overview list medical necessity for genetic testing.

**Summary of Literature**

It has been estimated that between 5 and 10% of breast cancers are thought to be genetic. The majority of hereditary breast cancers are associated with inherited mutations in one of the breast-cancer-susceptibility genes, BRCA1 and BRCA2. Individuals that carry the Braca1 and the BRCA2 mutation have an increased lifetime risk of about 80% for those who live to age 70. In the contralateral breast, the lifetime risk of cancer is about 40%, and for ovarian cancer, the lifetime risk is approximately 40% with the BRCA1 mutation and 20% with the BRCA2 mutation (ECRI, 2015). The BRCA mutations can be transmitted via maternal and/or paternal lineage. However, not all who inherit the genetic mutation develop cancer.

Hereditary breast and ovarian cancer syndrome is a familial cancer syndrome that is related to mutations in the BRCA genes located on chromosome 17q21 (BRCA1) and 13q 12-13 (BRCA2). Identification of patients with the genetic mutation can result in enhanced screening and surveillance which could lead to improved outcomes.
The characteristics of BRCA1 and BRCA2 gene are different and are considered together since their similarities outweigh their differences. There are commercial test available for BRCA1 and BRCA2 mutation assessment.

Prior to genetic testing, an expanded family medical history which includes first-, second- and third-degree relatives is an essential and integral component to identify men and women who may be candidates for genetic counseling and for BRCA testing for specific risk interventions. Family medical history should include all types of cancers, age of cancer diagnosis, risk reducing surgeries, carcinogen exposure and documentation records of primary cancers.

Available resources concur that widespread screening of the general population for BRCA gene mutations is not recommended, nor for screening individuals that are unaffected with no personal or family history of breast and/or ovarian cancer or in individuals younger than 18 years of age. There is no established clinical utility for the use of genetic testing for BRCA mutations in individuals younger than 18 years of age. This is due to the fact that there is no change in the management of this particular age group with the knowledge of the presence or absence of this genetic mutation. There is also the risk of potential harms related to stigmatization and discrimination based on BRCA testing. The Society of Gynecologic Oncologists (Lancaster et al. 2014) have documented that the risk of developing breast or ovarian cancer in an individual younger than age 21 is very low, regardless of families with inherited cancer susceptibility as a result of hereditary breast and ovarian cancer syndrome.

A variety of tools have been developed to determine the probability of identifying BRCA1 and BRCA2 gene variants. These tools assist in identifying suitable candidates for testing. Examples of available Screening Tools include:

- Ontario Family History Assessment Tool (FHAT)
- Manchester Scoring System
- Referral Screening Tool (RST)
- Pedigree Assessment Tool (PAT)
- FHS-7

Genetic Counseling
The 2015 NCCN guidelines for genetic counseling have counseling services divided into pre-test and post-test categories. The pre-test counseling requirements include:

- Collection of a comprehensive family history (close blood relatives include first, second and third degree relatives on each side of the family);
- Evaluation of a patient's cancer risk;
- Generation of a differential diagnosis and education of the patient on inheritance patterns, penetrance, variable expressivity and the possibility of genetic heterogeneity.

Post-test counseling includes:

- Providing results along with their significance and impact and recommended medical management options;
- Informing and testing at- risk family members;
- Providing available resources such as disease specific support groups and research studies.

The National Society of Genetic Counselors (NSGC) has recommended that genetic testing be performed utilizing the informed decision-making process (Berliner et al., 2013). Issues included in the process should include the following:

- Obtaining all pertinent personal medical and family history data
- Psychosocial assessment

- Discussion of cancer and mutation risk and how personalized risk estimates are derived
- Facilitation of the informed consent process through discussion of the risks, benefits, limitations, and likelihood of identifying a mutation with genetic susceptibility testing
- Result disclosure, when appropriate
- Discussion of medical management options
- Review of issues related to genetic discrimination

Cell cycle checkpoint kinase 2 (CHEK2) involves DNA repair and human cancer predisposition similar to BRCA1 and BRCA2. CHEK2 is normally activated in response to DNA double strand breaks and it regulates the function of BRCA1 protein in DNA repair. CHEK2 also exerts critical roles in cell cycle control and apoptosis. The Chek2 mutation is identified as 1100delC in exon 10 and has been associated with familial breast cancers. CHEK2 mutations account for approximately one third of mutations identified in BRCA-negative patients, however the CHEK2 mutations are rate making accurate estimates of risk less precise.

In a recent study (Tung et al. 2015) performed an assessment of the frequency of pathogenic mutations among patients with breast cancer that had been referred for BRCA1/2 testing. The study included 2 cohorts. Cohort 1 consisted of 1781 patients referred for *BRCA1/2* testing between November 2012 and April 2013. A total of 241 (13.5%) individuals were found to have a mutation in at least 1 of the 25 genes tested, 162 in *BRCA1/2*, and 76 in at least one of the other genes. Of the mutation-positive, *BRCA1/2*-negative patients, the most common mutation identified was in *CHEK2* (n=29), accounting for approximately one-third of the additional mutations identified in *BRCA*-negative patients, and 12% of mutations overall. The second cohort consisted of 377 samples from patients who were referred to Beth Israel Deaconess Medical Center for genetic testing between 1998 and 2013 and had previously tested negative for *BRCA1/2*. Mutations were identified in additional genes in 14 women, of which *CHEK2* was the most frequent (n=5), comprising approximately 33% of mutations identified in mutation-positive, *BRCA*-negative patients.

Despite studies showing that the CHEK2 mutation appears to account for one-third of mutations identified in BRCA1/2-negative patients, it is relatively rare and accurate risk estimates, which have been studied in population- and family-based case controls, they are subject to bias.

National Comprehensive Cancer Network guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (v.1.2015) state that in a patient with a *CHEK2* mutation, intervention is warranted based on gene and/or risk level. The intervention that is recommended is annual breast magnetic resonance imaging (for women who have a lifetime risk of developing breast cancer of >20%, as defined by models that are largely dependent on family history). Evidence is insufficient to recommend risk reduction mastectomy intervention.

Additional studies are needed to determine if patients with a CHEK2 mutation have a risk that is similar to the risk with a high-penetration mutation. Clinical management recommendations for individuals with breast cancer and CHEK@ mutation are not standardized. The evidence is not sufficient to determine the effects of this technology on health outcomes.

Other studies have looked at the results of prostate cancer screening in men with *BRCA* mutations. The IMPACT study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were *BRCA* mutation carriers and 95 control patients. At the baseline screen, biopsies were performed in 7.0% of patients with a prostate-specific antigen (PSA) level greater than 3.0, and prostate cancer was identified in 3.3%. This resulted in a positive predictive value of 47.6%, which is considerably higher than that estimated for normal risk men.

Also, the grade of tumor identified was intermediate in 67% of cancers and high in 11%. This differs from the expected distribution of cancer grade in average risk men, with more than 60% expected to have low-grade cancer.

Members of the Jewish community who trace their roots to Central or Eastern Europe are known as Ashkenazi Jews. For centuries this ethnic population were geographically isolated. The isolation experienced by this population means it members can trace their ancestry back to a small number of members known as 'founders'. Approximately 1 in 40 individuals of Ashkenazi Jewish descent is a carrier for BRCA mutation, leaving these individuals at a higher risk of developing breast and ovarian cancer. This is compared to mutation frequency of 1 in 500 in the general population. These mutations are inherited in an autosomal dominant pattern, so males and females with such a mutation, whether or not they develop cancer or not, have a 50% chance of passing on the gene mutation to the next generation.

Just as Ashkenazi women have an increased risk for the BRCA genetic mutation, males of this ethnic population have a higher risk of developing male breast cancer and prostate cancer. Men that inherit the BRCA1/2 gene have a 6% risk of developing breast cancer and are three to seven more times likely than average to develop prostate cancer.

## AUTHORIZATION and CODING REQUIREMENTS:

**Procedure Codes**

| Procedure Code | Description |
|---|---|
| 81162 | BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis |
| 81211 | BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (e.g., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) |
| 81212 | BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants |
| 81213 | BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants |
| 81214 | BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) |
| 81215 | BRAC1 (breast cancer 1) (e.g., 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 |
| 88271 | Molecular cytogenetics; DNA probe, each (e.g., FISH) |
| 88272 | Molecular cytogenetics; DNA probe, each; chromosomal in situ hybridization, analyze 3-5 cells (e.g., for derivatives and markers) |
| 88273 | Molecular cytogenetics; DNA probe, each; chromosomal in situ hybridization, analyze 10-30 cells (e.g. for microdeletions) |
| 88274 | Molecular cytogenetics; DNA probe, each; interphase in situ hybridization, analyze 25-99 cells |
| 88275 | Molecular cytogenetics; DNA probe, each; interphase in situ hybridization, analyze 100-300 cells |

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| 96040 | Medical genetics and genetic counseling services, each 30 minutes, face-to-face with patient/family |
| HCPCS Coding | Description |
| S0265 | Genetic counseling, under physician supervision, each 15 minutes |

**Diagnosis Codes**

| ICD-10 Diagnosis Codes | Description |
|---|---|
| C25.0 | Malignant neoplasm of head of pancreas |
| C25.1 | Malignant neoplasm of body of pancreas |
| C25.2 | Malignant neoplasm of tail of pancreas |
| C25.3 | Malignant neoplasm of pancreatic duct |
| C25.4 | Malignant neoplasm of endocrine pancreas |
| C25.7 | Malignant neoplasm of other parts of pancreas |
| C25.8 | Malignant neoplasm of overlapping sites of pancreas |
| C25.9 | Malignant neoplasm of pancreas, unspecified |
| C48.1 | Malignant neoplasm of specified parts of peritoneum |
| C48.2 | Malignant neoplasm of peritoneum, unspecified |
| C48.8 | Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum |
| C50.011 | Malignant neoplasm of nipple and areola, right female breast |
| C50.012 | Malignant neoplasm of nipple and areola, left female breast |
| C50.019 | Malignant neoplasm of nipple and areola, unspecified female breast |
| C50.111 | Malignant neoplasm of central portion of right female breast |
| C50.112 | Malignant neoplasm of central portion of left female breast |
| C50.119 | Malignant neoplasm of central portion of unspecified female breast |
| C50.211 | Malignant neoplasm of upper-inner quadrant of right female breast |
| C50.212 | Malignant neoplasm of upper-inner quadrant of left female breast |
| C50.219 | Malignant neoplasm of upper-inner quadrant of unspecified female breast |
| C50.311 | Malignant neoplasm of lower-inner quadrant of right female breast |
| C50.312 | Malignant neoplasm of lower-inner quadrant of left female breast |
| C50.319 | Malignant neoplasm of lower-inner quadrant of unspecified female breast |
| C50.411 | Malignant neoplasm of upper-outer quadrant of right female breast |
| C50.412 | Malignant neoplasm of upper-outer quadrant of left female breast |
| C50.419 | Malignant neoplasm of upper-outer quadrant of unspecified female breast |
| C50.511 | Malignant neoplasm of lower-outer quadrant of right female breast |
| C50.512 | Malignant neoplasm of lower-outer quadrant of left female breast |
| C50.519 | Malignant neoplasm of lower-outer quadrant of unspecified female breast |
| C50.611 | Malignant neoplasm of axillary tail of right female breast |
| C50.612 | Malignant neoplasm of axillary tail of left female breast |
| C50.619 | Malignant neoplasm of axillary tail of unspecified female breast |
| C50.811 | Malignant neoplasm of overlapping sites of right female breast |
| C50.812 | Malignant neoplasm of overlapping sites of left female breast |
| C50.819 | Malignant neoplasm of overlapping sites of unspecified female breast |

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|---|---|
| C50.911 | Malignant neoplasm of unspecified site of right female breast |
| C50.912 | Malignant neoplasm of unspecified site of left female breast |
| C50.919 | Malignant neoplasm of unspecified site of unspecified female breast |
| C50.021 | Malignant neoplasm of nipple and areola, right male breast |
| C50.022 | Malignant neoplasm of nipple and areola, left male breast |
| C50.029 | Malignant neoplasm of nipple and areola, unspecified male breast |
| C50.121 | Malignant neoplasm of central portion of right male breast |
| C50.122 | Malignant neoplasm of central portion of left male breast |
| C50.129 | Malignant neoplasm of central portion of unspecified male breast |
| C50.221 | Malignant neoplasm of upper-inner quadrant of right male breast |
| C50.222 | Malignant neoplasm of upper-inner quadrant of left male breast |
| C50.229 | Malignant neoplasm of upper-inner quadrant of unspecified male breast |
| C50.321 | Malignant neoplasm of lower-inner quadrant of right male breast |
| C50.322 | Malignant neoplasm of lower-inner quadrant of left male breast |
| C50.329 | Malignant neoplasm of lower-inner quadrant of unspecified male breast |
| C50.421 | Malignant neoplasm of upper-outer quadrant of right male breast |

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