Medical Policy Bulletin

Title:

Genetic Testing for Inherited Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) Mutations (AmeriHealth Administrators)

Policy #:

06.02.06s

Policy

This policy only applies to members for whom AmeriHealth Administrators serves as the claims administrator and whose group has not enrolled in the UM vendor program. For those groups who have been given the option to enroll in the UM vendor program, this policy is no longer applicable upon their renewal effective date. Individual member benefits must be verified before/prior to providing services.

The intent of this policy is to communicate the coverage positions for genetic testing for inherited breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) gene mutations.

For information on policies related to this topic, refer to the Cross References section in this policy.

The provision of benefits for all services related to Genetic Testing for Inherited Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) Mutations is in accordance with the individual's benefit contract and varies by product and group. Therefore, individual member benefits must be verified. Some services may be subject to medical necessity criteria, coverage limits, or existing contractual exclusions.

For the purpose of this medical policy and the associated medical necessity criteria below, first-degree relatives include parents, children, and siblings. Second-degree relatives include grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings. Third-degree relatives include great-grandparents, great-aunts, great-uncles, great-grandchildren, and first-cousins. For the purpose of familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal). For purposes of this policy, first-, second- and third-degree relatives are considered close relatives.

When the medical necessity criteria outlined below are met for an individual, refer to the TESTING STRATEGY in the Guidelines Section of this medical policy bulletin for particular order / sequence of testing, (eg., testing for familial variants versus common variants versus full gene sequencing of BRCA1 and/or BRCA2), per specific clinical scenarios.

The Policy Statements and Criteria in this section of the medical policy bulletin are based on current clinical guidelines from National Comprehensive Cancer Network (NCCN), and are in alignment with current clinical guidelines from American Society of Clinical Oncology and Society of Gynecologic Oncologists.

MEDICALLY NECESSARY

TESTING FOR PATHOGENIC VARIATIONS IN THE BRCA1 AND/OR BRCA2 GENES
Genetic testing for inherited breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) gene mutations is considered medically necessary and, therefore, covered for any of the following individuals:

Unaffected/Asymptomatic Individuals

- Biologically related individual of a family with a known BRCA1/BRCA2 gene mutation
- First- or second-degree blood relative meeting any of the criteria outlined under the affected / symptomatic section below
- 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/primary peritoneal cancer

Affected/Symptomatic Individuals

- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer at any age with two or more close blood relatives with breast/and or ovarian/fallopian tube/primary peritoneal cancer and/or pancreatic or prostate cancer at any age
- Personal history of breast cancer and one or more of the following:
  - Diagnosed at age 45 years or younger, with or without family history
  - Diagnosed at age less than 50 years with a unknown or limited family history
  - 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/primary peritoneal cancer at any age
  - Two breast primaries when first breast cancer diagnosis occurred prior to or at age 50 years. (Two breast primaries include bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.)
  - Diagnosed at age 60 years or younger with a triple negative (ER-, PR-, HER2-) breast cancer.
  - Diagnosed at any age, with at least one close blood relative with breast cancer diagnosed at age 50 or less
  - Diagnosed at any age, with at least two close blood relatives with breast cancer diagnosed at any age
  - Diagnosed at any age, with at least one close blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer diagnosed at any age
  - Diagnosed at any age, with at least two close blood relatives with pancreatic cancer **o**r prostate cancer diagnosed at any age
  - Close male blood relative with breast cancer
  - Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
  - For an individual of an ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish), no additional family history may be required.

TESTING FOR GENOMIC REARRANGEMENTS OF THE BRCA1 AND BRCA2 GENES

Testing for genomic rearrangements of the BRCA1 and BRCA2 genes is considered medically necessary and, therefore, covered for individuals who meet the criteria for BRCA testing above and whose testing for point mutations, (i.e., an alteration in DNA sequence caused by a single nucleotide base change,

insertion, or deletion), is negative. (See the TESTING STRATEGY in the Guidelines Section of this medical policy bulletin for more information).

GENETIC COUNSELING

Pre-test and post-test genetic counseling is considered medically necessary and, therefore, covered as an adjunct to genetic testing.

EXPERIMENTAL/INVESTIGATIONAL

Unless medical necessity criteria listed above are met, genetic testing for inherited breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) gene mutations is considered experimental/investigational and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

Panels of tests that include the testing of BRCA1 and/or BRCA2 gene variants, (e.g., myRisk Hereditary Cancer Panel, BRCAplus, BreastNext Next-Gen Cancer Panel, OvaNext Next-Gen Cancer Panel, and CancerNext Next-Gen Cancer Panel) as a component or components of the panel testing, are considered experimental/investigational and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

NOT MEDICALLY NECESSARY

Genetic testing for inherited breast cancer 1 (BRCA1) and inherited breast cancer (BRCA2) gene mutations is considered not medically necessary and, therefore, not covered for any of the following individuals:

- Individuals younger than 18 years of age, as it is not known how these test results would change medical management
- Unaffected individuals in the absence of a known BRCA1 or BRCA2 gene mutation (ie, individuals with no personal and/or familial history of breast and/or ovarian cancer)

When a benefit exists, genetic testing is an eligible service only for the covered individual’s clinical benefit. Testing, (including genetic testing), of associated family members, without a Company benefit, is not eligible for reimbursement.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the service.

Guidelines

For purposes of this policy, breast cancer is inclusive of invasive and ductal carcinoma in situ breast cancers.

Individuals who have received an allogenic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to contamination by donor DNA. DNA should be extracted from a fibroblast culture.

Independent consideration of the maternal and paternal sides of the family is typically made for familial patterns of breast and/or epithelial ovarian/fallopian tube, and/or pancreatic, and/or primary peritoneal cancer.

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).

TESTING STRATEGY FOR INDIVIDUALS WHO MEET THE MEDICALLY NECESSARY CRITERIA

When medical necessity criteria are met for BRCA1 and BRCA2 testing, the following testing strategy is supported:

KNOWN FAMILIAL VARIANT
In individuals with a known familial *BRCA* mutation, targeted testing (ie., testing of familial variants for the specific mutation is recommended (CPT code 81215 and/or CPT code 81217).

UNKNOWN FAMILIAL VARIANT
In individuals with an unknown familial *BRCA* mutation:

Non-Ashkenazi Jewish Descent

- To identify clinically significant mutations, National Comprehensive Cancer Network (NCCN) advises testing a relative who has breast or ovarian cancer, especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer, because that individual has the highest likelihood for a positive test result.
- If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1*/*BRCA2* mutations (e.g., prostate cancer, pancreatic cancer, melanoma).
- If no familial mutation can be identified, two possible testing strategies are:
  - Full sequencing followed by testing for *common* large genomic rearrangements (deletions/duplications) only if sequencing detects no mutation (negative result).
    - More than 90% of *BRCA* mutations will be detected by full sequencing.
  - Alternatively, simultaneous full sequencing and testing for *common* large genomic rearrangements (also known as comprehensive BRCA testing may be considered, as is recommended by NCCN (CPT Code: 81211).
    - Comprehensive testing can detect 92.5% of *BRCA*1/*BRCA2* mutations. Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone (CPT Code: 81211).
- If comprehensive *BRCA* testing is negative, testing for *uncommon* large genomic rearrangements (eg, BART™) is an option, if medical necessity criteria for this testing are met (81213).
  - Testing for *uncommon* large rearrangements should not be done unless both sequencing and testing for *common* large rearrangements have been performed and are negative.
    - Among individuals with negative comprehensive testing, BART™ identified a deleterious mutation (positive result) in less than 1% of individuals tested.

Ashkenazi Jewish Descent

- In individuals of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first (CPT code 81212).
- If testing is negative for founder mutations, comprehensive genetic testing may be considered (CPT Code: 81211).
    - Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone (CPT Code: 81211).

OTHER CONSIDERATIONS AND RECOMMENDATIONS

TESTING UNAFFECTED INDIVIDUALS
In unaffected family members of potential *BRCA* mutation families, most test results will be negative and uninformative. Therefore, it is strongly recommended by NCCN 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), DNA from an unaffected family member can be tested specifically for the same mutation of the affected family member without having to sequence the entire gene. Interpreting 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 for an established disease-associated mutation but leads to difficulties in interpreting negative test results (uninformative negative) or mutations of uncertain significance because the possibility of a causative *BRCA*mutation is not ruled out.

HIGH-RISK ETHNIC GROUPS
Testing in eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations 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 testing for founder mutations is negative, comprehensive mutation analysis may then be considered. [Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone (CPT Code: 81211)].

PROSTATE CANCER
Men with known *BRCA* mutations have an increased risk of prostate cancer, and men with known *BRCA*mutations may therefore consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in a man, or in a family, is not itself considered sufficient justification for *BRCA* testing.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, genetic testing for inherited breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) gene mutations is covered under the medical benefits of the Company’s products when the medical necessity criteria listed in this medical policy are met.

However, services that are identified in this policy as not medically necessary or experimental/investigational are not eligible for coverage or reimbursement by the Company.

Genetic testing is appropriate only when offered in a setting with adequately trained health care professionals to provide appropriate pre- and post-test counseling. A qualified Clinical Laboratory Improvement Amendments (CLIA) laboratory should perform the test.

The Company’s laboratory network has extensive genetic testing capabilities; therefore, providers should refer members only to participating laboratories for covered services. In the unusual circumstance that a specific covered test and related services are not available through a participating laboratory, providers must contact the Company to obtain preapproval.

Members who have out-of-network benefits may choose to use a non-participating laboratory for a medically necessary service, but they will have greater out-of-pocket costs associated with that service. In addition, the member will be financially responsible for the entire cost of any service that is non-covered (e.g., a service that is considered experimental/investigational).

BILLING GUIDELINES

Genetic counseling provided by a trained genetic counselor to an individual or family to investigate family genetic history and assessment of the associated risks should be reported using the specific Current Procedural Terminology (CPT) code (96040) or Healthcare Common Procedure Coding System (HCPCS) level II code (S0265) for this service.

For genetic counseling and education provided by a physician to an individual, report the appropriate level evaluation and management (E&M) service.

Inclusion of a code in this policy does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Description

Familial cancer research has identified breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) genes that may determine an individual's future risk for developing breast and/or ovarian cancer. BRCA gene mutations are inherited in an autosomal-dominant pattern through either the maternal or the paternal lineage in families with a high risk of mutation in the BRCA1 or BRCA 2 gene. Normally, these genes act as tumor suppressors; however, an abnormality (mutation) in the deoxyribonucleic acid (DNA) sequencing of these genes may indicate a possibility of developing hereditary breast and/or ovarian cancer.

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 in common causative mutations in *BRCA* (breast cancer susceptibility) genes. 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, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and 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.

Germline mutations in the *BRCA1*and *BRCA2* genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, *BRCA* mutations are responsible only for 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.

Although the characteristics of BRCA1 and BRCA2 gene mutations are modestly different, they are commonly considered together, as their similarities outweigh their differences. Commercial testing is available for BRCA1 and BRCA2 defect assessment. The defect can be transmitted through the maternal and/or paternal sides of the family, but not all children inherit the mutation. In addition, not everyone who inherits the mutation develops cancer.

An expanded family medical history that includes first-, second-, and third-degree relatives (parents, children, siblings, aunts, uncles, nieces, nephews,

grandparents, grandchildren, half-siblings, great-grandparents, great-aunts, great-uncles, great-grandchildren, first cousins) is integral to identifying men and women who may be candidates for genetic counseling and for BRCA testing for specific risk interventions. Family medical history may include types of cancers, age at diagnosis, risk-reducing surgeries, carcinogen exposure, and documentation records of primary cancers. While both maternal and paternal family histories are important, each lineage must be considered separately. Families suspected of hereditary breast and/or ovarian cancer typically present with cancer occurring at an early age, in multiple generations, and often bilaterally, suggesting an autosomal-dominant pattern of inheritance. However, even when an individual has family members who are identified in one of the aforementioned groups, the predisposition does not guarantee that the individual will develop cancer.

The goal of genetic testing for BRCA gene mutations is to assess an individual's risk for developing breast and/or ovarian cancer, not to determine whether cancer will develop or to provide a timeframe for cancer development. The results of genetic testing for BRCA gene mutations should directly affect the medical management of the individual and/or family. Genetic counseling is generally beneficial to the individual and/or family before and after testing for BRCA gene mutations to review the individual's history, discuss the role of heredity in the disease, communicate genetic risks, and provide psychosocial support. In general, genetic counseling may have clinical value to any individual who is undergoing genetic testing to confirm, diagnose, or exclude any genetic condition. Current literature suggests health benefits for both women and men associated with the early communication of hereditary risks.

Breast cancer has been associated with other hereditary conditions, such as Li-Fraumeni syndrome, Cowden disease, and ataxia telangiectasia; however, there are no studies linking these conditions to BRCA mutations.

According to current published literature, screening of the general population for BRCA gene mutations is not recommended, nor is widespread screening recommended for those unaffected individuals with no personal or family history of breast and/or ovarian cancer, or individuals younger than 18 years of age. Clinical utility has not been established for the use of genetic testing for BRCA mutations has limited or no clinical utility in individuals younger than 18 years of age. This is because there is no change in management for individuals younger than 18 years of age as a result of knowledge of the presence or absence of a deleterious mutation. In its updated (2014) statement on risk assessment for inherited gynecologic cancer, the Society of Gynecologic Oncologists (SGO) acknowledged that the risk of developing breast or ovarian cancer in a woman younger than age 21 is very low, “even in families with inherited cancer susceptibility as a result of hereditary breast and ovarian cancer (HBOC) syndrome.” Because detection of an HBOC-associated mutation “would change the management of very few women in this age group,” and because of potential negative consequences of testing, SGO - in its most recent recommendations - “does not recommend genetic testing of women younger than age 21 for HBOC in the absence of a family history of extremely early-onset cancer.”

BRCA1 and BRCA2 gene testing typically involves the direct sequence analysis of the BRCA1 and BRCA2 coding regions and splice junctions, and testing for large genomic rearrangements in high-risk individuals who are negative for a sequence variant. For individuals with Ashkenazi Jewish (AJ) ancestry, the first step in the analysis is typically testing for the three most common variants in this population (c.68_69delAG [commonly referred to as 187delAG] and c.5266dupC [commonly referred to as 5385insC] in *BRCA*, and c.5947delT [commonly referred to as 6174delT] in *BRCA2).*For individuals from families transmitting a known pathogenic *BRCA1* or *BRCA2* gene variant, American College of Obstetricians and Gynecologists (ACOG) recommends testing specifically for the familial variant is generally sufficient. A number of studies have shown that a significant percentage of women with a strong family history of breast cancer and negative tests for BRCA gene mutations have large genomic rearrangements (including deletions or duplications) in one of these genes. The BRACAnalysis Large Rearrangement Test (BART) is performed to detect these additional large genomic rearrangements in both BRCA1 and BRCA2 genes that are not currently identified as part of standard BRCA analysis testing. BART is intended for use in individuals at high risk for breast cancer who have previously tested negative for sequence mutations and common large rearrangements.

The interpretation of a BRCA1 and BRCA2 gene test result often depends on a individual's family history. In general, the possible outcomes of BRCA1 and BRCA2 gene testing are a positive test result (the identification of a variant known to be deleterious), a negative test result (no disease-causing variant identified), or the identification of a variant of unknown clinical significance (VUS). However, while a negative result in a family transmitting a known BRCA1 and BRCA2 gene variant would be considered a true-negative, a negative result in an unaffected individual from a family without a genetically defined diagnosis of HBOC may be considered uninformative. Consequently, it is recommended that BRCA1 and BRCA2 gene testing be performed first in an affected family member prior to any predisposition testing in unaffected relatives.

An important limitation of BRCA1 and BRCA2 gene testing is the identification of VUS, the frequency of which may range from 4.4% to 16.2% according to the data published by Pal et al., 2005; Simard et al., 2007; Palma et al., 2008; Haffty et al., 2009; Seong et al., 2009; Hall et al., 2010; Alsop et al., 2012. A variety of methods exist for assessing the pathogenicity of a BRCA1 and BRCA2 VUS. One of the largest studies examining the classification of BRCA1 and BRCA2 VUS retrospectively analyzed the results from 70,000 BRCA1 and BRCA2 gene tests (Easton et al., 2007). This analysis yielded 1433 VUS in 4623 individuals. Three separate measures were utilized to estimate the probability of a specific variant being deleterious: (1) the co-occurrence of a VUS with a deleterious variant in a single individual; (2) personal and family history profiles consistent with those carrying a pathogenic variant versus those with no deleterious alteration; and (3) cosegregation of the VUS with disease in pedigrees. Based on analyses using these measures, 133 (9.3%) VUS had odds ratio of at least 100:1 in favor of being neutral (or nonpathogenic) and 43 (6.6%) VUS had odds of at least 20:1 in favor of being deleterious (Easton et al., 2007).

The likelihood of identifying a disease-causing BRCA1 or BRCA2 gene variant depends on the individual's personal and family histories. A variety of tools have been developed to determine the probability of identifying a deleterious BRCA1 and BRCA2 gene variant, in order to identify suitable candidates for testing. Available models, each of which has its own advantages and disadvantages, include the Couch model, the BRCAPRO computer program, the Myriad Prevalence Tables, the Manchester Scoring System, the Ontario Family History Risk Assessment Tool (FHAT), the University of Pennsylvania (Penn) II Risk Model, and the National Cancer Institute (NCI) Breast Cancer Risk Estimation Tool. Some other ecommended screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in *BRCA1*or *BRCA2* are Referral Screening Tool (RST), Pedigree Assessment Tool (PAT), and Family History Screen (FHS-7).

In sum, hereditary breast and ovarian cancer (HBOC) syndrome describes the familial cancer syndromes that are related to mutations in the *BRCA* genes (*BRCA1* located on chromosome 17q21 and *BRCA2* located on chromosome 13q12-13). Identification of individuals with *BRCA* mutations may lead to enhanced screening and/or surveillance that could lead to improved outcomes. The presence of a *BRCA1* or *BRCA2* mutation confers a high lifetime risk for breast and ovarian cancer among affected women. These mutations may be gene sequence variations or large rearrangements/deletions. Knowledge of mutation status in individuals at risk of a *BRCA* mutation may impact health care decisions to reduce risk. Risk-reducing options include intensive surveillance, chemoprophylaxis, prophylactic mastectomy, or prophylactic oophorectomy. Criteria for testing high-risk women have been developed by the National Comprehensive Cancer Network (NCCN), the U.S. Preventive Services Task Force (USPSTF), and other professional bodies. Definitions of high risk vary somewhat, and there is not widespread agreement on optimal criteria that should be used for defining high risk. When testing high-risk women, health outcomes are improved; therefore, testing high-risk women for *BRCA1* and *BRCA2* mutations may have clinical value.

References

American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jun 15 2003;21(12):2397-2406. PMID 12692171.

Antoniou AC, Beesley J, McGuffog L, et al. Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: implications for risk prediction. Cancer research. Dec 1 2010;70(23):9742-9754. PMID 21118973.

Armstrong J, Toscano M, Kotchko N, et al. American BRCA Outcomes and Utilization of Testing (ABOUT) Study: A Pragmatic Research Model that Incorporates Personalized Medicine/Patient-Centered Outcomes in a Real World Setting. J Genet Couns. Sep 12 2014. PMID 25209347.

Begg CB. On the use of familial aggregation in population-based case probands for calculating penetrance. J Natl Cancer Inst. Aug 21 2002;94(16):1221-1226. PMID 12189225.

Bianco A, Quaresima B, Pileggi C, et al. Polymorphic repeat length in the AIB1 gene and breast cancer risk in BRCA1 and BRCA2 mutation carriers: a meta-analysis of observational studies. PLoS One. 2013;8(3):e57781. PMID 23483928.

Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). BRCA1 and BRCA2 testing to determine the risk of breast and ovarian cancer. TEC Assessments 1997; volume 12, tab 4.

Casadei S, Norquist BM, Walsh T, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer research. Mar 15 2011;71(6):2222-2229. PMID 21285249.

Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. May 10 2013;31(14):1748-1757. PMID 23569316.

Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. Feb 2007;16(2):342-346. PMID 17301269.

Cox DG, Simard J, Sinnett D, et al. Common variants of the BRCA1 wild-type allele modify the risk of breast cancer in BRCA1 mutation carriers. Human molecular genetics. Sep 16 2011. PMID 21890493.

de Ruijter TC VJ, de Hoon JPJ, et al. Characteristics of triple-negative breast cancer. J Cancer Res Clin Oncol. 2011;137:183-192.

Engel C, Versmold B, Wappenschmidt B, et al. Association of the variants CASP8 D302H and CASP10 V410I with breast and ovarian cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. Nov 2010;19(11):2859-2868. PMID 20978178.

Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jan 20 2009;27(3):433-438. PMID 19064968.

Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. American journal of human genetics. Mar 1998;62(3):676-689. PMID 9497246.

Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Mar 15 2002;20(6):1480-1490. PMID 11896095.

Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci U S A. Sep 30 2014;111(39):14205-14210. PMID 25192939.

Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. Apr 1 2010;16(7):2115-2121. PMID 20215531.

Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling and Testing Guidelines. The American College of Medical Genetics, Practice Guideline: 1999; https://www.acmg.net/. Accessed September 16, 2014.

Gershoni-Baruch R, Patael Y, Dagan, et al. Association of the I1307K APC mutation with hereditary and sporadic breast/ovarian cancer: more questions than answers. British journal of cancer. Jul 2000;83(2):153-155. PMID 10901363.

Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. Mar 1 2011;17(5):1082-1089. PMID 21233401.

Grann VR, Whang W, Jacobson JS, et al. Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Feb 1999;17(2):494-500. PMID 10080590.

Hartge P, Struewing JP, Wacholder S, et al. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. American journal of human genetics. Apr 1999;64(4):963-970. PMID 10090881.

Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. The New England journal of medicine. Jan 14 1999;340(2):77-84. PMID 9887158.

Hirst JE, Gard GB, McIllroy K, et al. High rates of occult fallopian tube cancer diagnosed at prophylactic bilateral salpingo-oophorectomy. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. Jul 2009;19(5):826-829. PMID 19574767.

Hodgson SV, Heap E, Cameron J, et al. Risk factors for detecting germline BRCA1 and BRCA2 founder mutations in Ashkenazi Jewish women with breast or ovarian cancer. Journal of medical genetics. May 1999;36(5):369-373. PMID 10353781.

Hruban RH, Canto MI, Goggins M, et al. Update on familial pancreatic cancer. Advances in surgery. 2010;44:293-311. PMID 20919528.

Kandel MJ SD, Masciari S et al. Prevalence of BRCA1 mutations in triple negative breast cancer (BC). J Clin Onc. 2006;24(18S):508.

Kleibl Z, Havranek O, Kormunda S, et al. The AIB1 gene polyglutamine repeat length polymorphism and the risk of breast cancer development. Journal of cancer research and clinical oncology. Feb 2011;137(2):331-338. PMID 20422428.

King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. Oct 24 2003;302(5645):643-646. PMID 14576434.

King MC, Levy-Lahad E, Lahad A. Population-based screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA. Sep 17 2014;312(11):1091-1092. PMID 25198398.

Kirchhoff T, Kauff ND, Mitra N, et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clinical cancer research : an official journal of the

American Association for Cancer Research. May 1 2004;10(9):2918- 2921. PMID 15131025.

Lancaster JM, Powell CB, Chen LM, et al. Statement on risk assessment for inherited gynecologic cancer predispositions. Gynecologic oncology. Sep 17 2014. PMID 25238946.

Langston AA, Malone KE, Thompson JD, et al. BRCA1 mutations in a population-based sample of young women with breast cancer. The New England journal of medicine. Jan 18 1996;334(3):137-142. PMID 8531967.

Lesnock JL, Darcy KM, Tian C, et al. BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study. British journal of cancer. Apr 2 2013;108(6):1231-1237. PMID 23462720.

Malone KE, Daling JR, Thompson JD, et al. BRCA1 mutations and breast cancer in the general population: analyses in women before age 35 years and in women before age 45 years with first-degree family history. JAMA : the journal of the American Medical Association. Mar 25 1998;279(12):922-929. PMID 9544766.

Malone KE, Daling JR, Doody DR, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. Cancer research. Aug 15 2006;66(16):8297-8308. PMID 16912212.

Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. Journal of the National Cancer Institute. Jun 5 2013;105(11):812-822. PMID 23628597.

Menkiszak J, Rzepka-Gorska I, Gorski B, et al. Attitudes toward preventive oophorectomy among BRCA1 mutation carriers in Poland. European journal of gynaecological oncology. 2004;25(1):93-95. PMID 15053071.

Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. Jun 15 2004;22(12):2328-2335. PMID 15197194.

Metcalfe K, Lubinski J, Lynch HT, et al. Family history of cancer and cancer risks in women with BRCA1 or BRCA2 mutations. Journal of the National Cancer Institute. Dec 15 2010;102(24):1874-1878. PMID 21098759.

Mitra AV, Bancroft EK, Barbachano Y, et al. Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study. BJU Int. Jan 2011;107(1):28-39. PMID 20840664.

Moller P, Borg A, Evans DG, et al. Survival in prospectively ascertained familial breast cancer: analysis of a series stratified by tumour characteristics, BRCA mutations and oophorectomy. International journal of cancer. Journal international du cancer. Oct 20 2002;101(6):555-559. PMID 12237897.

Moslehi R, Chu W, Karlan B, et al. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet. Apr 2000;66(4):1259-1272. PMID 10739756.

Moyer VA. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. Feb 18 2014;160(4):271-281. PMID 24366376.

Myriad Genetics. Myriad PRO™. BRACAnalysis® large rearrangement test (BART): BART prevalence table and FAQ. https://www.myriadpro.com/hereditary-cancer-testing/hereditary-breast-and-ovarian-cancer-hbocsyndrome/ bracanalysis-large-rearrangement-test-bart/. Accessed October 16, 2014.

Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. Nat Rev Cancer. Sep 2004;4(9):665-676. PMID 15343273.

NCCN Clinical Practive Guidelines in Oncology. Genetic/familial high-risk assessment: breast and ovarian (discussion update in progress), version 2.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#genetics_screening. Accessed September 16, 2014.

Nelson HD, Fu R, Goddard K et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 101. AHRQ Publication No. 12-05164-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2013.

Nelson HD, Pappas M, Zakher B, et al. Risk assessment, genetic counseling, and genetic testing for BRCA related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. Feb 18 2014;160(4):255-266. PMID 24366442.

Olopade OI, Artioli G. Efficacy of risk-reducing salpingo-oophorectomy in women with BRCA-1 and BRCA-2 mutations. The breast journal. Jan-Feb 2004;10 Suppl 1:S5-9. PMID 14984481.

Osorio A, Milne RL, Alonso R, et al. Evaluation of the XRCC1 gene as a phenotypic modifier in BRCA1/2 mutation carriers. Results from the consortium of investigators of modifiers of BRCA1/BRCA2. British journal of cancer. Apr 12 2011;104(8):1356-1361. PMID 21427728.

Palmetto GBA®. MolDX® approved gene testing (M00041), last updated 09/17/2014. http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx Website~MolDx~Browse By Topic~Covered Tests~9BMLRK6738?open&navmenu=Browse^By^Topic|||. Accessed October 15, 2014.

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 research. Sep 1 2008;68(17):7006-7014. PMID 18703817.

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. Clinical genetics. Sep 2006;70(3):198-206. PMID 16922722.

Powell CB, Swisher EM, Cass I, et al. Long term follow up of BRCA1 and BRCA2 mutation carriers with unsuspected neoplasia identified at risk reducing salpingo-oophorectomy. Gynecologic oncology. May 2013;129(2):364-371. PMID 23391663.

Ramus SJ, Kartsonaki C, Gayther SA, et al. Genetic variation at 9p22.2 and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers. Journal of the National Cancer Institute. Jan 19 2011;103(2):105-116. PMID 21169536.

Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. The New England journal of medicine. May 23 2002;346(21):1616-1622. PMID 12023993.

Rennert G, Bisland-Naggan S, Barnett-Griness O, et al. Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. The New England journal of medicine. Jul 12 2007;357(2):115-123. PMID 17625123.

Robson M, Offit K. Clinical practice. Management of an inherited predisposition to breast cancer. The New England journal of medicine. Jul 12 2007;357(2):154-162. PMID 17625127.

Satagopan JM, Offit K, Foulkes W, et al. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev. May 2001;10(5):467-473. PMID 11352856.

Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Mar 1 2002;20(5):1260-1268. PMID 11870168.

Stein R. Researcher urges wider genetic screening for breast cancer. National Public Radio Shots: health news from NPR, 09/08/2014. http://www.npr.org/sections/health-shots/2014/09/08/346770167/researcher-urges-wider-genetic-screening-for-breast-cancer?utm_source=npr_email_a_friend&utm_medium=email&utm_content=20140909&utm_campaign=storyshare&utm_term. Accessed October 13, 2014.

Thorlacius S, Struewing JP, Hartge P, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet. Oct 24 1998;352(9137):1337-1339. PMID 9802270.

Trainer AH, Meiser B, Watts K, et al. Moving toward personalized medicine: treatment-focused genetic testing of women newly diagnosed with ovarian cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. Jul 2010;20(5):704-716. PMID 20973257.

U.S. Preventive Services Task Force. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA Related Cancer in Women, December 2013. http://www.uspreventiveservicestaskforce.org/uspstf/uspsbrgen.htm. Accessed September 16, 2014.

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 : the journal of the American Medical Association. Mar 22 2006;295(12):1379-1388. PMID 16551709.

Warner E, Foulkes W, Goodwin P, et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst. Jul 21 1999;91(14):1241-1247. PMID 10413426.

Weitzel JN, McCaffrey SM, Nedelcu R, et al. Effect of genetic cancer risk assessment on surgical decisions at breast cancer diagnosis. Archives of surgery. Dec 2003;138(12):1323-1328; discussion 1329. PMID 14662532.

Winchester DP. Breast cancer in young women. The Surgical clinics of North America. Apr 1996;76(2):279-287. PMID 8610264.

Young SR, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC cancer. 2009;9:86. PMID 19298662.

Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecologic oncology. May 1 2011;121(2):353-357. PMID 21324516.

Zhou GW, Hu J, Peng XD, et al. RAD51 135G>C polymorphism and breast cancer risk: a meta-analysis. Breast cancer research and treatment. Jan 2011;125(2):529-535. PMID 20623332.

Coding

CPT Procedure Code Number(s)

0172U, 81162, 81212, 81215, 81216, 81217, 81163, 81164, 81165, 81166, 81167

THE FOLLOWING CODE IS APPROPRIATE WHEN REPORTED BY A GENETIC COUNSELOR. WHEN PERFORMED BY A PHYSICIAN OR OTHER QUALIFIED HEALTH CARE PROFESSIONAL, THE PHYSICIAN OR OTHER QUALIFIED HEALTH CARE PROFESSIONAL SHOULD USE THE APPROPRIATE EVALUATION AND MANAGEMENT EXAM CODES:

96041

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

See Attachment A.

HCPCS Level II Code Number(s)

THE FOLLOWING CODE IS USED TO REPRESENT INTERPRETATION AND REPORT:

G0452 Molecular pathology procedure; physician interpretation and report

THE FOLLOWING CODE IS USED TO REPRESENT GENETIC COUNSELING BEFORE AND AFTER GENETIC TESTING FOR BRCA1 AND BRCA2:

S0265 Genetic counseling, under physician supervision, each 15 minutes

Revenue Code Number(s)

N/A

Cross Reference

Attachment A: Genetic Testing for Inherited Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) Mutations (AmeriHealth Administrators)
Description: ICD-10 codes

Policy History

Revisions From 06.02.06s:

01/01/2025	This version of the policy is effective as of 01/01/2025 due to code updates. The following procedure code has been added to the policy: 96041 The following procedure code has been deleted from the policy because it is termed: 96040

Revisions From 06.02.06r:

05/29/2024	**This policy has been reissued in accordance with the Company's annual review process.**
08/09/2023	This policy has been reissued in accordance with the Company's annual review process.
07/01/2022	This policy has been reissued in accordance with the Company's annual review process. The following disclaimer language...: *This policy only applies to members for whom AmeriHealth Administrators serves as the claims administrator and whose group has not enrolled in the UM vendor program. For those groups who have been given the option to enroll in the UM vendor program, this policy is no longer applicable upon their renewal effective date. Individual member benefits must be verified before/prior to providing services.* ... is replacing this disclaimer language...: *This policy only applies to members for whom AmeriHealth Administrators serves as the claims administrator. For all other Independence members, refer to the policy entitled eviCore Lab Management Program.*
06/01/2022	This policy has been reissued in accordance with the Company's annual review process.
10/01/2021	This version of the policy is a result of code updates effective 10/01/2021. The following diagnosis codes were added: C56.3 and C79.63.

Revisions From 06.02.06q:

06/02/2021	This policy has been reissued in accordance with the Company's annual review process.
09/09/2020	This policy has been reissued in accordance with the Company's annual review process.
07/01/2020	This version of the policy is effective as of 07/01/2020. Procedure code 0172U has been added to this policy due to a code update.

Revisions From 06.02.06p:

11/06/2019	This policy has been reissued in accordance with the Company's annual review process.
01/01/2019	Effective 01/01/2019, the following changes have been made to this policy due to coding updates: The following procedure codes have been deleted: 81211 81213 81214 Narratives of the following procedure codes have been revised: 81162 81212 81215 81216 81217 The following procedure codes have been added: 81163 81164 81165

	81166 81167

Revisions From 06.02.06o:

11/21/2018	This policy has been reissued in accordance with the Company's annual review process.
11/22/2017	This policy has been reissued in accordance with the Company's annual review process.

Effective 10/05/2017 this policy has been updated to the new policy template format.

Version Effective Date: 01/01/2025

Version Issued Date: 01/31/2025

Version Reissued Date: N/A