Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1/BRCA2)

Policy Number: 2.04.02  Last Review: 1/2017
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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for genetic testing for hereditary breast and/or ovarian cancer when it is determined to be medically necessary because the criteria shown below are met.

Note: Genetic testing may be excluded in some contracts. Verify benefits prior to review of Medical Necessity.

When Policy Topic is covered
Genetic testing should be performed in a setting that has suitably trained healthcare providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments (CLIA)-licensed laboratory that offers comprehensive mutation analysis (see Considerations: Comprehensive mutation analysis).

Patients with Cancer
Genetic testing for BRCA1 and BRCA2 mutations in cancer-affected individuals may be considered medically necessary under any of the following circumstances:

- Individual from a family with a known BRCA1/BRCA2 mutation
- Personal history of breast cancer and ≥1 of the following:
  - Diagnosed age ≤45 years
  - 2 primary breast cancers when 1st breast cancer diagnosis occurred age ≤50 years
  - Diagnosed age ≤50 years AND:
    - ≥1 1st-, 2nd-, or 3rd-degree relative with breast cancer at any age, or
    - Unknown or limited family history
  - Diagnosed age ≤60 years with a triple negative (ER–, PR–, HER2–) breast cancer
Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relative with breast cancer diagnosed ≤50 years
Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast cancer at any age
Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relative with epithelial ovarian/fallopian tube/primary peritoneal CA
Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with pancreatic cancer or prostate cancer at any age
1st-, 2nd-, or 3rd-degree male relative with breast cancer
Ethnicity associated with deleterious founder mutations, e.g., Ashkenazi Jewish descent
- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or prostate cancer at any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with any of the following at any age. For pancreatic cancer, if Ashkenazi Jewish ancestry, only 1 additional affected relative is needed.
  - Breast cancer
  - Ovarian/fallopian tube/primary peritoneal cancer
  - Pancreatic or prostate cancer

Patients Without Cancer or Without History of Cancer
(see Considerations: Testing unaffected individuals)

Genetic testing for BRCA1 and BRCA2 mutations of cancer-unaffected individuals may be considered medically necessary under any of the following circumstances:
- Individual from a family with a known BRCA1/BRCA2 mutation
- 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients with Cancer
- 3rd-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast cancer (≥1 at age ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer

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).
- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

For example, fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage. In families with a large number of unaffected female relatives, the likelihood of mutation detection may be very low.
For the purpose of familial assessment, prostate cancer is defined as Gleason score $\geq 7$.

Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first (see Considerations: High risk ethnic groups)

Under the Patient Protection and Affordable Care Act, preventive services with a USPSTF recommendation grade of A or B will be covered with no cost sharing requirements. Plans that have been grandfathered are exceptions to this rule and are not subject to this coverage mandate.

**When Policy Topic is not covered**

Unless they meet the criteria above, genetic testing for either those affected with breast, ovarian, fallopian tube, or primary peritoneal cancer or for unaffected individuals, including those with a family history of pancreatic cancer, is considered investigational.

Genetic testing in minors for BRCA1 and BRCA2 mutations is investigational.

**Considerations**

The Policy Statements above are based on current guidelines from the National Comprehensive Cancer Network (NCCN).

Testing for genomic rearrangements of the BRCA1 and BRCA2 genes should only be performed on patients who meet criteria for BRCA testing, whose testing for point mutations is negative.

Current U.S. Preventive Services Task Force (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 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:
- Ontario Family History Assessment Tool (FHAT)
- Manchester Scoring System
- Referral Screening Tool (RST)
- Pedigree Assessment Tool (PAT)
- Family History Screen (FHS-7)

**A Recommended Testing Strategy**

Patients who meet criteria for genetic testing as outlined in the Policy Statements above should be tested for mutations in BRCA1 and BRCA2.
- In patients with a known familial BRCA mutation, targeted testing for the specific mutation is recommended.
- In patients with unknown familial BRCA mutation:
Non-Ashkenazi Jewish descent

- To identify clinically significant mutations, 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 (eg, 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; see Comprehensive Mutation Analysis, below) may be performed as is recommended by NCCN.
    - Comprehensive testing can detect 92.5% of \( BRCA1/BRCA2 \) mutations.
- If comprehensive \( BRCA \) testing is negative, testing for uncommon large genomic rearrangements (eg, BART™) may be done.
  - 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 patients with negative comprehensive testing, BART™ identified a deleterious mutation (positive result) in less than 1%.

Ashkenazi Jewish descent

- In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder mutations (185delAG and 5182insC in \( BRCA1 \); 6174delT in \( BRCA2 \)) first.
- If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Mutation Analysis, below).

**Comprehensive Mutation Analysis**

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. In addition, before August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative \( BRCA \)
testing before this time may consider repeat testing for the rearrangements (see Considerations for criteria).

**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 (see Rationale). When testing for founder mutations is negative, comprehensive mutation analysis should then be performed.

**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 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.

**Prostate Cancer**
Patients with BRCA mutations have an increased risk of prostate cancer, and patients with known BRCA mutations may therefore consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in an individual, or in a family, is not itself felt to be sufficient justification for BRCA testing.

**Genetic Counseling**
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Description of Procedure or Service**

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Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1/BRCA2) 2.04.02
Individuals:
• With either a personal or family history of cancer and criteria that suggest a risk of hereditary breast/ovarian cancer syndrome

Interventions of interest are:
• Genetic testing for a BRCA1/2 mutation

Comparators of interest are:
• No genetic testing

Relevant outcomes include:
• Overall survival
• Disease-specific survival
• Test accuracy
• Test validity
• Morbid events
• Quality of life
• Treatment-related morbidity

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). Families with HBOC syndrome have an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, cancer of the fallopian tube and primary peritoneal cancer and other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

For individuals who have cancer or a personal or family cancer history and meeting criteria suggesting a risk of HBOC syndrome who receive genetic testing for a BRCA1 or BRAC2 mutation, the evidence includes a TEC Assessment and studies of mutation prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, quality of life, and treatment-related morbidity. The accuracy of mutation testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA mutation have shown a risk as high as 85%. Knowledge of BRCA mutation status in individuals at risk of a BRCA mutation may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Background
Several genetic syndromes with an autosomal dominant pattern of inheritance that features 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 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, 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. For this policy, both will be 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.

**Rationale**

This evidence review was developed following a 1997 TEC Assessment(1) and has been updated on a regular basis with literature searches for articles that contain information regarding professional guidelines for *BRCA* testing, testing of unaffected family members, and testing of high-risk ethnic populations. The most recent update covered the period through October 7, 2015 (see Appendix Table 1 for genetic testing categories).

**Testing for *BRCA1* and *BRCA2* Mutations in High-Risk Women**

Nelson et al (2013) conducted a systematic review that included meta-analysis estimates of the prevalence and penetrance of *BRCA* mutations, in order to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.,(2) The authors search literature to July 30, 2013, and 72 articles to address 5 key questions were included. *BRCA* prevalence and penetrance were estimated to assess clinical validity of mutation testing. In high-risk women with positive test results, cumulative risks for developing breast cancer by age 70 were 46% for *BRCA1* and 50% for *BRCA2* when a single family member is tested, and 70% for *BRCA1* and 71% for *BRCA2* when multiple family members are tested; cumulative risks for developing ovarian cancer by age 70 were 41% for *BRCA1* and 17% for *BRCA2* when a single family member is tested, and 46% for *BRCA1* and 23% for *BRCA2* when multiple family members are tested. For Ashkenazi Jewish women with positive test results, cumulative risks for developing breast or ovarian cancer by age 75 were 34% and 21%, respectively.

Gabai-Kapara et al (2014) studied breast and ovarian cancer risks among 211 Ashkenazi Jewish female *BRCA1/BRCA2* founder mutation carriers who were identified through an unaffected male carrier relative.(3) All study participants underwent *BRCA1/BRCA2* genotyping for 3 founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT) that account for 11% of breast cancer and 40% of ovarian cancer in this population. Approximately half of identified carriers were from low-risk families who would not have satisfied criteria for testing. Cumulative risks for developing breast or ovarian cancer were similar to those observed in female *BRCA1/BRCA2* mutation carriers from high-risk families who satisfy criteria for testing. (For example: Cumulative risks for developing breast or
ovarian cancer by age 60 and 80 were 60% and 83%, respectively, for \textit{BRCA1} mutation carriers, and 33% and 76%, respectively, for \textit{BRCA2} mutation carriers; for breast cancer only, cumulative risks were 41% and 60%, respectively, for \textit{BRCA1} mutation carriers, and 26% and 40%, respectively, for \textit{BRCA2} mutation carriers; for ovarian cancer only, cumulative risks were 27% and 53%, respectively, for \textit{BRCA1} mutation carriers, and 7% and 62%, respectively, for \textit{BRCA2} mutation carriers. Among \textit{BRCA2} mutation carriers, higher than expected cumulative risk of ovarian cancer and lower than expected cumulative risk of breast cancer were attributed to reduced prevalence of nongenetic risk factors for breast cancer, eg, late age at first pregnancy, in the study sample and therefore reduced competing risk.) Duration of follow-up was not specified. Based on these findings, several authors of this study advocated universal screening of women for \textit{BRCA1}/\textit{BRCA2} mutation status.(4) However, despite the authors’ assertion that results of this study are “widely applicable,” this is unlikely to be true; as the authors themselves stated, “The Ashkenazi Jewish population is unusual.” Others have questioned whether radical surgery (prophylactic mastectomy, oophorectomy) in \textit{BRCA1}/\textit{BRCA2} mutation carriers identified through population screening who may not have developed cancer constitutes a net health benefit.(5)

Early estimates of lifetime risk of cancer for \textit{BRCA} mutation carriers (penetrance), based on studies of families with extensive history of disease, have been as high as 85%. Because other factors that influence risk may be present in families with extensive breast and ovarian cancer histories, early penetrance estimates may have been biased upward.(6) Studies of founder mutations in ethnic populations (eg, Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history indicated lower penetrance estimates, in the range of 40% to 60% for \textit{BRCA1} and 25% to 40% for \textit{BRCA2}.(7-10) However, a genotyping study of Ashkenazi Jewish women with incident, invasive breast cancer, selected regardless of family history of cancer, and their family members resulted in an 82% lifetime risk of breast cancer for carriers of any of 3 \textit{BRCA} founder mutations (185delAG, 5382insC, 6174delT).(11) Importantly, the risk of cancer in mutation carriers from families with little history of cancer (≈50% of all carriers) was not significantly different. Lifetime risks of ovarian cancer were 54% for \textit{BRCA1} and 23% for \textit{BRCA2} mutation carriers.

Women with a history of breast cancer and a \textit{BRCA} mutation have a significant risk of contralateral breast cancer; in 1 prospective study (2004), the risk was 29.5% at 10 years for women with initial stage I or II disease.(12) In a 2013 prospective study (EMBRACE), the cumulative risk of contralateral breast cancer by age 70 years was 83% in \textit{BRCA1} mutation carriers and 62% for \textit{BRCA2} mutation carriers.(13) These investigators also reported cumulative risks of breast cancer by age 70 years in women without previous cancer of 60% in \textit{BRCA1} carriers and 55% in \textit{BRCA2} carriers. Similarly, the cumulative risks of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for \textit{BRCA1} carriers and 17% for \textit{BRCA2} carriers.

Thus, the risk of cancer in a \textit{BRCA} mutation carrier is significant, and knowledge of mutation status in individuals at potentially increased risk of a \textit{BRCA} mutation may
impact healthcare decisions to reduce risk.(14-21) Risk-reducing options include intensive surveillance, chemoprophylaxis, prophylactic mastectomy, or prophylactic oophorectomy. Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90% or more but is invasive and disfiguring.(15) Prophylactic oophorectomy significantly reduces the risk of ovarian cancer to less than 10%(18, 19) and reduces the risk of breast cancer by approximately 50%.(19) In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.(17) Studies indicate that genotyping results significantly influence treatment choices.(16, 20, 21)

Prevalence of BRCA Mutations
Nelson et al included meta-analysis estimates of BRCA prevalence in their 2013 systematic review for USPSTF.(2) In unselected women, BRCA mutation prevalence estimates were 0.2% to 0.3%; in women with breast cancer, 1.8% for BRCA1 and 1.3% for BRCA2; in women with breast cancer onset at age 40 years or younger, 6%; in women from high-risk families, 13.6% for BRCA1, 7.9% for BRCA2, and 19.8% for BRCA1 or BRCA2; in unselected Ashkenazi Jewish women, 2.1%; and in Ashkenazi Jewish women from high-risk families, 10.2%.

The prevalence of BRCA mutations is approximately 0.1% to 0.2% in the general population. Prevalence may be much higher for particular ethnic groups with characterized founder mutations (eg, 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for BRCA mutation. Age and, in some cases, ethnic background can also be independent risk factors. Malone et al (2006) reported on racial and ethnic differences in the prevalence of BRCA1 and BRCA2 in American women.(22) Among their subjects, 2.4% and 2.3% carried deleterious mutations in BRCA1 and BRCA2, respectively. BRCA1 mutations were significantly more common in “white” (2.9%) versus “black” (1.4%) cases and in Jewish (10.2%) versus non-Jewish (2.0%) cases; BRCA2 mutations were slightly more frequent in “black” (2.6%) versus “white” (2.1%) cases.

Clinical Features Suggestive of BRCA Mutation
Young age of onset of breast cancer, even in the absence of family history, has been demonstrated to be a risk factor for BRCA1 mutations. Winchester(23) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30. In several studies, BRCA mutations are independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years).(23-26) In cancer-prone families, the mean age of breast cancer diagnosis among women carrying BRCA1 or BRCA2 mutations is in the 40s.(27) In the Ashkenazi Jewish population, Frank et al(24) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had BRCA mutations. In a similar study, 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had BRCA mutations.(28) Additional studies indicate that early age of breast cancer diagnosis is a significant predictor of BRCA mutations in the absence of family history in this population.(10, 29, 30)
As in the general population, family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a BRCA mutation in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a BRCA mutation depending on the extent and nature of the family history. Several other studies document the significant influence of family history.\(^{(7, 10, 28-30)}\)

In patients with breast cancer that is “triple-negative,” ie, negative for expression of estrogen and progesterone receptors and for overexpression of HER2 receptors, there is an increased incidence of BRCA mutations. Pathophysiologic research has suggested that the physiologic pathway for development of triple-negative breast cancer is similar to that for BRCA-associated breast cancer.\(^{(31)}\) In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center,\(^{(32)}\) there was a greater than 3-fold increase in the expected rate of BRCA mutations. BRCA1 mutations were found in 39.1% of patients and BRCA2 mutations in 8.7%. Young et al\(^{(33)}\) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for BRCA testing. A total of 6 BRCA mutations, 5 BRCA1, and 1 BRCA2, were found for a mutation rate of 11%. Finally, in a study of 77 patients with triple-negative breast cancer, 15 patients (19.5%) had BRCA mutations: 12 in BRCA1 and 3 in BRCA2.\(^{(34)}\)

**Testing Results**

Unaffected individuals with a family history suggestive of hereditary breast and/or ovarian cancer 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 familial mutation.\(^{(24, 35)}\) 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 BRCA mutations may have uncertain significance in the absence of a family study, and negative results offer no useful information, ie, the patient may still be at increased risk of a disease-associated mutation in an as yet undiscovered gene.

**BRCA Mutation Associated With Pancreatic Cancer**

Unaffected individuals also may be at high risk due to other patterns of non-breast-cancer malignancies. A personal history of pancreatic cancer is estimated to raise the risk of a BRCA mutation by 3.5- to 10-fold over the general population.\(^{(36)}\) Couch et al\(^{(37)}\) reported on screening for BRCA2 mutations in 2 cohorts of families at high risk for pancreatic cancer. In the first cohort of high-risk families, there were a total of 5 BRCA mutations in 151 probands (3%), and in the second cohort, there were another 5 BRCA2 mutations in 29 probands (17%). The combined BRCA2 mutation rate for these 2 cohorts was 6% (10/180). Ferrone et al\(^{(38)}\) tested 187 Ashkenazi Jewish patients with pancreatic cancer for BRCA mutations and found that 5.5% (8/187) had a BRCA mutation.
**BRCA Mutation Associated With Ovarian Cancer**

Women with a personal history of ovarian cancer also have an increased rate of BRCA mutations. In a 2010 systematic review of 23 studies, Trainer et al estimated the rate of BRCA mutations among women with ovarian cancer to be 3% to 15%.(39) In this review, 3 U.S. studies tested for both BRCA1 and BRCA2; incidences of BRCA mutations were 11.3%, 15.3%, and 9.5%. In a 2011 population-based study of 1342 unselected patients with invasive ovarian cancer in Canada, 176 women had BRCA mutations, for a rate of 13.3%.(40) Mutation prevalence was higher for women in their 40s (24.0%) and for women with serous ovarian cancer (18.0%). Ethnicity was an additional risk factor for BRCA, with higher rates seen in women of Italian (43.5%), Jewish (30.0%), and Indo-Pakistani origin (29.4%). In the 2013 systematic review for USPSTF by Nelson et al, meta-analysis estimates of BRCA prevalence among women with ovarian cancer were 4.4% for BRCA1 and 5.6% for BRCA2.(2)

**BRCA Mutation Associated With Fallopian Tube Cancer**

A 2009 publication described the high rate of occult fallopian tube cancers in at-risk women having prophylactic bilateral salpingo-oophorectomy.(41) In this prospective series of 45 women, 4 (9%) were found to have fallopian tube malignancies. The authors noted that this supports other studies that have demonstrated the fimbrial end of the fallopian tube as an important site of cancer in those with BRCA1 or BRCA2 mutations. Similarly, current National Comprehensive Cancer Network (NCCN) guidelines for assessing high risk in breast and ovarian cancer(42) include both fallopian tube and primary peritoneal cancer as other malignancies that should be documented when assessing family history for BRCA1 and BRCA2 genotyping decisions. Thus, these 2 conditions are added to the Policy Statements and Policy Guidelines sections.

A long-term study (median follow-up, 7 years; range, 3-14 years) followed 32 BRCA mutation carriers with occult malignancy (4 ovarian, 23 fallopian tube, 5 ovarian and fallopian tube) diagnosed at prophylactic salpingo-oophorectomy.(43) Among 15 women with invasive carcinoma (median age, 50 years), 7 (47%) experienced recurrence at a median of 33 months, and overall survival (OS) was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One patient (6%) who did not receive chemotherapy experienced recurrence at 43 months. OS was 100%. The authors concluded that, in BRCA mutation carriers, unsuspected invasive carcinoma has a relatively high rate of recurrence, but noninvasive neoplasms rarely recur and may not require adjuvant chemotherapy.

**Clinical Outcomes in BRCA Mutation Carriers**

A clinical approach to these patients was published in 2007 by Robson and Offit(44) Phillips et al (2006) reported that although uptake of prophylactic surgery and screening was associated with knowing one’s mutation status, in their cohort of 70 unaffected female mutation carriers who had chosen to receive results, a minority had risk-reducing surgery (11% had bilateral mastectomy and 29% bilateral oophorectomy) or chemoprevention.(45)
Rennert et al (2007) reported that breast cancer-specific rates of death among Israeli women were similar for carriers of a \textit{BRCA} founder mutation and noncarriers. (46)

Lesnock et al (2013) compared OS in 393 women with \textit{BRCA1}-mutated and \textit{BRCA1}-nonmutated epithelial ovarian cancer who were treated with intraperitoneal or intravenous-only chemotherapy. (47) All patients had "optimally resected" (<1 cm residual disease) stage III disease. \textit{BRCA1} mutation status was determined by blinded review of immunohistochemistry assays of archived tumor samples. Treatment regimens were intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel (IP therapy) or intravenous paclitaxel and cisplatin (IV therapy). In 204 women with nonmutated \textit{BRCA1}, median OS was not statistically different between treatment groups (58 months vs 50 months in the IP therapy and IV therapy groups, respectively; \( p=0.82 \)). In 189 women with mutated \textit{BRCA1}, median OS was significantly longer in the IP therapy group (84 months vs 47 months, respectively; \( p<0.001 \)).

In their 2013 systematic review for USPSTF, Nelson et al assessed efficacy of risk-reducing surgery in \textit{BRCA}-positive women. (2, 48) For high-risk women and mutation carriers, bilateral mastectomy reduced breast cancer incidence by 85\% to 100\% and breast cancer mortality by 81\% and 100\%, respectively; salpingooophorectomy reduced breast cancer incidence by 37\% to 100\%, ovarian cancer incidence by 69\% to 100\%, and all-cause mortality by 55\% to 100\%, respectively. Some women experienced reduced anxiety. Although comparison groups varied across studies, results were consistent. Adverse events included physical complications of surgery, postsurgical symptoms, and changes in body image. Limitations of the analysis included the small number of studies (\( N=7 \)) and small sample sizes. As the authors observed, whether \textit{BRCA} mutation testing reduces cause-specific or all-cause mortality and improves quality of life is currently unknown. Harms associated with false-negative results or variants of uncertain significance also are unknown.

\textbf{BRCA Mutation Associated With Prostate Cancer}

A number of studies have indicated that \textit{BRCA} mutations are associated with increased risk of prostate cancer in men. In a 2010 study of 832 Ashkenazi Jewish men diagnosed with localized prostate cancer, and 454 Ashkenazi Jewish men without prostate cancer, the presence of a \textit{BRCA2} mutation was associated with a more than 3-fold increased risk of prostate cancer (odds ratio [\( OR \)], 3.18; 95\% confidence interval [\( CI \)], 1.52 to 6.66). (49) In a similar population of 251 Ashkenazi Jewish men with prostate cancer and 1472 volunteers without prostate cancer, the presence of a \textit{BRCA} mutation was associated with a more than 3-fold increased risk of prostate cancer (\( OR=3.41; 95\% \text{ CI}, 1.64 \text{ to } 7.06 \)). (50) When analyzed by type of \textit{BRCA} mutation, \textit{BRCA2} was associated with an almost 5-fold increased risk (\( OR=4.82; 95\% \text{ CI}, 1.87 \text{ to } 12.25 \)), and \textit{BRCA1} mutations were not associated with an increased risk (\( OR=2.20; 95\% \text{ CI}, 0.72 \text{ to } 6.70 \)). A 2013 retrospective analysis compared prostate cancer outcomes in 79 \textit{BRCA} mutation carriers (18 \textit{BRCA1}, 61 \textit{BRCA2}) and 2019 noncarriers. (51) Men with \textit{BRCA
mutations more often had Gleason scores of 8 or higher (p<0.001), nodal involvement (p<0.001) and metastases at diagnosis (p=0.005) than noncarriers. Median OS was 8.1 years in carriers and 12.9 years in noncarriers (hazard ratio [HR]=1.9; 95% CI, 1.1 to 3.3; p=0.012). In subgroup analyses, BRCA2 mutations were independently associated with reduced OS (HR=1.9; 95% CI, 1.1 to 3.1; p=0.004), but BRCA1 mutations were not, possibly due to small sample size and limited follow-up.

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 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.

**Candidate Modifier Genes**
There has been interest in further risk-stratifying patients with known BRCA mutations to further assist in clinical decision making. Numerous recent publications have identified a large number of candidate modifier genes, and nongenetic modifying factors also have been examined. Antoniou et al examined the risk of breast cancer associated with 9 genetic polymorphisms, most of which had previously shown an increase cancer risk among BRCA carriers. Seven of the 9 polymorphisms were confirmed to increase breast cancer risk. The magnitude of increased risk varied by whether the patient was a BRCA1 versus a BRCA2 carrier, and the polymorphisms appeared to interact multiplicatively to increase risk.

Kleibl et al reported that the AIB1 (amplified in breast 1) genotype in general did not influence breast cancer risk in BRCA carriers but that the specific AIB1 genotype consisting of 28 glutamine repeats in both alleles (28/28) conferred a decreased risk of breast cancer (HR=0.64; 95% CI, 0.41 to 0.99; p=0.045). In 2013, Bianco et al conducted a meta-analysis to examine the effect of AIB1 polyglutamine repeats on breast cancer risk in BRCA mutation carriers. Seven case-control and cohort studies of 28 of 28, 29 of 29, and 26 or fewer repeats in 1 or both alleles were included. No statistically significant association with breast cancer risk was observed for polyglutamine repeats of any length in BRCA, BRCA1, or BRCA2 mutation carriers. Statistical heterogeneity was significant in the analyses of 28 of 28 repeats in BRCA1 and BRCA2 mutation carriers.

Zhou et al reported an increased risk of cancer in BRCA carriers who also had the RAD51 135G>C polymorphism (OR=1.34; 95% CI, 1.01 to 1.78; p=0.04). Metcalfe et al reported that family history provided additional predictive information in BRCA carriers. For each first-degree relative with breast cancer before age 50 years, the risk of ovarian cancer increased 1.6-fold (HR=1.61; 95%
CI, 1.21 to 2.14) in \( BRCA1 \) mutation carriers, and the risk of breast cancer increased 1.7-fold in \( BRCA2 \) mutation carriers (HR=1.67; 95% CI, 1.04 to 2.07).

**BRCA Testing in Minors**

The use of genetic testing for \( BRCA \) mutations has limited or no clinical utility in minors. This is because 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.

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.” (63) 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 “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.”

**Testing for Large \( BRCA \) Rearrangements**

Over the past few years, a number of studies have shown that a significant percentage of women with a strong family history of breast cancer and negative tests for \( BRCA \) mutations have large genomic rearrangements (including deletions or duplications) in one of these genes. For example, in 2006 Walsh et al reported on probands from 300 U.S. families with 4 or more cases of breast or ovarian cancer but with negative (wild-type) commercial genetic tests for \( BRCA1 \) and \( BRCA2 \). (64) These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected mutations, including 35 (12%) with genomic rearrangement of \( BRCA1 \) or \( BRCA2 \).

A 2008 study evaluated 251 patients with an estimated \( BRCA \) mutation prevalence by the Myriad II model of at least 10%. (65) In 136 non-Ashkenazi Jewish probands, 36 (26%) had \( BRCA \) point mutations and 8 (6%) had genomic rearrangements, 7 in \( BRCA1 \) and 1 in \( BRCA2 \). Genomic rearrangements comprised 18% of all identified \( BRCA \) mutations. No genomic rearrangements were identified in the 115 Ashkenazi Jewish probands, but 47 (40%) had point mutations. The authors indicated that the estimated prevalence of a mutation did not predict the presence of a genomic rearrangement.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

Aetna is developing a research network, ABOUT (American BRCA Outcomes and Utilization of Testing), of patients for whom a preauthorization request for \( BRCA \) testing is submitted and who consent to enrollment. (66) The goal is to examine in a real-world, nonacademic setting the clinical use and impact of genetic testing for
common conditions, such as cancer. Patient-centered outcomes—eg, understanding of information before and after testing; disparities in experiences related to BRCA testing (eg, in access to information, services, or care); perceived risks of developing cancer; intentions for risk management (eg, screening, chemoprevention, and/or surgery); and plans for sharing information with at-risk relatives—are prioritized. ABOUT Network is part of PCORnet, a national patient-centered clinical outcomes research network established by PCORI (the Patient-Centered Outcomes Research Institute).

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01851109</td>
<td>Prevention of Ovarian Cancer in Women Participating in Mammography</td>
<td>458</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>NCT00685256</td>
<td>Standard Genetic Counseling With or Without a Decision Guide in Improving Communication Between Mothers Undergoing BRCA1/2 Testing and Their Minor-Age Children</td>
<td>400</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>NCT00287898</td>
<td>Telephone-Based Genetic Counseling or Standard Genetic Counseling in Women at Risk of Carrying the BRCA1 or BRCA2 Mutation</td>
<td>600</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>NCT02133703</td>
<td>Decision Making Interventions for Women Receiving Uninformative BRCA1/2 Test Results or Positive BRCA1/2 Test Results</td>
<td>600</td>
<td>Jul 2017</td>
</tr>
<tr>
<td>NCT02225015</td>
<td>Cancer Prevention in Women With a BRCA Mutation: A Follow-up Genetic Counselling Intervention</td>
<td>500</td>
<td>Jan 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Summary of Evidence

The evidence for genetic testing for BRCA mutations in patients who have cancer or a family history of cancer and criteria that would suggest a possibility of HBOC includes a TEC Assessment and studies of mutation prevalence and cancer risk. Outcomes of interest are overall survival, disease-specific survival, test accuracy and test validity. The accuracy of the test has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA mutation have shown a risk as high as 85%. Knowledge of mutation status in individuals at risk of a BRCA mutation may impact health care decisions to reduce risk, including intensive surveillance, chemoprophylaxis and/or prophylactic intervention. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an
endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2010 Input
In response to requests, input was received through 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) while this policy was under review for January 2010. Those providing input were in general agreement with the Policy statements considering testing for genomic rearrangements of BRCA1 and BRCA2 as medically necessary and with adding fallopian tube and primary peritoneal cancer as additional BRCA-associated malignancies to assess when obtaining the family history.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
The current NCCN guideline for Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer (v.2.2015) includes criteria for identifying individuals who should be referred for further risk assessment, and separate criteria for genetic testing. (42) Patients who satisfy any of the testing criteria listed in Table 1 should undergo “further personalized risk assessment, genetic counseling, and often genetic testing and management.” For these criteria, both invasive and in situ breast cancers are included. Maternal and paternal sides of the family should be considered independently for familial patterns of cancer. Testing of unaffected individuals should be considered “only when an appropriate affected family member is unavailable for testing.”

Table 1. NCCN Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria With Comparison to SGO Criteria for Genetic Assessment (Counseling With or Without Testing)

<table>
<thead>
<tr>
<th>NCCN(42)</th>
<th>SGO(63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Individual from a family with a known BRCA1/BRLA2 mutation</td>
<td>√</td>
</tr>
<tr>
<td>2. Personal history of breast cancer and ≥1 of the following:</td>
<td></td>
</tr>
<tr>
<td>a. Diagnosed age ≤45 years</td>
<td>√</td>
</tr>
<tr>
<td>b. 2 primary breast cancers when 1st breast cancer diagnosis occurred age ≤50 years</td>
<td>√/f</td>
</tr>
<tr>
<td>c. Diagnosed age ≤50 years AND:</td>
<td></td>
</tr>
<tr>
<td>i. One or more 1st-, 2nd-, or 3rd-degree relative with breast cancer at any age, or</td>
<td></td>
</tr>
<tr>
<td>ii. Unknown or limited family history</td>
<td>√</td>
</tr>
<tr>
<td>d. Diagnosed age ≤60 years with a triple negative (ER–, PR–, HER2–) breast cancer</td>
<td>√</td>
</tr>
<tr>
<td>e. Diagnosed any age AND one or more 1st-, 2nd-, or 3rd-degree relatives with breast cancer diagnosed ≤50 years</td>
<td>√</td>
</tr>
<tr>
<td>f. Diagnosed any age AND two or more 1st-, 2nd-, or 3rd-degree relatives with breast cancer at any age</td>
<td>√</td>
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<tr>
<td>---</td>
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</tr>
<tr>
<td>g.</td>
<td>Diagnosed any age AND one or more 1st-, 2nd-, or 3rd-degree relative(^a) with epithelial ovarian/fallopian tube/primary peritoneal CA</td>
</tr>
<tr>
<td>h.</td>
<td>Diagnosed any age AND two or more 1st-, 2nd-, or 3rd-degree relatives(^a) with pancreatic cancer or prostate cancer(^c) at any age</td>
</tr>
<tr>
<td>i.</td>
<td>1st-, 2nd-, or 3rd-degree male relative with breast cancer</td>
</tr>
<tr>
<td>j.</td>
<td>For individuals of ethnicity associated with increased mutation frequency (eg, Ashkenazi Jewish), no additional family history may be required(^d)</td>
</tr>
<tr>
<td>3.</td>
<td>Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer</td>
</tr>
<tr>
<td>4.</td>
<td>Personal history of male breast cancer</td>
</tr>
<tr>
<td>5.</td>
<td>Personal history of pancreatic cancer or prostate cancer(^c) at any age AND two or more 1st-, 2nd-, or 3rd-degree relatives(^a) with any of the following at any age. For pancreatic cancer, if Ashkenazi Jewish ancestry, only 1 additional affected relative is needed:</td>
</tr>
<tr>
<td>a.</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>b.</td>
<td>Ovarian/fallopian tube/primary peritoneal cancer</td>
</tr>
<tr>
<td>c.</td>
<td>Pancreatic or prostate cancer(^c)</td>
</tr>
<tr>
<td>6.</td>
<td>Family history only(^e):</td>
</tr>
<tr>
<td>a.</td>
<td>1st- or 2nd-degree blood relative meeting any of the above criteria</td>
</tr>
<tr>
<td>b.</td>
<td>3rd-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast cancer (≥1 at age ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer</td>
</tr>
</tbody>
</table>

NCCN: National Comprehensive Cancer Network; SGO: Society of Gynecologic Oncology

\(^a\) Blood relatives on the same side of the family (maternal or paternal).
- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

\(^b\) For example, fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage.

\(^c\) Gleason score ≥7.

\(^d\) Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first.

\(^e\) Significant limitations of interpreting test results for an unaffected individual should be discussed.

\(^f\) SGO does not include age restriction.

\(^g\) SGO does not include qualifier for Ashkenazi-Jewish patients.
For unaffected women, this SGO criterion states, “A first or several close relatives who meet one of the above criteria.” SGO additionally recommends genetic assessment for unaffected women who have a male relative with breast cancer.

American Society of Clinical Oncology
The American Society of Clinical Oncology recommended in 2003 (67) that cancer predisposition testing be offered when (1) there is a personal or family history suggesting genetic cancer susceptibility, (2) the test can be adequately interpreted, and (3) results will influence medical management of the patient or family member at hereditary risk of cancer. A 2010 update of this policy statement recommended that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”(68)

American College of Medical Genetics
In 1999, the American College of Medical Genetics (ACMG) (69) published guidelines for BRCA testing under the auspices of a grant from the New York State Department of Health to the ACMG Foundation. This guideline was retired in 2013.

Society of Clinical Oncology
In 2014, Society of Clinical Oncology (SGO) updated its 2007 evidence-based consensus statement on risk assessment for inherited gynecologic cancer.(63) The statement includes criteria for recommending genetic assessment (counseling with or without testing) to patients who may be genetically predisposed to breast or ovarian cancer. Overall, SGO and NCCN recommendations align. Differences are: exclusion of women with breast cancer onset at age 50 years or younger who have one or more first-, second-, or third-degree relatives with breast cancer at any age; women with breast cancer of history of breast cancer who have a first-, second-, or third-degree male relative with breast cancer; and men with a personal history of breast cancer. SGO additionally recommends genetic assessment for unaffected women who have a male relative with breast cancer. SGO allows that some patients who do not satisfy criteria may still benefit from genetic assessment, eg, few female relatives, hysterectomy or oophorectomy at a young age in multiple family members, or adoption in the lineage.

U.S. Preventive Services Task Force
Current U.S. Preventive Services Task Force (USPSTF) recommendations for genetic testing of BRCA1/BRCA2 mutations in women are listed next. (70) Screening tools recommended for assessment of genetic risk are: the Ontario Family History Assessment Tool; Manchester Scoring System; Referral Screening Tool; Pedigree Assessment Tool; and Family History Screen-7.

- 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; 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)

Medicare National Coverage
Palmetto’s MolDx Program has determined that BRCA1/BRCA2 targeted mutation analysis (familial or founder mutation), sequencing with common deletion/duplication analysis, and uncommon deletion/duplication analysis meets Medicare criteria for a covered service.(71)

References
1. 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.


Billing Coding/Physician Documentation Information

81162 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (New code 1/1/2016)
81211 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and
ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510 bp, exon 8-9 del 7.1 kb)

81212 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants

81213 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants

81214 BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, 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 BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

81216 BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81217 BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known family variant

ICD-10 Codes

C50.011- C50.929 Malignant neoplasm of nipple and breast, code range
C56.0- C56.9 Malignant neoplasm of ovary; code range
C79.60- C79.62 Secondary malignant neoplasm of ovary, code range
C79.81 Secondary malignant neoplasm of breast
D05.01- D05.99 Carcinoma in situ of breast; code range
D07.30- D07.39 Carcinoma in situ of other and unspecified female genital organs; code range
Z13.71- Z13.79 Encounter for screening for genetic and chromosomal anomalies code range
Z85.3 Personal history of malignant neoplasm of breast, female or male
Z80.3 Family history of malignant neoplasm of breast
Z80.41 Family history of malignant neoplasm of ovary

Effective in 2012, there are specific CPT codes for genetic testing for breast cancer.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

1/1/04 New policy. Added to the Medical and Laboratory sections
1/1/05 No policy statement changes.
1/1/06 No policy statement changes.
1/1/07  No policy statement changes.
1/1/08  No policy statement changes.
1/1/09  Policy title changed to omit “Inherited BRCA1 or BRCA2 Mutations.”
        Policy statements and policy guidelines revised to include men affected
        with breast cancer at any age as medically necessary and women
        affected with both breast and ovarian cancer as medically necessary.
1/1/10  No policy statement changes.
5/1/10  Two policy statements were added: one to indicate testing for genomic
        rearrangements may be considered medically necessary in specific
        situations and a second that testing for CHEK2 mutations is
        investigational.
1/1/11  Fallopian tube cancer and primary peritoneal cancer added to policy
        statements and policy guidelines as additional cancers to be assessed in
        determining family history to assess risk. Previously was included as a
        “note” in the topic coverage section. The policy statement regarding
        testing for genomic rearrangements was revised under option 1 to
        require 3 or more family members (previously was 4 or more family
        members).
1/1/12  Policy statement on CHEK2 testing amended to read: “Testing for
        mutations other than BRCA1 and BRCA2, such as the CHEK2
        abnormality (mutations, deletions, etc.) is considered investigational in
        affected and unaffected patients with breast cancer, irrespective of the
        family history.” Codes updated.
1/1/13  Policy statement edited for clarity and redundancy around epithelial
        ovarian/fallopian tube/primary peritoneal cancer. Additional medical
        necessary statement for testing added for women with breast cancer
        and two or more close relatives with pancreatic cancer. Medically
        necessary testing for rearrangements (BART) changed to remove
        additional criteria required for testing.
1/1/14  Including those with a family history of pancreatic cancer” added to
        investigational policy statement.
5/1/14  Policy updated to replace 2005 USPSTF recommendations with 2013
        USPSTF recommendations; Policy Statement, Description and Rationale
        updated; Considerations rewritten for clarity and updated with current
        NCCN guidelines. Statement about PPACA legislation added to Policy
        section.
1/1/15  CHEK2 eliminated from policy and from policy statements. Testing
        strategy added to Considerations. Title changed to reflect focus on
        hereditary breast and ovarian cancer syndrome (HBOC). Moved
        "Testing for genomic rearrangements of the BRCA1 and BRCA2 genes
        may be considered medically necessary in patients who meet criteria for
        BRCA testing, whose testing for point mutations is negative" to the
        Considerations section.
1/1/16  New CPT code. No policy statement changes.
1/1/17  No policy statement changes.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.