MEDICAL POLICY – 12.04.504
Genetic Testing for Hereditary Breast / Ovarian Cancer Syndrome (BRCA1/BRCA2)

BCBSA Ref. Policy: 2.04.02

Effective Date: Jan. 1, 2017
Last Revised: Nov. 1, 2017
Replaces: N/A

RELATED MEDICAL POLICIES:
12.04.63 Use of Common Genetic Variants (Single Nucleotide Polymorphisms) to Predict Risk of Non-familial Breast Cancer
12.04.93 Genetic Cancer Susceptibility Panels Using Next - Generation Sequencing

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Hereditary breast and ovarian cancer (HBOC) syndrome increases the risk of specific cancers. This syndrome is caused by mutations (changes) to the BRCA1 and BRCA2 genes. The mutations can be passed from parent to child. These mutations increase the risk of breast cancer, ovarian cancer and other cancers related to mutations in the BRCA genes.

This policy describes when genetic testing to look for BRCA1 and BRCA2 mutations is medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
The Policy statements below are based on current guidelines from NCCN (see NCCN Position Statement).

Note that for the purpose of familial assessment, first-, second-, or third-degree relatives are blood relatives on the same side of the family (maternal or paternal). The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medical Necessity</th>
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</thead>
<tbody>
<tr>
<td>Patients with cancer or with personal history of cancer (81211/81212)</td>
<td>Genetic testing for BRCA1 and BRCA2 mutations in cancer-affected individuals may be considered medically necessary under any of the following circumstances:</td>
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<tr>
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<td>• Individual from a family with a known BRCA1/BRA2 mutation</td>
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<td></td>
<td>• Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer</td>
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<td>• Personal history of male breast cancer</td>
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<td>• Personal history of breast cancer and one or more of the following:</td>
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<td>o Diagnosed age ≤45 years</td>
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<td>o Two primary breast cancers (unilateral or bilateral) when first breast cancer diagnosis occurred age ≤50 years</td>
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<td>o Diagnosed age ≤50 years</td>
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<td><strong>AND</strong></td>
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<td>• One or more first-, second-, or third-degree relative with breast cancer, pancreatic cancer or prostate cancer (Gleason 7 and above) at any age</td>
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<td><strong>OR</strong></td>
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<td>• Unknown or limited family history</td>
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<td>o Diagnosed age ≤60 years with a triple negative (ER−, PR−, HER2−) breast cancer</td>
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<td>o Diagnosed any age AND 1 or more first-, second-, or third-degree relatives with breast cancer diagnosed ≤50 years</td>
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<td>o Diagnosed any age AND 2 or more first-, second-, or third-degree relatives with breast cancer at any age</td>
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<td>o Diagnosed any age AND 1 or more first-, second-, or third-degree relatives with epithelial ovarian/fallopian tube/primary peritoneal cancer</td>
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<td>Indication</td>
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|                                                                            | degree relatives with pancreatic cancer or prostate cancer Gleason 7 and above at any age  
  o First-, second-, or third-degree male relative with breast cancer  
  o Ethnicity associated with deleterious founder mutations, e.g., Ashkenazi Jewish descent (testing for Ashkenazi Jewish or other founder mutation[s] (81212)  
  • Personal history of pancreatic cancer or prostate cancer Gleason 7 and above at any age with either:  
    o One or more first-, second-, or third-degree relatives with either ovarian cancer at any age or breast cancer at age 50 or younger  
    OR  
    o Two or more first-, second-, or third-degree relatives with breast, pancreatic cancer, or prostate cancer at any age  
  • Personal history of pancreatic cancer or prostate cancer Gleason 7 and above at any age with two or more first-, second-, or third-degree relatives with breast, pancreatic cancer or prostate cancer at any age.  
  • Personal history of pancreatic cancer and Ashkenazi Jewish ancestry |
|                                                                            | Unless criteria above are met, genetic testing is considered investigational.                                                                                                                                                                                      | Genetic testing for BRCA1 and BRCA2 mutations of cancer-unaffected individuals may be considered medically necessary under either of the following circumstances:  
  • Individual from a family with a known BRCA1/BRCA2 mutation  
  OR  
  • The affected family member is unavailable or unwilling to be tested  
    AND  
    o First- or second-degree blood relative meeting any criterion listed above for patients with cancer  
  OR  
  o Third-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND two |
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<th>Indication</th>
<th>Medical Necessity</th>
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<tbody>
<tr>
<td>or more first-, second-, or third-degree relatives with breast cancer (≥1 at age ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer</td>
<td>Unless criteria above are met, genetic testing is considered investigational.</td>
</tr>
<tr>
<td>Note: Significant limitations of interpreting test results for an unaffected individual should be discussed. Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing. See Testing Unaffected Individuals in Related Information.</td>
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<tr>
<td>BART (BRAC analysis large rearrangement test) (81213)</td>
<td>Testing for genomic rearrangements of the BRCA1 and BRCA2 genes (also known as BART) may be considered medically necessary in patients who meet criteria for BRCA testing AND whose testing for prior mutations (full sequence and common variants) is negative or detects a variant of unknown significance.</td>
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<tr>
<td>Note: Documentation must be submitted indicating that standard BRCA sequence analysis (full sequence and common variants) is negative or detects a variant of unknown significance.</td>
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<tr>
<td>Unless the above criteria are met, BART testing is considered not medically necessary.</td>
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<tr>
<td>Testing of affected family member not covered by plan</td>
<td>Testing of the affected family member not covered by the Plan may be considered medically necessary to provide the medical information necessary for decision making for the unaffected plan member only when all of the following criteria are met:</td>
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<tr>
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<td>• The information is needed to adequately assess risk in the Plan member AND</td>
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<td>• The information will be used in the immediate care plan of the Plan member AND</td>
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<td></td>
<td>• The non-Plan member’s benefit plan (if any) will not cover the test. A copy of the denial letter from the non-Plan member’s benefit plan must be provided.</td>
</tr>
</tbody>
</table>
### Indication

**Medical Necessity**

Unless criteria above are met genetic testing is considered not medically necessary.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81162</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis</td>
</tr>
<tr>
<td>81211</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1</td>
</tr>
<tr>
<td>81212</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delIT variants</td>
</tr>
<tr>
<td>81213</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants [BART]</td>
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<tr>
<td>81214</td>
<td>BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
</tr>
<tr>
<td>81215</td>
<td>BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81216</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81217</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
</tr>
</tbody>
</table>

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### Related Information
Definition of Terms

First-, second-, or third-degree relative: For the purpose of familial assessment, first-, second-, or third-degree relatives are blood relatives on the same side of the family (maternal or paternal). The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

- First-degree relatives are parents, siblings, and children.
- Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- Third-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

Unknown or limited family history: Limited family history represents fewer than two first- or second-degree female relatives having lived beyond age 45 in either lineage. (Age 45 years was selected based on the expected age-specific penetrance of disease in BRCA mutation carriers.) Cause of death at age 45 or younger does not need to be known. Unknown family history is typically because of adoption.

Background

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, 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. 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 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.

**Suggested Testing Strategy**

It is suggested that patients who meet criteria for genetic testing as outlined in the Policy statements above 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 (e.g., prostate cancer, pancreatic cancer, melanoma).
  - If no familial mutation can be identified, two possible testing strategies are:
    a) 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.\(^4\)
    b) 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 (e.g., BART™) may be done.
  
  a) 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 or other known Founder Mutation restricted groups (81212)
  
  - In patients of known groups at risk for Founder Mutations, such as Ashkenazi Jewish descent, the recommendation is to test first for the known founder mutations, for example, in Ashkenazi patients testing for 185delAG and 5182insC in BRCA1; 6174delT in BRCA2).

  - If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Mutation Analysis, below).

### Comprehensive Mutation Analysis and BRAC Analysis Large Rearrangement Test (BART)

Genetic testing should be performed in a setting that has suitably trained healthcare providers who can give appropriate pretest and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments (CLIA)-licensed laboratory that offers 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 such as BART 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 Policy Coverage 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 Evidence). When testing for founder mutations is negative, comprehensive mutation analysis should then be performed.

Note: Founder mutations are associated with certain ethnic backgrounds and are not necessarily tied to specific countries. Requests for founder mutation testing other than Ashkenazi Jewish heritage will be considered on a case-by-case basis.

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 considered sufficient justification for BRCA testing.

Evidence Review
Evidence

This medical policy was developed following a 1997 TEC Assessment 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.

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.6 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.7 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 BRCA1 mutation carriers, and 33% and 76%, respectively, for BRCA2 mutation carriers; for breast cancer only, cumulative risks were 41% and 60%, respectively, for BRCA1 mutation carriers, and 26% and 40%, respectively, for BRCA2 mutation carriers; for ovarian cancer only, cumulative risks were 27% and 53%, respectively, for BRCA1 mutation carriers, and 17% and 30%, respectively, for BRCA2 mutation carriers.)
Carriers, and 7% and 62%, respectively, for BRCA2 mutation carriers. Among 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, e.g., 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 BRCA1/BRCA2 mutation status. 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 BRCA1/BRCA2 mutation carriers identified through population screening who may not have developed cancer constitutes a net health benefit.

Early estimates of lifetime risk of cancer for 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. Studies of founder mutations in ethnic populations (e.g., Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history indicated lower penetrance estimates, in the range of 40% to 60% for BRCA1 and 25% to 40% for BRCA2. 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 BRCA founder mutations (185delAG, 5382insC, 6174delT). 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 BRCA1 and 23% for BRCA2 mutation carriers.

Women with a history of breast cancer and a 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. In a 2013 prospective study (EMBRACE), the cumulative risk of contralateral breast cancer by age 70 years was 83% in BRCA1 mutation carriers and 62% for BRCA2 mutation carriers. These investigators also reported cumulative risks of breast cancer by age 70 years in women without previous cancer of 60% in BRCA1 carriers and 55% in BRCA2 carriers. Similarly, the cumulative risks of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for BRCA1 carriers and 17% for BRCA2 carriers.

Thus, the risk of cancer in a BRCA mutation carrier is significant, and knowledge of mutation status in individuals at potentially increased risk of a BRCA mutation may impact healthcare decisions to reduce risk. Risk-reducing options include intensive surveillance, 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. Prophylactic oophorectomy significantly reduces the risk of ovarian cancer to less than 10% and reduces the risk of breast cancer by approximately 50%. In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse. Studies indicate that genotyping results significantly influence treatment choices.

### Prevalence of BRCA Mutations

Nelson et al included meta-analysis estimates of BRCA prevalence in their 2013 systematic review for USPSTF. 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 (e.g., 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. 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 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). In cancer-prone families, the mean age of breast cancer diagnosis among women carrying BRCA1 or BRCA2 mutations is in the 40s. In the Ashkenazi Jewish population, Frank et al 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. 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.  

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. 

In patients with breast cancer that is “triple-negative,” i.e., 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. In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, there was a greater than threefold 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 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. 

**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 frame shift 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. 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, i.e., 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. Couch et al 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 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%. 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%. 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.

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. 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 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. 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. 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. Rennert et al (2007) reported that breast cancer-specific rates of death among Israeli women were similar for carriers of a BRCA founder mutation and noncarriers.

Lesnock et al (2013) compared OS in 393 women with BRCA1-mutated and BRCA1-nonmutated epithelial ovarian cancer who were treated with intraperitoneal or intravenous-only chemotherapy. All patients had “optimally resected” (<1 cm residual disease) stage III disease. 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 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 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 BRCA-positive women. 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; salpingo-oophorectomy 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 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.

BRCA Mutation Associated with Prostate Cancer

A number of studies have indicated that 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 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).52 In a similar population of 251 Ashkenazi Jewish men with prostate cancer and 1472 volunteers without prostate cancer, the presence of a BRCA mutation was associated with a more than threefold increased risk of prostate cancer (OR=3.41; 95% CI: 1.64 to 7.06).53 When analyzed by type of BRCA mutation, BRCA2 was associated with an almost 5-fold increased risk (OR=4.82; 95% CI: 1.87 to 12.25), and BRCA1 mutations were not associated with an increased risk (OR=2.20; 95% CI: 0.72 to 6.70). A 2013 retrospective analysis compared prostate cancer outcomes in 79 BRCA mutation carriers (18 BRCA1, 61 BRCA2) and 2019 noncarriers.54 Men with 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) then 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.55 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 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

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.”66 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 BRCA2.67 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%.68 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.69 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—e.g., understanding of information before and after testing; disparities in experiences related to BRCA testing (e.g., in access to information, services, or care); perceived risks of developing cancer; intentions for risk management (e.g., 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. Name Active Trials of BRCA Mutation Testing Listed at ClinicalTrials.gov

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02133703</td>
<td>Decision Support Following Genetic Testing for Breast-Ovarian Cancer Susceptibility</td>
<td>600</td>
<td>Jul 2017</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>NCT01851109</td>
<td>Prevention of Ovarian Cancer in Women Participating in Mammography</td>
<td>458</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>NCT02225015</td>
<td>Cancer Prevention in Women With a BRCA Mutation</td>
<td>500</td>
<td>Jan 2018</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>
</tbody>
</table>

*Expected

*Estimated

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.

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.

The ages described in the policy statements are based on current guidelines from the National Comprehensive Cancer Network.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The current NCCN guideline for Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer (version 2.2015) includes criteria for identifying individuals who should be referred for further risk assessment, and separate criteria for genetic testing. Patients who satisfy any of the testing criteria listed in Table 2 should undergo “further personalized risk assessment, genetic counseling, and often genetic testing and management.”1 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.”1
Table 2. 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>NCCN1</th>
<th>SGO66</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Individual from a family with a known BRCA1/BRCA2 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>✓ ✓</td>
</tr>
<tr>
<td>c) Diagnosed age ≤50 years AND:</td>
<td></td>
</tr>
<tr>
<td>i. One or more first-, second-, or third-degree relative(^a) with breast cancer at any age, or</td>
<td>✓</td>
</tr>
<tr>
<td>ii. Unknown or limited family history(^b)</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 first-, second-, or third-degree relatives(^a) with breast cancer diagnosed ≤50 years</td>
<td>✓</td>
</tr>
<tr>
<td>f) Diagnosed any age AND two or more first-, second-, or third-degree relatives(^a) with breast cancer at any age</td>
<td>✓</td>
</tr>
<tr>
<td>g) Diagnosed any age AND one or more first-, second-, or third-degree relative(^a) with epithelial ovarian/fallopian tube/primary peritoneal CA</td>
<td>✓</td>
</tr>
<tr>
<td>h) Diagnosed any age AND TWO OR MORE first-, second-, or third-degree relatives(^a) with pancreatic cancer or prostate cancer(^c) at any age</td>
<td>✓</td>
</tr>
<tr>
<td>i) first-, second-, or third-degree male relative with breast cancer</td>
<td>✓</td>
</tr>
<tr>
<td>j) For individual of ethnicity associated with increased mutation frequency (e.g., Ashkenazi Jewish), no additional family history may be required(^d)</td>
<td>✓</td>
</tr>
<tr>
<td>3. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer</td>
<td>✓</td>
</tr>
<tr>
<td>4. Personal history of male breast cancer</td>
<td>✓</td>
</tr>
<tr>
<td>5. Personal history of pancreatic cancer or prostate cancer(^f) at any age AND two or more first-, second-, or third-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>
<td>✓ ✓</td>
</tr>
<tr>
<td>a) Breast cancer</td>
<td>✓</td>
</tr>
<tr>
<td>b) Ovarian/fallopian tube/primary peritoneal cancer</td>
<td>✓</td>
</tr>
<tr>
<td>c) Pancreatic or prostate cancer(^c)</td>
<td>✓</td>
</tr>
<tr>
<td>6. Family history(^g):</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Includes breast cancer in female and breast cancer in male. 

\(^{b}\) Includes breast cancer in female and breast cancer in male. 

\(^{c}\) Includes breast cancer in female and breast cancer in male. 

\(^{d}\) Includes breast cancer in female and breast cancer in male. 

\(^{e}\) Includes breast cancer in female and breast cancer in male. 

\(^{f}\) Includes breast cancer in female and breast cancer in male. 

\(^{g}\) Includes breast cancer in female and breast cancer in male.

\(^{h}\) Includes breast cancer in female and breast cancer in male.
NCCN1

<table>
<thead>
<tr>
<th>a)</th>
<th>first- or second-degree blood relative meeting any of the above criteria</th>
<th>SGO66</th>
</tr>
</thead>
<tbody>
<tr>
<td>b)</td>
<td>third-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND ≥2 first-, second-, or third-degree relatives with breast cancer (≥1 at age ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer</td>
<td>✓/h</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.
h 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 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.”

American College of Medical Genetics

In 1999, the American College of Medical Genetics (ACMG) 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. 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, e.g., 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 (USPSTF) Recommendations

Population – Women who have family members with breast, ovarian, tubal, or peritoneal cancer

The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 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).

Population – Women whose family history is not associated with an increased risk

The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1 or BRCA2 genes (Grade D recommendation).
Several risk tools are available. The USPSTF 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)

The USPSTF recognizes that each risk assessment tool has limitations and found insufficient comparative evidence to recommend one tool over another.

To determine which patients would benefit from BRCA risk assessment, primary care providers should not use general breast cancer risk assessment models (for example, the National Cancer Institute Breast Cancer Risk Assessment Tool, which is based on the Gail model) because they are not designed to determine which women should receive genetic counseling or BRCA testing.

**Medicare National Coverage**

Palmetto’s MoIDx Program has determined that BRCA1/BRCAX 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.73

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Per the genetests.org website, there are currently 6 CLIA-certified U.S. laboratories that offer sequence analysis of the entire coding and 4 that offer deletion/duplication/copy number analysis. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.
Myriad Genetic Laboratories (Salt Lake City, UT) offers (1) Comprehensive BRACAnalysis® that includes complete sequencing of BRCA1/BRCA2 and gap polymerase chain reaction for 5 common rearrangements (deletions/duplications) in BRCA1; (2) BRACAnalysis® Large Rearrangement Test (BART™), which may be ordered as a reflex for patients who test negative for Comprehensive BRACAnalysis® to detect uncommon large rearrangements in BRCA1 and BRCA2; and (3) Integrated BRACAnalysis®, which includes BART as part of BRCA1/BRCA2 analysis.

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

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

References

5. 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. PMID


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/08/05</td>
<td>New PR Policy – PR.2.04.504Replace Policy – Replace Policy-instituted. Replaces BC.2.04.02</td>
</tr>
<tr>
<td>02/14/06</td>
<td>Replace Policy – Policy reviewed with literature search; no change to policy statement.</td>
</tr>
<tr>
<td>02/22/06</td>
<td>Codes updated – No other changes, effective date unchanged.</td>
</tr>
<tr>
<td>06/30/06</td>
<td>Update Scope and Disclaimer – No other changes.</td>
</tr>
<tr>
<td>01/04/06</td>
<td>Replace Policy – Policy updated with literature review; reference added. No change in policy statement.</td>
</tr>
<tr>
<td>02/13/07</td>
<td>Replace Policy – Policy updated with literature review; references added. No change in policy statement.</td>
</tr>
<tr>
<td>03/13/07</td>
<td>Replace Policy – Explanation of BART test, as subset of BRCA, added to Policy Guidelines.</td>
</tr>
<tr>
<td>03/21/07</td>
<td>Codes Updated – No other changes.</td>
</tr>
<tr>
<td>05/08/07</td>
<td>Replace Policy – Policy statement clarified with substitution of ACMG criteria.</td>
</tr>
<tr>
<td>07/10/07</td>
<td>Cross Reference Update – No other changes.</td>
</tr>
<tr>
<td>06/10/08</td>
<td>Replace Policy – Policy updated with literature search. Policy statement modified to reflect USPTF guidelines: High risk age changed from &lt;45 to &lt;50, family history of ovarian cancer decreased from 3 to 2 relatives, Ashkenazi heritage added to criteria of those with breast or ovarian cancer. Revision of investigational statement to include assessment of risk of pancreatic, prostate and colon cancer. Rationale and References updated. Reviewed and recommended for adoption by Oncology Advisory Panel, May 22, 2008.</td>
</tr>
<tr>
<td>12/08/09</td>
<td>Replace Policy – Policy updated with literature search. Reference added. No change to the policy statement.</td>
</tr>
<tr>
<td>04/13/10</td>
<td>Replace Policy – Policy updated with literature search, references added, clinical input reviewed. Two policy statements added: one to indicate testing for genomic rearrangements (BART) may be considered medically necessary in specific situations and a second that testing for CHEK2 mutations in investigational. Fallopian tube and primary peritoneal cancer added to ovarian as additional cancers to consider in assessing risk. Reviewed by OAP on February 18, 2010.</td>
</tr>
<tr>
<td>02/17/11</td>
<td>OAP Review – Reviewed by OAP with recommendation of changing CHEK2 from investigational to medically necessary</td>
</tr>
<tr>
<td>05/10/11</td>
<td>Replace Policy – Policy updated with literature search, references added, clinical input reviewed. No change to the policy statement. CHEK2 remains investigational.</td>
</tr>
<tr>
<td>01/24/12</td>
<td>CPT codes 81211 – 81217 added to policy.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>04/16/12</td>
<td>Related Policies updated: 2.01.45 and 7.01.09 removed, as these have been archived.</td>
</tr>
<tr>
<td>05/08/12</td>
<td>Replace Policy. Policy updated with literature search, references added. Policy statement revised to indicate that BRCA testing may be considered medically necessary for women with a personal history of ovarian, fallopian tube, peritoneal cancer, triple negative breast cancer and pancreatic cancer when criteria are met. Also, BRCA testing may be considered medically necessary for women with breast cancer with a family history of 2 or more first degree relatives with pancreatic cancer. Clarification added to Guidelines regarding founder mutations.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.504 (previously 2.04.504) and reassigned to new Genetic Testing category. Related Policies updated; 2.04.57 renumbered to 12.04.57.</td>
</tr>
<tr>
<td>07/25/12</td>
<td>Update Related Policies – 12.04.63 has been added.</td>
</tr>
<tr>
<td>09/10/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>10/15/12</td>
<td>Replace Policy. Two bullets in &quot;No personal history&quot; section of policy statement re-worded to clarify intent. No functional change to the policy statement.</td>
</tr>
<tr>
<td>01/14/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
</tr>
<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>06/10/13</td>
<td>Interim update. Benefit Application section updated with federal preventative care mandate language which covers genetic counseling and evaluation for BRCA testing within the outlined patient population. No change in policy statements.</td>
</tr>
<tr>
<td>08/12/13</td>
<td>Replace policy. “One first degree relative with bilateral breast cancer” added to Personal History section for clarification of policy statement. Clarification added to Guidelines that the presence of prostate cancer alone does not justify BRCA testing. Prostate cancer studies added to Rationale. NCCN v4.2013 revisions to criteria for mutation testing and CHEK2 testing added to Rationale.</td>
</tr>
<tr>
<td>01/13/14</td>
<td>Replace policy. Policy statement revised to allow testing for unaffected individuals not meeting criteria in Personal History or No Personal History section when additional criteria are met. In limited circumstances, a non-Plan affected family member may qualify for BRCA testing. Notation added to indicate that NCCN guidelines are provided for informational purposes only and are not meant to replace the criteria in the policy statement. Definition of “close blood relative” added. Title changed, removing “BRCA1 and BRCA2 Mutations” to “Hereditary Breast and/or Ovarian Cancer”. USPSTF 2013 Recommendations added to Rationale. Deleted CPT codes 83890 – 83912 removed; 81479 and 81599 removed (they refer to a different policy); modifiers 0A and 0B removed, along with ICD-9 procedure code 99.99 (this policy is not auto adjudicated); and deleted HCPCS codes S3818 - S3823 removed from policy.</td>
</tr>
<tr>
<td>06/27/14</td>
<td>Update Related Policies. Remove 12.04.57 as it was deleted.</td>
</tr>
<tr>
<td>07/24/14</td>
<td>Update Related Policies. Remove 12.04.91.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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</tr>
<tr>
<td>05/12/15</td>
<td>Annual review. Policy statement extensively revised based on guidelines from NCCN. Information on BART retained and CHEK2 deleted. Reference to “early age” deleted and replaced by criteria-specific ages. Clarification added regarding family lineage and founder mutations. Qualifying criteria added regarding prostate cancer. Rationale and References revised.</td>
</tr>
<tr>
<td>06/16/15</td>
<td>Clarification only. Policy section reformatted to provide improved clarity; no change in content, additions or deletions.</td>
</tr>
<tr>
<td>02/09/16</td>
<td>Annual Review. Policy updated with literature review through October 7, 2015; no references added. Policy statement regarding BART clarified; documentation must be submitted indicating that patient met criteria for BRCA testing and that standard BRCA sequence analysis was negative. Unless those criteria are met, BART is considered not medically necessary. Coding update – New CPT code 81162, effective 1/1/16, added to policy.</td>
</tr>
<tr>
<td>05/04/16</td>
<td>Update related policies. Policy 7.01.09 was deleted and replaced with policy 7.01.561.</td>
</tr>
<tr>
<td>11/01/16</td>
<td>Interim Update, approved October 11, 2016. Policy statement regarding pancreatic and prostate cancer revised to reflect current NCCN guidelines. Clarification of the definitions of unknown or limited family history. Policy moved into new format: removed repeated content and reordered some content in Related Information and Evidence sections.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Interim review, approved December 13, 2016. Language added to Evidence Review section to indicate the ages described in the policy statements are based on current guidelines from the NCCN. Policy statement revised: Moved clarification note regarding familial assessment to top of Policy Coverage criteria and added language of medical necessity for BART when comprehensive testing is negative or VUS detected. Testing of 3 variants of common founder mutations (CPT 81212) clarified: It is recommended, although not required, that those with a personal history of breast cancer and of Ashkenazi Jewish descent be tested for the common founder mutations before proceeding to comprehensive testing.</td>
</tr>
<tr>
<td>03/01/17</td>
<td>Updated Related Policies, removed 12.04.516 as it was deleted (contents moved to 12.04.126).</td>
</tr>
<tr>
<td>03/07/17</td>
<td>Minor formatting update.</td>
</tr>
<tr>
<td>06/01/17</td>
<td>Minor edit, reformatted bullets in the Policy Criteria section for clarity.</td>
</tr>
<tr>
<td>11/01/17</td>
<td>Updated Related Policies, removed 7.01.561 as it was archived.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review
and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHQ Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Deutsche (German):

Iloko (Ilocano):

Italiano (Italian):
اللغة العربية (Arabic):
هذا الإشعار يحتوي على معلومات قيمة. إذا كنت في حاجة إلى تأكيد الممتلكات المنزلية الخاصة بك، قد تحتاج إلى استخدام رقم 800-722-1471 (TTY: 800-842-5357). الرجاء الاتصال بمكتب الرعاية الصحية الخاص بك.

اللغة الإسبانية (Spanish):
Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

اللغة البولندية (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie podmiotu wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanych z kosztami. Macie prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

اللغة البلجيكية (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

اللغة الفرنسية (French):

اللغة الروسية (Russian):
Есть важная информация. Это уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

اللغة الأوكرانية (Ukrainian):
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اللغة البولندية (Polish):

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اللغة العربية (Arabic):