Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers

Policy Number: 2.04.02  Last Review: 1/2019

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 post-test 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 or With Personal History of Cancer
Genetic testing for BRCA1 and BRCA2 variants in cancer-affected individuals may be considered medically necessary under any of the following circumstances:

- Individual from a family with a known BRCA1 or BRCA2 variant
- Personal history of breast cancer and one or more of the following:
  - Diagnosed at age ≤45 years
  - Diagnosed 46 to 50 years with:
    - An additional breast cancer primary at any age
    - ≥1 close relative with breast cancer at any age
    - ≥1 close relative with high grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history
  - Diagnosed ≤60 years with:
    - Triple-negative breast cancer
Diagnosed at any age with:
- ≥1 close blood relative with:
  - Breast cancer diagnosed ≤50 years; or
  - Ovarian carcinoma; or
  - Male breast cancer; or
  - Metastatic prostate cancer; or
  - Pancreatic cancer
- ≥2 additional diagnoses of breast cancer at any age in patient and/or close blood relative
  - Ashkenazi Jewish ancestry
- Personal history of ovarian carcinoma
- Personal history of male breast cancer
- Personal history of pancreatic cancer
- Personal history of metastatic prostate cancer
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:
  - ≥1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer <50 years; or
  - ≥2 close blood relatives with breast or prostate cancer (any grade) at any age; or
  - Ashkenazi Jewish ancestry
- BRCA1 or BRCA2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic or likely pathogenic variant analysis
- Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood relatives meeting any of the above criteria.

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

Genetic testing for BRCA1 and BRCA2 variants of cancer-unaffected individuals may be considered medically necessary under any of the following circumstances:
- Individual from a family with a known BRCA1/BRCA2 variant
- 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

a For 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.

*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**
Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met is considered *investigational*.

Genetic testing in minors for BRCA1 and BRCA2 variants is *investigational*.

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

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 variants in *BRCA1* and *BRCA2*.
- In patients with a known familial *BRCA* variant, targeted testing for the specific variant is recommended.
- In patients with unknown familial *BRCA* variant:
  - Non-Ashkenazi Jewish descent
    - To identify clinically significant variant, 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 \textit{BRCA1/BRCA2} variants (eg, prostate cancer, pancreatic cancer, melanoma).

- If no familial variant 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 variant (negative result).
    - More than 90\% of \textit{BRCA} variants will be detected by full sequencing.
  - Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive \textit{BRCA} testing; see Comprehensive Mutation Analysis, below) may be performed as is recommended by NCCN.
    - Comprehensive testing can detect 92.5\% of \textit{BRCA1/BRCA2} variants.

- If comprehensive \textit{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 variant (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 \textit{BRCA1}; 6174delT in \textit{BRCA2}) first.
    - If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Variant Analysis, below).

\textbf{Comprehensive Mutation Analysis}

Comprehensive variant 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 \textit{BRCA} testing before this time may consider repeat testing for the rearrangements (see Considerations for criteria).

\textbf{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 variants. For example, founder mutations account for approximately three quarters of the \textit{BRCA} mutations found in Ashkenazi Jewish populations (see
Rationale). When testing for founder mutations is negative, comprehensive variant 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 variant 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 variant but leads to difficulties in interpreting negative test results (uninformative negative) or mutations of uncertain significance because the possibility of a causative BRCA variant is not ruled out.

**Testing Minors**
The use of genetic testing for BRCA variants 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 variant. In addition, there are potential harms related to stigmatization and discrimination.

**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**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<tr>
<td>• With cancer or personal or family cancer history and</td>
<td>• Genetic testing for a BRCA1 or</td>
<td>• Standard of care without</td>
<td>• Overall survival</td>
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<td>• Disease-specific survival</td>
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<td>• Test validity</td>
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criteria suggesting risk of hereditary breast/ovarian cancer syndrome | BRCA2 variant | genetic testing | • Quality of life
---|---|---|---
Individuals:  
• With other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate) | Interventions of interest are:  
• Genetic testing for a BRCA1 or BRCA2 variant | Comparators of interest are:  
• Standard of care without genetic testing | Relevant outcomes include:  
• Overall survival  
• Disease-specific survival  
• Test validity  
• Quality of life

Hereditary breast and ovarian cancer syndrome describes the familial cancer syndromes related to variants in the \textit{BRCA} genes (\textit{BRCA1} located on chromosome 17q21, \textit{BRCA2} located on chromosome 13q12-13). Families with hereditary breast and ovarian cancer syndrome have an increased susceptibility to the following types of cancer: breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer (at any age), cancer of the fallopian tube, primary peritoneal cancer, prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer syndrome who receive genetic testing for a \textit{BRCA1} or \textit{BRCA2} variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a \textit{BRCA} variant have shown a risk as high as 85%. Knowledge of \textit{BRCA} variant status in individuals at risk of a \textit{BRCA} variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with \textit{BRCA1} or \textit{BRCA2} variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and overall survival. Knowledge of \textit{BRCA} variant status in individuals diagnosed with breast cancer may impact treatment decisions. A randomized controlled trial has reported that patients with human epidermal growth factor receptor 2–negative metastatic breast cancer and a \textit{BRCA} variant experienced significantly longer progression-free survival with a targeted therapy vs standard therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate) who receive genetic testing for a \textit{BRCA1} or \textit{BRCA2} variant, the evidence includes studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Knowledge of \textit{BRCA} variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
**Background**

**Hereditary Breast and Ovarian Cancer Syndrome**

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative variants 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 evidence review, BCBSA refers collectively to both as *hereditary breast and/or ovarian cancer*.

Germline variants 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 cancer, *BRCA* variants are responsible only for a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members at increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

**Clinical Features Suggestive of BRCA Variant**

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30. In several studies, *BRCA* variants were 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* variants is in the 40s. In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* variants. In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants. Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of *BRCA* variants 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* variant in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a *BRCA* variant.
depending on the extent and nature of the family history. Several other studies have documented the significant influence of family history.

In patients with “triple-negative” breast cancer (ie, negative for expression of estrogen, progesterone, and overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of BRCA variants. 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, Kandel et al (2006) reported there was a greater than 3-fold increase in the expected rate of BRCA variants. BRCA1 variants were found in 39.1% of patients and BRCA2 variants in 8.7%. Young et al (2009) 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. Six BRCA variants (5 BRCA1, 1 BRCA2) were found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had BRCA variants (12 in BRCA1, 3 in BRCA2).

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 offers the following tests:

- Comprehensive BRACAnalysis® test includes complete sequencing of BRCA1 and BRCA2 and gap polymerase chain reaction for 5 common rearrangements (deletions, duplications) in BRCA1
- BRACAnalysis® Large Rearrangement Test (BART™) is a reflex test for patients who test negative on the Comprehensive BRACAnalysis® test to detect uncommon large rearrangements in BRCA1 and BRCA2
- Integrated BRACAnalysis® test includes BART™ as part of BRCA1 or BRCA2 analysis
- BRACAnalysis CDxs® is intended to detect germline BRCA1 and BRCA2 variants to identify patients with breast or ovarian cancer who may be considered for treatment with olaparib, niraparib, or talazoparib.

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

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

**Rationale**

This evidence review was created in July 1997 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through September 4, 2018.

This review was informed by a TEC Assessment (1997).15

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Testing for BRCA1 and BRCA2 variants in INDIVIDUALS at risk for Hereditary breast/ovarian cancer syndrome or other high-risk cancers**

**Clinical Context and Test Purpose**

The purpose of testing for BRCA1 and BRCA2 variants in individuals at high-risk for hereditary breast and ovarian cancer (HBOC) syndrome is to evaluate whether variants are present and, if so, to determine the appropriate surveillance and treatment to decrease the risk of mortality from breast and/or ovarian cancer.

The question addressed in this evidence review is: Does testing for BRCA1 and BRCA2 variants improve the net health outcome in individuals with or suspected of having HBOC syndrome or other high-risk cancers?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest is patients with cancer (ie, breast cancer, epithelial ovarian, fallopian tube, primary peritoneal cancer), or patients with a personal or family history of cancer and criteria that might suggest they are at risk of HBOC syndrome.
**Intervention**
The intervention of interest is *BRCA1* and *BRCA2* variant testing.

For patients without a cancer diagnosis who are assessing cancer risk, results may guide potential prophylactic measures such as surveillance, chemoprevention, or prophylactic mastectomy, and/or oophorectomy.

For patients with a cancer diagnosis, results may guide treatment decisions.

**Comparator**
The following practice is currently being used to manage HBOC syndrome or other high-risk cancers: standard of care without genetic testing.

**Outcomes**
The outcomes of interest are overall survival, disease-specific (breast and ovarian cancer) survival, test validity, and quality of life (e.g., anxiety).

**Timing**
Testing for *BRCA1* and *BRCA2* variants is conducted in adults when appropriate treatment and/or prophylactic treatment options are available.

**Setting**
Variant testing is offered in a primary care setting (e.g., for people without cancer) or the specialty setting (e.g., multidisciplinary oncology care) through various test manufacturers and institutions.

**Study Selection Criteria**
For the evaluation of clinical validity, studies of variant prevalence and cancer risk were included. For the evaluation of clinical utility, studies that represent the intended clinical use of the technology in the intended population were included. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings.

Evidence for the 2 indications is presented together because there is overlap in the evidence base for the 2 populations: (1) patients at risk of HBOC syndrome, and (2) patients with other high-risk cancers such as cancers of the fallopian tube, pancreas, and prostate.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
Prevalence of BRCA Variants and Risks of Cancer and Survival

The prevalence of BRCA variants is approximately 0.1% to 0.2% in the general population. The 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 variant; additionally, age and ethnicity could be independent risk factors.

Systematic Reviews

A systematic review published by Zhu et al (2016) found a significantly lower risk of overall survival in breast cancer patients with BRCA1 (pooled hazard ratio, 1.69; 95% confidence interval, 1.35 to 2.12) and with BRCA2 (pooled hazard ratio, 1.50; 95% confidence interval, 1.02 to 2.09; p=0.034). However, in patients with breast cancer, BRCA1 and BRCA2 were not associated with a lower breast cancer–specific survival.

Nelson et al (2013) conducted a systematic review that included meta-analytic estimates of the prevalence and penetrance of BRCA variants; this review was used to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for BRCA-related cancer. 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 was tested, and 70% for BRCA1 and 71% for BRCA2 when multiple family members were tested; cumulative risks for developing ovarian cancer by age 70 were 41% for BRCA1 and 17% for BRCA2 when a single family member was tested; and 46% for BRCA1 and 23% for BRCA2 when multiple family members were 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. Nelson et al included meta-analytic estimates of BRCA prevalence in their review for USPSTF. In unselected women, BRCA variant 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%.

Estimates of lifetime risk of cancer for BRCA variant carriers (penetrance), based on studies of families with an extensive history of the disease, have been as high as 85%. For example, Kuchenbaecker et al (2017) found that the cumulative risk of breast cancer up to age 80 was 72% in BRCA1 carriers and 69% in BRCA2 carriers. 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 have 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).\textsuperscript{22} Importantly, the risk of cancer in variant carriers from families with little history of cancer (≈50% of all carriers) did not differ significantly. Lifetime risk estimates of ovarian cancer were 54% for BRCA1 and 23% for BRCA2 variant carriers.

**Prospective Studies**

Women with a history of breast cancer and a BRCA variant have a significant risk of contralateral breast cancer. In a prospective study by Metcalfe et al (2004), the 10-year risk was 29.5% for women with initial stage I or II diseases.\textsuperscript{23} In a prospective study, Epidemiological Study of Familial Breast Cancer, Mavaddat et al (2013) reported that the cumulative risk of contralateral breast cancer by age 70 years was 83% in BRCA1 variant carriers, and 62% for BRCA2 variant carriers.\textsuperscript{24} These investigators also reported cumulative risks of breast cancer by age 70 in women without previous cancer (60% in BRCA1 carriers, 55% in BRCA2 carriers). Similarly, the cumulative risk estimates of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for BRCA1 carriers and 17% for BRCA2 carriers.

**BRCA Variant Rates Associated With Ovarian Cancer**

Women with a personal history of ovarian cancer have an increased rate of BRCA variants. In a systematic review of 23 studies, Trainer et al (2010) estimated the rate of BRCA variants among women with ovarian cancer to be 3% to 15%.\textsuperscript{25} In this review, 3 U.S. studies tested for both BRCA1 and BRCA2; incidences of BRCA variants were 11.3%, 15.3%, and 9.5%. In the systematic review for USPSTF by Nelson et al (2013), meta-analytic estimates of BRCA prevalence among women with ovarian cancer were 4.4% for BRCA1 and 5.6% for BRCA2.\textsuperscript{17} Table 1 lists results from several additional studies measuring the presence of BRCA variants among patients with ovarian cancer.\textsuperscript{26-30} One study noted that variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%).\textsuperscript{26} Ethnicity was another risk factor for BRCA, with higher rates seen in women of Italian (43.5%), Jewish (30%), and Indo-Pakistani (29.4%) origin.\textsuperscript{26}

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>BRCA Variant, n (%)</th>
<th>BRCA1</th>
<th>BRCA2</th>
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<tbody>
<tr>
<td>Harter et al</td>
<td>Patients with invasive ovarian cancer across 20 medical centers</td>
<td>523</td>
<td>81 (15.5)</td>
<td>29 (5.5)</td>
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<td>(2017)\textsuperscript{30}</td>
<td></td>
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<td>Kurian et al</td>
<td>Patients with invasive ovarian cancer tested for hereditary cancer risk from a commercial laboratory database</td>
<td>5020\textsuperscript{a}</td>
<td>255 (15.5)</td>
<td>199 (5.5)</td>
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<td>(2017)\textsuperscript{27}</td>
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<td>Langer et al</td>
<td>Patients with ovarian cancer tested for hereditary cancer risk from a commercial laboratory database</td>
<td>3088</td>
<td>153 (4.9)</td>
<td>124 (4.0)</td>
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<td>Norquists et al</td>
<td>Patients with invasive ovarian cancer, from 2 phase 3 clinical trials and a gynecologic oncology tissue bank</td>
<td>1915</td>
<td>182 (9.5)</td>
<td>98 (5.1)</td>
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<td>Zhang et al</td>
<td>Patients with invasive ovarian cancer</td>
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<td>107 (8.0)</td>
<td>67 (5.0)</td>
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<td>(2011)\textsuperscript{26}</td>
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Total N was reported as 5020, however, the percentage of BRCA variants as reported in article is inconsistent with 5020 as the denominator.

**BRCA Variant Rates Associated With Fallopian Tube Cancer**

A study by Hirst et al (2009) 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%) had fallopian tube malignancies. Reviewers noted that these findings supported other studies that have demonstrated the fimbrial end of the fallopian tube as an important site of cancer in those with BRCA1 or BRCA2 variants.

A long-term study by Powell et al (2013; median follow-up, 7 years; range, 3-14 years) followed 32 BRCA variant carriers with occult malignancy (4 ovarian, 23 fallopian tube, 5 ovarian and fallopian tube) diagnosed of 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 was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One (6%) patient who did not receive chemotherapy experienced recurrence at 43 months. Overall survival was 100%. The authors concluded that, in BRCA variant carriers, unsuspected invasive carcinoma has a relatively high rate of recurrence, but noninvasive neoplasms rarely recur and may not require adjuvant chemotherapy.

**BRCA Variant Rates 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 variant by 3.5- to 10-fold over the general population. Table 2 lists results from several studies measuring the presence of BRCA variants among patients with pancreatic adenocarcinoma. Patients with pancreatic adenocarcinoma of Jewish descent appear to have a higher prevalence of BRCA variants compared with the general population of patients with pancreatic adenocarcinoma.

### Table 2. BRCA Variant Rates in Patients With Pancreatic Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>BRCA Variant, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al (2018)</td>
<td>Patients with pancreatic adenocarcinoma from a prospective pancreatic cancer registry</td>
<td>3030</td>
<td>18 (0.6) 59 (1.9)</td>
</tr>
<tr>
<td>Yurgelun et al (2018)</td>
<td>Patients with pancreatic adenocarcinoma from 3 medical centers</td>
<td>289</td>
<td>3 (1.0) 4 (1.4)</td>
</tr>
<tr>
<td>Shindo et al (2017)</td>
<td>Patients with pancreatic adenocarcinoma from 1 medical center</td>
<td>854</td>
<td>3 (0.3) 12 (1.4)</td>
</tr>
<tr>
<td>Holter et al (2015)</td>
<td>Patients with pancreatic adenocarcinoma from a large academic health care complex</td>
<td>306</td>
<td>3 (1.0) 11 (3.6)</td>
</tr>
<tr>
<td>Ferrone et al (2009)</td>
<td>Jewish patients with pancreatic adenocarcinoma from 1 hospital</td>
<td>145</td>
<td>2 (1.3) 6 (4.1)</td>
</tr>
<tr>
<td>Couch et al (2007)</td>
<td>Probands from high-risk families identified through pancreatic cancer clinics and a pancreatic tumor registry</td>
<td>180</td>
<td>10 (5.5)</td>
</tr>
</tbody>
</table>
a Case-control study; rates for BRCA1 and BRCA2 variants in controls were 0.2 and 0.3, respectively.

**BRCA Variant Rates Associated With Prostate Cancer**

Table 3 lists the results from several studies measuring the presence of BRCA variants among patients with prostate cancer.40-42

**Table 3. BRCA Variant Rates in Patients With Prostate Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>BRCA Variant, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abida et al (2017)</td>
<td>Patients with prostate cancer from 1 clinical practice</td>
<td>221</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pritchard et al (2016)</td>
<td>Patients with metastatic prostate cancer from 7 case series across multiple centers</td>
<td>692</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Edwards et al (2003)</td>
<td>Patients with prostate cancer diagnosed before age 56 from 2 cancer study groups</td>
<td>263</td>
<td>6 (2.3)</td>
</tr>
</tbody>
</table>

**Testing for Large BRCA Rearrangements**

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 variants have large genomic rearrangements (including deletions or duplications) in one of these genes. For example, Walsh et al (2006) 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 BRCA2.43 These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected variants, including 35 (12%) with genomic rearrangement of BRCA1 or BRCA2.

A study by Palma et al (2008) evaluated 251 patients with an estimated BRCA variant prevalence using the Myriad II model of at least 10%.44 In 136 non-Ashkenazi Jewish probands, 36 (26%) had BRCA point mutations and 8 (6%) had genomic rearrangements (7 in BRCA1, 1 in BRCA2). Genomic rearrangements comprised 18% of all identified BRCA variants. 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 variant did not predict the presence of a genomic rearrangement.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are
intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Knowledge of variant status in individuals at potentially increased risk of a BRCA variant may impact health care decisions to reduce risk.\(^{45-52}\) Risk-reducing options include intensive surveillance, chemoprevention, prophylactic mastectomy, or prophylactic oophorectomy. Among patients already diagnosed with cancer, BRCA variant status may guide treatment decisions.\(^{53}\)

Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90%.\(^{46}\) Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more\(^{49,50,54}\) and reduces the risk of breast cancer by approximately 50%.\(^{50}\) In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.\(^{48}\) Prophylactic oophorectomy or salpingo-oophorectomy in women with BRCA1 or BRCA2 reduced the risk of all-cause mortality by 60% to 77%.\(^{54,55}\) For patients at risk for both breast and ovarian cancer, a study by Elmi et al (2018), drawing on data from the American College of Surgeon’s National Surgical Quality Improvement Program dataset, found that prophylactic mastectomy with concurrent salpingo-oophorectomy was not associated with significant additional morbidity compared with prophylactic mastectomy alone.\(^{56}\)

Systematic reviews of observational studies comparing prophylactic surgeries with observation in women who had BRCA1 and BRCA2 variants have demonstrated that contralateral prophylactic mastectomy in women with breast cancer is associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality.\(^{57-59}\) Studies have indicated that the results of genotyping significantly influenced treatment choices.\(^{47,51,52}\)

In a systematic review for USPSTF, Nelson et al (2014) assessed the efficacy of risk-reducing surgery in BRCA-positive women.\(^{60}\) The literature search, conducted through December 2012, identified 27 studies for inclusion. For high-risk women and variant carriers, bilateral mastectomy reduced breast cancer incidence by 85% to 100% and breast cancer mortality by 81% to 100%; 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%. 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 reviewers observed, it is still currently unknown whether BRCA variant testing reduces cause-specific or all-cause mortality, or if it improves the quality of life. Harms associated with false-negative results or variants of uncertain significance also are unknown.

Robson et al (2017) published a phase 3 RCT in which patients with human epidermal growth factor receptor 2–negative metastatic breast cancer and a
germline BRCA variant were randomized to olaparib (n=205) or standard therapy (n=97). After a median follow-up of 14.5 months, patients receiving olaparib experienced significantly longer progression-free survival compared with patients receiving standard therapy (hazard ratio, 0.6; 95% confidence interval, 0.4 to 0.8). The rate of grade 3 or higher adverse events was lower in the group receiving olaparib (37%) compared with the group receiving standard therapy (51%).

Other studies have looked at the results of prostate cancer screening in men with BRCA variants. The Immunotherapy for Prostate Adenocarcinoma Treatment study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were BRCA variant carriers and 95 control patients. At the baseline screen, biopsies were performed in 7.0% of men with a prostate-specific antigen level greater than 3.0 ng/mL, 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 men at normal risk. Moreover, 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.

**Section Summary: Testing for BRCA1 and BRCA2 Variants in Individuals at Risk for Hereditary Breast/Ovarian Cancer Syndrome or Other High-Risk Cancers**

Evidence for the clinical validity of BRCA1 and BRCA2 variant testing consists of multiple studies that calculated BRCA1 and BRCA2 variant prevalence among samples of patients with HBOC syndrome, fallopian tube cancer, pancreatic cancer, and prostate cancer.

Evidence for the clinical utility of BRCA1 and BRCA2 variant testing involves measuring changes in the management of patients with positive results. In terms of prophylactic measures (mastectomy and oophorectomy), RCTs would be difficult to conduct. However, retrospective analyses have shown that prophylactic mastectomy and/or oophorectomy greatly reduced the risk of breast cancer and ovarian cancer (80%-90%). An RCT was conducted on women with breast cancer and a BRCA variant in which patients received a targeted therapy or standard chemotherapy. Women treated with the targeted therapy experienced significantly longer progression-free survival and fewer high-level adverse events.

**Summary of evidence**

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of HBOC syndrome who receive genetic testing for a BRCA1 or BRCA2 variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA variant have shown a risk as high as 85%. Knowledge of BRCA variant status in individuals at risk of a BRCA variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic
intervention. In individuals with *BRCA1* or *BRCA2* variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and overall survival. Knowledge of *BRCA* variant status in individuals diagnosed with breast cancer may impact treatment decisions. A randomized controlled trial has reported that patients with human epidermal growth factor receptor 2–negative metastatic breast cancer and a *BRCA* variant experienced significantly longer progression-free survival with a targeted therapy vs standard therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate) who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Knowledge of *BRCA* variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Supplemental Information**

**Clinical Input 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.

In response to requests, input was received for 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) while this policy was under review in 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 *BRCA*-associated malignancies to assess when obtaining the family history.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

**Breast Cancer and Ovarian Cancer**

Current National Comprehensive Cancer Network (NCCN) guidelines on genetic and familial high-risk assessment of breast and ovarian cancers (v.2.2019) include 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 Error! Reference source not found. should
undergo “further personalized risk assessment, genetic counseling, and often genetic testing and management.” For these criteria, both invasive and in situ breast cancers were 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.”

*BRCA1* and *BRCA2* somatic variants are uncommon. NCCN recommends if a somatic variant is identified through tumor profiling, then *BRCA1* and *BRCA2* germline testing is recommended.

**Table 4. BRCA1 and BRCA2 Testing Criteria for Hereditary Breast and Ovarian Cancer Syndrome**

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Individual from a family with a known <em>BRCA1/BRCA2</em> mutation</td>
</tr>
<tr>
<td>2. Personal history of breast cancer and ≥1 of the following:</td>
</tr>
<tr>
<td>a. Diagnosed age ≤45 years</td>
</tr>
<tr>
<td>b. Diagnosed age ≤ 46 to 50 years AND:</td>
</tr>
<tr>
<td>An additional breast cancer primary</td>
</tr>
<tr>
<td>≥1 close blood relative with breast cancer at any age</td>
</tr>
<tr>
<td>≥1 close relative with pancreatic cancer</td>
</tr>
<tr>
<td>≥1 close relative with prostate cancer (Gleason score ≥7), or</td>
</tr>
<tr>
<td>Unknown or limited family history</td>
</tr>
<tr>
<td>c. Diagnosed age ≤60 years with a triple-negative (ER−, PR−, HER2−) breast cancer</td>
</tr>
<tr>
<td>d. Diagnosed any age AND</td>
</tr>
<tr>
<td>≥2 additional diagnoses of breast cancer at any age in patient and/or in close blood relatives</td>
</tr>
<tr>
<td>≥1 close blood relative with breast cancer diagnosed at age 50 or younger or ovarian carcinoma or male breast cancer or metastatic prostate cancer or pancreatic cancer</td>
</tr>
<tr>
<td>3. Personal history of ovarian carcinoma</td>
</tr>
<tr>
<td>4. Personal history of male breast cancer</td>
</tr>
<tr>
<td>5. Personal history of metastatic prostate cancer or high grade prostate cancer (Gleason score ≥7) at any age AND ≥1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer at or before age 50 or ≥2 relatives with breast, pancreatic or prostate cancer (any grade) at any age.</td>
</tr>
<tr>
<td>6. Personal history of pancreatic cancer</td>
</tr>
<tr>
<td>7. BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis</td>
</tr>
<tr>
<td>8. An individual who does not meet the other criteria but with ≥1 1st- or 2nd-degree blood relative meeting any of the above criteria</td>
</tr>
<tr>
<td>9. Regardless of family history, some individuals with a <em>BRCA</em>-related cancer may benefit from genetic testing to determine eligibility for targeted treatment</td>
</tr>
</tbody>
</table>

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; PR: progesterone receptor.

**Pancreatic Adenocarcinoma**

Current NCCN guidelines for pancreatic adenocarcinoma (v.2.2018) refers to the NCCN guidelines on genetic/familial high-risk assessment of breast and ovarian detailed above, and state: “Consider germline testing for patients with a personal history of cancer, a family history of cancer, or if there is a clinical suspicion of inherited susceptibility.”

\[\text{\textsuperscript{63}}\]
**Prostate Cancer**

Current NCCN guidelines (v.4.2018) for prostate cancer state: “Consider testing for mutation in these genes (germline and somatic): BRCA1, BRCA2, ATM, PALB2, FANCA,” and that if positive, “this information may be used for genetic counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors).”

**American Society of Clinical Oncology**

The American Society of Clinical Oncology has released statements on genetic and genomic testing for cancer susceptibility since 1996. The Society (2003) recommended that cancer predisposition testing be offered when 3 factors are at play: (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 statement recommended that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”

**Society of Gynecologic Oncology**

The Society of Gynecologic Oncology (SGO; 2015) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer. The statement included 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 are very similar; the main differences is the exclusion of: women with breast cancer onset at age 50 years or younger who have 1 or more first-, second-, or third-degree relatives with breast cancer at any age; women with breast cancer or 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. Additionally, SGO recommended genetic assessment for unaffected women who have a male relative with breast cancer. Moreover, SGO indicated 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).

**American College of Obstetricians and Gynecologists**

The American College of Obstetricians and Gynecologists (2017) published a practice bulletin on hereditary breast and ovarian cancer syndrome. The following recommendation was based primarily on consensus and expert opinion (level C): “Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management.”
**U.S. Preventive Services Task Force**

Current U.S. Preventive Services Task Force (USPSTF) recommendations for genetic testing of \textit{BRCA1} and \textit{BRCA2} variants in women state:\textsuperscript{17}

“\textsuperscript{17}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 (\textit{BRCA1} or \textit{BRCA2}). Women with positive screening results should receive genetic counseling and, if indicated after counseling, \textit{BRCA} testing. (B recommendation)

The USPSTF recommends against routine genetic counseling or \textit{BRCA} testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the \textit{BRCA1} or \textit{BRCA2} gene. (D recommendation)"

Recommended screening tools included the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and Family History Screen–7.

**Medicare National Coverage**

There are no national coverage determinations. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 5.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02154672</td>
<td>Prostate Cancer Screening in Men With Germline \textit{BRCA2} Mutations</td>
<td>100</td>
<td>May 2018 (ongoing)</td>
</tr>
<tr>
<td>NCT02225015</td>
<td>Cancer Prevention in Women With a \textit{BRCA} Mutation</td>
<td>300</td>
<td>Jun 2019</td>
</tr>
<tr>
<td>NCT03246841</td>
<td>Investigation of Tumour Spectrum, Penetration and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes</td>
<td>500</td>
<td>Dec 2023</td>
</tr>
<tr>
<td>NCT02321228</td>
<td>Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in \textit{BRCA1/2} Gene Mutation Carriers (TUBA)</td>
<td>510</td>
<td>Jan 2035</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**References**


15. 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


### Billing Coding/Physician Documentation Information

**0129U** Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)

**0131U** Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)

**0132U** Hereditary ovarian cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)

**0134U** Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure)

**0135U** Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)

**0137U** PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)

**0138U** BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA
sequence analysis (List separately in addition to code for primary procedure)

**81162**
BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis

**81163**
BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis (New code 1/1/2019)

**81164**
BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) (New code 1/1/2019)

**81165**
BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis (New code 1/1/2019)

**81166**
BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) (New code 1/1/2019)

**81167**
BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) (New code 1/1/2019)

**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) (Code deleted 1/1/2019)

**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 (Code deleted 1/1/2019)

**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) (Code deleted 1/1/2019)

**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
Secondary malignant neoplasm of ovary, code range C79.60-
C79.62
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
Z13.70-
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.
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.

1/1/18 First medically necessary policy statement updated to reflect changes to NCCN recommendation.

1/1/19 First medically necessary policy statement updated to reflect changes to NCCN recommendation. Title of policy changed to “Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers”. Updated wording on Investigational statement, no change in intent.

APPENDIX

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.02

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
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<tr>
<td>2b. Prognostic</td>
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<tr>
<td>2c. Therapeutic</td>
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<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
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<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td>X</td>
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<tr>
<td>5. Reproductive testing</td>
<td></td>
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<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
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<tr>
<td>5b. Carrier testing: prenatal</td>
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<tr>
<td>5c. In utero testing: aneuploidy</td>
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<tr>
<td>5d. In utero testing: familial variants</td>
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<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
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</tr>
</tbody>
</table>

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in
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