Clinical Policy Title: Genetic testing for risk for breast and ovarian cancer

Clinical Policy Number: 02.01.02

Effective Date: September 1, 2013
Initial Review Date: March 21, 2013
Most Recent Review Date: April 10, 2018
Next Review Date: April 2019

Related policies:

CP# 02.01.14 Gene expression profile testing for breast cancer.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of BRCA1, BRCA2, and BRCAnalysis Rearrangement Testing (BART™) to be clinically proven and, therefore, medically necessary for women or men at high risk for BRCA gene mutation when one or more of the following criteria are met (Lancaster, 2015; National Cancer Care Network [NCCN], 2018):

- Member with a current or history of a personal cancer diagnosis, with any of the following:
  - High-grade epithelial ovarian, tubal, or peritoneal cancer.
  - Breast cancer at or before age 45.
  - Breast cancer with one or more close relatives with breast cancer diagnosed at any age, including male breast cancer, or with a close relative with epithelial ovarian, tubal, or peritoneal cancer diagnosed at any age.
  - Breast cancer diagnosed at or before age 50, with a limited availability of family history.
  - Breast cancer, with two or more close relatives diagnosed with breast cancer at any age, or with pancreatic cancer or aggressive prostate cancer (indicated by a Gleason score of 7 or more.
  - Breast cancer with two primary lesions, with at least one diagnosed at or before age 50.
  - Triple negative breast cancer diagnosed at or before age 60 years.

Policy contains:
- BRCA1/BRCA2 testing for breast and ovarian cancer.
- BART™ (BRCAnalysis® Rearrangement Testing).
Breast cancer, and has Ashkenazi Jewish ancestry.

- Pancreatic cancer with two or more close relatives with breast, ovarian, tubal, peritoneal, pancreatic, or aggressive prostate cancer (Gleason score of 7 or more).
- Profiling of any tumor type has revealed BRCA1 or BRCA2 mutation without germline mutation analysis.

- Member has no personal history of breast cancer, but has any of the following:
  - At least one first-degree relative, or several close relatives, who meet one of the above criteria.
  - A genetic predisposition demonstrated by having one or more close relatives known to have a BRCA1 or BRCA2 gene mutation.
  - A close male relative with breast cancer.

BART testing may be offered to individuals who otherwise meet the criteria for BRCA1 or BRCA2 testing but are found to have negative results on BRCA1 or BRCA2 testing.

Individuals considered for testing should be offered genetic counseling by an appropriately trained genetic counselor before testing with BRCA1, BRCA2, or BART. Further diagnostic studies may be covered, including annual mammography and magnetic resonance imaging (MRI) of the breast. Prophylactic bilateral mastectomy and salpingo-oophorectomy are covered for individuals who have a positive result.

For purposes of genetic linkages, “close family relative” is defined as first-degree (parent, sibling, child), second-degree (grandparent, grandchild, uncle, aunt, nephew, niece, and half-sibling), and third-degree (first cousin, great-grandparent, and great-grandchild) relatives (Lancaster, 2015).

In Pennsylvania, individuals not meeting any of the above criteria may be offered BRCA1, BRCA2, or BART testing if determined through both independent formal genetic counseling and a validated quantitative risk assessment tool to have at least a 10 percent pre-test probability of carrying a BRCA1 or BRCA2 mutation.

Select Health of South Carolina may require some form of genetic counseling for each test, but it does not have to be by a geneticist or genetic counselor, as one may not be readily accessible to consumers in certain areas of Pennsylvania.

A genetic test is considered medically necessary if the results are expected to make a difference in the recipient’s care or their treatment plan, or the recipient (or a responsible family member or legal guardian) intends to use the information in making decisions about their care or treatment plan. An example would be family planning decisions or planning of other indicated testing in light of the diagnosis. Genetic testing is medically necessary if it is a currently accepted method of diagnosis of a condition or disease.

In the event that the member has no knowledge of family history because of adoption or other limitations on obtaining family history, BRCA1 or BRCA2 testing is allowed if the testing is considered medically necessary and the results will influence care management.
All requests may be reviewed individually, even if the above guideline criteria are not met.

Limitations:

All other uses of BRCA1, BRCA2, and BART are not medically necessary, including genetic risk assessment of breast and/or ovarian cancer.

Other limitations:

- For testing panels, including, but not limited to, multiple genes or multiple conditions, and in cases where a tiered approach or method is clinically available, testing would be covered only for the number of genes or tests that are reasonable and necessary to obtain necessary information for therapeutic decision making.
- Individual has not previously received genetic testing for the disease or condition. In general, diagnostic genetic testing for a disease should be performed once in a lifetime.

Alternative covered services:

Standard diagnostic studies such as physical examination, mammography, ultrasound, and surgical biopsy.

Background

Overall, breast cancer is the leading cause of cancer deaths among women in the U.S., and significant disparities exist between racial/ethnicity groups. Incidence (new diagnosis) rates are similar for Caucasian and African-American women, and lower among Asian, Hispanic, and Native women. While mortality rates have overall been falling, African-American women remain disproportionately affected, with the highest mortality due to breast cancer among all other groups. The incidence of new diagnoses per 100,000 women per year is 124.8 among Caucasian women, 122.4 among African-American women, 91.8 among Hispanic women, 90.0 among Asians/Pacific Islander women, and 73.7 among Native American women (age-adjusted, at 95% confidence interval, based on 2014 data) (Centers for Disease Control [CDC], 2017). African-American women have the highest rate at 28.1 deaths per 100,000 women per year, whereas the rates for Caucasian, Hispanic, Asian, and Native women are at 20, 14.6, 13, and 10.8 deaths per 100,000 women per year, respectively. Because of the high incidence of breast cancer, new ways to identify those most at risk have been sought.

In 5 percent to 10 percent of women with breast cancer, a significant family history can be found. For those with a strong family history of breast or ovarian cancer, mutations of the BRCA1 or BRCA2 genes account for the majority of cases. The American Congress of Obstetricians and Gynecologists (ACOG) estimates between one in 300 and one in 800 individuals within the general population carry a mutation in the BRCA1 or BRCA2 gene (ACOG, 2009). The BRCA1 and BRCA2 genes in their unmutated states act as suppressors of breast or ovarian cancer. The mutation removes this protective attribute, enhancing the risk of such malignancies. Mutation of BRCA1 or BRCA2 does not guarantee that breast or ovarian cancer will develop.
but that there will be a higher risk of breast or ovarian cancer developing. A meta-analysis estimated the risk of breast cancer and ovarian cancer developing in women by age 70 who are BRCA1 or BRCA2 positive is 57 percent and 40 percent, respectively (Chen, 2006).

There are three main types of tests used to detect BRCA1 and BRCA2 gene mutations:

- **Full nucleotide screening** is a comprehensive, full sequencing analytic tool that is considered the gold standard because it can detect single-point mutations in either the BRCA1 or BRCA2 gene.

- **Allele-specific oligonucleotide (ASO) hybridization** is generally used if there is an already-known BRCA mutation within the family. This test detects the carrier potential of the individual being tested. If positive, more full nucleotide screening would be considered.

- **Protein truncation assays** detect shortened protein products. However, it will not detect proteins of normal length that may have aberrant sequences.

BART is a genetic test used to detect large genomic rearrangements in BRCA1 and BRCA2 not detected through BRCA1/BRCA2 testing. The BRCA1 and BRCA2 mutations do not represent all errors of the tumor suppression gene. Other large rearrangements of the BRCA genes have been associated with higher risk of breast and ovarian cancers. Studies by Palma (2008), Walsh (2006), and Unger (2000) have found evidence of large rearrangements of the BRCA genes associated with higher risk of breast and ovarian cancers. To date, studies have not demonstrated reductions in mortality associated with detection of large rearrangements by using BART. However, because of increased detection of breast and ovarian cancer risk in patients whose results were negative for BRCA1/BRCA2 and who otherwise share the same breast and ovarian cancer risk, current recommendations are to test such individuals with BART.

Other genetic tests do not have population-based studies or peer-reviewed papers to demonstrate their impact and are considered investigational and not medically necessary. These include testing for single nucleotide polymorphisms, RAD51C, CHEK2, CASP8, TGFβ1, ataxia telangiectasia, and BRIP1 PALB2. Because of concerns with interpretation of test results, it is currently recommended that ordering and interpretation of results be performed in conjunction with a trained geneticist.

Individuals found to have the BRCA1 or BRCA2 germline mutation should be offered genetic counseling. NCCN Guidelines® indicate screening for breast cancer should begin 10 years before the age of diagnosis of the youngest family member. Men or women may consider annual mammography combined with MRI studies of the breasts with aggressive intervention if those studies detect disease. Lee (2008) found this strategy improved life expectancy by one year but did result in a rate between 11 percent and 30 percent higher of biopsies for benign disease.

Prophylactic mastectomy and salpingo-oophorectomy may be options for those at very high risk of disease. Among high-risk women and mutation carriers, risk-reducing mastectomy decreased breast cancer by 85 percent to 100 percent and breast cancer mortality by 81 percent to 100 percent compared with women without surgery. Risk-reducing salpingo-oophorectomy decreased breast cancer incidence by 37 percent to 100 percent, ovarian cancer by 69 percent to 100 percent, and all-cause mortality by 55 percent to 100
 Searches

Select Health of South Carolina searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on March 7, 2018. Search terms were: “prophylactic mastectomy,” “salpingo oophorectomy,” “breast neoplasms” [MeSH], “ovarian neoplasms” [MeSH] and “BRCA.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Policy updates:

**May 2014**

Select Health of South Carolina identified no new systematic reviews, economic analyses, or evidence-based guidelines for this policy update.

**May 2015**

Select Health of South Carolina identified no new systematic reviews, economic analyses, or evidence-based guidelines for this policy update.

**April 19, 2016**

Added the summary of clinical evidence section. Updated Local Coverage Determinations (LCDs).

**April 5, 2017**

Writing in *UpToDate*, Burst (2017) assessed the ability of contemporary genetic testing procedures to
influence management of cancer of the breast:

“To guide clinical decision-making, gene expression profiles such as the RS, EndoPredict, the Breast Cancer Index (BCI), and the PAM50 intrinsic subtype assay have been developed to identify patients with such a low chance of recurrence that the absolute benefit of chemotherapy may not justify the risk of toxicities. By contrast, patients with higher scores on these assays have a sufficiently high risk of recurrence despite endocrine therapy that the addition of chemotherapy outweighs the risk of toxicities. Moreover, given that the response to treatment is not uniform among all cancers, these assays may identify those cancers that, based on their biologic profile, are likely to have an excellent outcome with endocrine therapy alone versus those in which the addition of chemotherapy would substantially reduce the risk of recurrence.”

March 2018

Three professional society guidelines/other were added to the reference list and three were updated. Four peer-reviewed publications were added to the reference list. The coverage policy was revised in consideration of the Society for Gynecologic Oncology’s recommendations (Lancaster, 2015) and the revised NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) on genetic/familial high risk assessment (2018). The NCCN Guidelines®, which include detailed algorithms, are periodically updated and it is recommended to consult the NCCN website for the most recent version. We note that the U.S. Preventive Services Task Force is in the process of updating their 2013 recommendations on genetic testing for BRCA-related cancers in women (Moyers, 2014).

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Burst (2017)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Adjuvant chemotherapy for</td>
<td>• RS, EndoPredict, the Breast</td>
</tr>
<tr>
<td>HER2-negative breast</td>
<td>Cancer Index (BCI), and the</td>
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<td>cancer.</td>
<td>PAM50 intrinsic subtype assay</td>
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<td>were suggested as means to identify patients with such a low chance of recurrence that the absolute benefit of chemotherapy may not justify the risk of toxicities.</td>
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<td></td>
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<td>• Given that the response to treatment is not uniform among all cancers, these assays may identify those cancers that, based on their biologic profile, are likely to have an excellent outcome with endocrine therapy alone versus those in which the addition of chemotherapy would substantially reduce the risk of recurrence.</td>
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<tr>
<td>Fox, et al. (2015)</td>
<td><strong>Key points:</strong></td>
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<td>The sooner the better:</td>
<td>• To determine when women with a diagnosis of high-grade serous ovarian cancer would prefer to undergo genetic testing and factors that influence this preference.</td>
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<tr>
<td>Genetic testing following</td>
<td>• Of the 355 women identified, 120 (33.8%) completed the questionnaires. The median age at time of ovarian cancer diagnosis was age 57 (range, 35 – 84). The majority of participants in this</td>
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</table>
study were offered (94.6%) and pursued (84.8%) genetic testing. In this cohort, testing was most frequently offered at diagnosis (41.8%) or during treatment (19.1%). In this study, women with high-grade serous ovarian cancer felt that genetic testing should be offered before or at the time of diagnosis (67.8%). Having a family history of breast or ovarian cancer was significantly ($p = 0.012$) associated with preferring genetic testing at an earlier time point in the disease course.

- Our results demonstrate that women with high-grade serous ovarian cancer acknowledge the personal and clinical utility of genetic testing and support test implementation at the time of cancer diagnosis.

### Levy, et al. (2009)

**Guidelines for genetic risk assessment of hereditary breast and ovarian cancer: early disagreements and low utilization**

**Key points:**

- To identify women at high risk of hereditary breast and ovarian cancer and estimate their awareness of and experience with genetic testing for cancer risk.
- Using guideline criteria, 0.96% of women were identified as being at high risk for hereditary breast and ovarian cancer.
- Among high-risk women, 54.04% were aware of genetic testing for cancer risk, 10.39% had discussed genetic testing with a health professional, and 1.41% had undergone testing for breast/ovarian cancer risk.
- Adjusting for survey year, women at high risk were more likely than women with an average risk to have heard of genetic testing for cancer risk (RR, 1.3; 95% CI: 1.2 – 1.4), to have discussed genetic testing with a health professional (RR, 5.2; 95% CI: 3.6 – 7.4), and to have undergone genetic testing for breast/ovarian cancer risk (RR, 6.8; 95% CI: 2.6 – 18.0).
- Low provision of guideline-recommended advice to women for whom testing may be appropriate and of significant clinical benefit.

### Nelson, et al. (2005)

**Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: Evidence synthesis**

**Key points:**

- To determine the balance of benefits and adverse effects of screening based on available evidence. The target population includes adult women without pre-existing breast or ovarian cancer presenting for routine care in the United States.
- Relevant papers were identified from multiple searches of MEDLINE® (1966 to October 1, 2004); Cochrane Library databases; and reference lists of pertinent studies, reviews, editorials, and websites, and by consulting experts.
- The evidence base for genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility as a screening strategy is limited by lack of studies demonstrating effectiveness, biases inherent in studies conducted in highly selected populations, and incomplete information on adverse effects.

### References

**Professional society guidelines/other:**


American College of Obstetricians and Gynecologists. Routine screening for hereditary breast and ovarian


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

There are multiple LCDs for Genetic Testing. CMS Medicare Coverage Database website: [https://www.cms.gov/medicare-coverage-database/search/search-results.aspx?CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=genetic+testing &KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAAAAAAAAAAAAA%3d%3d=&](https://www.cms.gov/medicare-coverage-database/search/search-results.aspx?CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=genetic+testing &KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAAAAAAAAAAAAA%3d%3d=&). Accessed March 7, 2018.

**Commonly submitted codes**
Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<th>CPT Code</th>
<th>Description</th>
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<tr>
<td>81162</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis</td>
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<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 (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>
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<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants</td>
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