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| <b>2.04.02</b>               | <b>Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers</b> |                        |                 |
| <b>Original Policy Date:</b> | October 15, 1997  | <b>Effective Date:</b> | January 1, 2019 |
| <b>Section:</b>              | 2.0 Medicine  | <b>Page:</b>           | Page 1 of 25    |

### Policy Statement

Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments–licensed laboratory that offers comprehensive variant analysis (see Policy Guidelines section: Comprehensive Variant Analysis).

#### Patients with Cancer or with Personal History of Cancer

Full sequence and duplication/deletion analysis genetic testing for *BRCA1* and *BRCA2* gene 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 (including invasive and ductal carcinoma in situ) and **one or more** of the following:
  - Diagnosed at age 45 or younger
  - Two primary breast cancers when first breast cancer diagnosis occurred on or before 50 years of age (includes bilateral [contralateral] disease or cases where there are two or more clearly separate [ipsilateral] primary tumors either synchronously or asynchronously)
  - Diagnosed on or before 50 years of age and:
    - One or more 1st-, 2nd-, or 3rd-degree relative(s)<sup>a</sup> with breast cancer at any age, pancreatic cancer, or prostate cancer<sup>b</sup>
    - Unknown or limited family history<sup>c</sup>
  - Diagnosed on or before 60 years of age with a triple-negative (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative) breast cancer
  - Diagnosed at any age AND one or more 1st-, 2nd-, or 3rd-degree relative(s)<sup>a</sup> with breast cancer diagnosed on or before 50 years of age
  - Diagnosed at any age AND two or more 1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with breast cancer at any age
  - Diagnosed at any age AND one or more 1st-, 2nd-, or 3rd-degree relative<sup>a</sup> with epithelial ovarian, fallopian tube, or primary peritoneal cancer
  - Diagnosed at any age AND two or more 1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with pancreatic cancer or prostate cancer<sup>b</sup> at any age
  - 1st-, 2nd-, or 3rd-degree male relative with breast cancer
  - Ethnicity associated with deleterious founder mutations (e.g., Ashkenazi Jewish descent<sup>d</sup>)
- Personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer AND Ashkenazi Jewish ancestry
- Personal history of high-grade pancreatic cancer or prostate cancer<sup>b</sup> at any age AND one or more 1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with **any** of the following:
  - Breast cancer at age 50 or younger
  - Ovarian, fallopian tube, or primary peritoneal cancer at any age
  - Pancreatic or prostate cancer<sup>b</sup>
- Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease)
- Personal history of pancreatic cancer or prostate cancer<sup>b</sup> at any age AND 2 or more 1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with breast, pancreatic, or prostate cancer<sup>b</sup> at any age

- *BRCA1* or *BRCA2* pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis

### Familial Assessment Descriptions

<sup>a</sup> 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

<sup>b</sup> For familial assessment, prostate cancer is defined as Gleason score greater than or equal to 7

<sup>c</sup> For example, fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage. In families with a large number of unaffected female relatives, the likelihood of variant detection may be very low

<sup>d</sup> Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first (see Policy Guidelines section: High-Risk Ethnic Groups)

### Patients without Cancer or without History of Cancer

(See Policy Guidelines section: Testing Unaffected Individuals)

Genetic testing for *BRCA1* and *BRCA2* (including deletions and duplications) variants of cancer-unaffected individuals may be considered **medically necessary** under **any** of the following circumstances:

- Individual from a family with a known *BRCA1* or *BRCA2* variant
- First- or second-degree blood relative meeting any criterion listed above for Patients with Cancer
- Third-degree blood relative with **both** of the following:
  - Breast cancer (including invasive and ductal carcinoma in situ) and/or ovarian, fallopian tube, or primary peritoneal cancer
  - Two or more 1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with breast cancer (at least one with breast cancer at age 50 or younger) and/or ovarian, fallopian tube, or primary peritoneal cancer

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 (including genetic screening in the general population) is considered **investigational**.

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

### Confirmatory BRCA Testing

Confirmatory BRCA testing may be considered **medically necessary** for patients who underwent over-the-counter (OTC) U.S. Food and Drug Administration (FDA) approved genetic screening and were found to have a pathogenic *BRCA1* or *BRCA2* mutation (including one of the three Ashkenazi founder mutations).

### Panel Testing

Large multi-gene panels including multiple genes that are not highly associated with hereditary breast and ovarian cancer (see Policy Guidelines) are considered **investigational**.

## Policy Guidelines

Testing related to hereditary colorectal cancer, see Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes.

Panel testing related to non-small-cell lung cancer, see Blue Shield of California Medical Policy: Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy).

Panel testing related to cancers other than breast, ovarian, colorectal, and non-small-cell lung cancer, see Blue Shield of California Medical Policy: Genetic Panel Testing for Susceptibility to Hereditary Cancers.

Current U.S. Preventive Services Task Force 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 variants 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)

**Note:** For payment authorization, this testing will be limited to single-site analysis of the mutation identified and will be performed at contracted laboratories.

### Recommended Testing Strategies

Complete testing includes at a minimum: Full sequence and duplication/deletion analysis of *BRCA1* and *BRCA2*. PALB2 is indicated if initial testing is negative (or may be included in an initial limited panel).

Patients who meet criteria for genetic testing as outlined in the policy statements above should have complete testing. Additional testing does not need to continue once a known harmful variant is found:

- In patients with a known familial *BRCA* variant, targeted testing for the specific variant is recommended as the first step
- In patients with unknown familial *BRCA* variant:
  - Non-Ashkenazi Jewish descent:
    - To identify clinically significant variants, 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 of obtaining a positive test result
    - If no living family member with breast or ovarian cancer is available for testing, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* variants (e.g., prostate cancer, pancreatic cancer, melanoma)
    - If no familial variant can be identified:
      - Full sequencing along with full testing for *common and uncommon* large genomic rearrangements (deletions, duplications)
        - ❖ More than 90% of *BRCA* variants will be detected by full sequencing alone
        - ❖ Adding common deletions and duplications will detect another 2.5%
        - ❖ Adding uncommon large deletions and duplications (e.g., BART or BRCA Analysis Rearrangement Test) detects less than 1% more
        - ❖ Full testing will detect 93.5% of *BRCA* related variants
  - Ashkenazi Jewish descent:

- In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first
- If testing is negative for founder mutations, or as an initial alternative, complete genetic testing may be done (full sequence and duplication/deletion analysis in *BRCA1* and *BRCA2* genes)

### High-Risk Ethnic Groups

Testing of eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations may begin with tests specifically for these variants. For example, founder mutations account for approximately three-quarters of the *BRCA* variants found in Ashkenazi Jewish populations (see Rationale section). When testing for founder mutations is negative, complete 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* variant 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 variants 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 and Pancreatic Cancer

Patients with *BRCA* variants have an increased risk of prostate and pancreatic cancer, and patients with known *BRCA* variants may, therefore, consider more aggressive screening approaches for prostate or pancreatic cancer in some cases.

### 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.

### Coding

The following CPT codes may be used for genetic testing for *BRCA1* and *BRCA2* variants:

- **81162:** *BRCA1*, *BRCA2* (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis  
**Note:** This code includes both 81163 and 81164 (and previously 81211 and 81213).

- **81163:** BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis (**Code effective 1/1/2019**)
- **81164:** BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) (**Code effective 1/1/2019**)
- **81165:** BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis (**Code effective 1/1/2019**)
- **81166:** BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) (**Code effective 1/1/2019**)
- **81167:** BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) (**Code effective 1/1/2019**)
- **81211:** 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) (**Deleted code effective 1/1/2019**)
- **81212:** BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
- **81213:** BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants (**Deleted code effective 1/1/2019**)  
**Note:** Previously used for BRCA Analysis Rearrangement Test, or BART.
- **81214:** 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) (**Deleted code effective 1/1/2019**)
- **81215:** BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
- **81216:** BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- **81217:** BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
- **81432:** Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
- **81433:** Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11

## Description

Hereditary breast and ovarian cancer syndrome describes the familial cancer syndromes related to variants in the *BRCA* genes (*BRCA1* located on chromosome 17q21, *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.

## Related Policies

- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk
- Risk-Reducing Mastectomy

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## 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 BRCAssure<sup>SM</sup> 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.

In 2018, the 23andMe Personal Genome Service (PGS) Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) was approved by FDA through the DeNova process. The PGS is indicated to be performed using the BeadChip v4 assay (Illumina Infinium HumanOmniExpress-

24 format chip), which covers more than 500,000 genetic markers. The BeadChip consists of silicon wafers etched to form wells loaded with silica beads, on which oligonucleotide capture probes are immobilized. DNA from saliva is fragmented and captured on a bead array by hybridization to immobilized SNP-specific primers, followed by extension with hapten-labeled nucleotides. The primers hybridize adjacent to the SNPs and are extended with a single nucleotide corresponding to the variant allele. The incorporated hapten-modified nucleotides are detected by adding fluorescently labeled antibodies in several steps to amplify the signals. The Tecan Evo and Illumina iScan instruments are used for extraction and processing of the DNA, and the BeadChip for scanning and quantification of the results. The genotype content is separated, analyzed, and then integrated into predefined report templates specific for each condition associated with each genotype. Genotypes are determined using the GenomeStudio and Coregen software packages. For the 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) information on three specific variants in the BRCA1/BRCA2 genes are integrated into the report: 185delAG and 5382insC variants in the BRCA1 gene and 6174delT variant in the BRCA2 gene.<sup>70</sup>

The 23andMe Personal Genome Service (PGS) uses qualitative genotyping to detect select clinically relevant variants in genomic DNA isolated from human saliva collected from individuals  $\geq 18$  years with the Oragene Dx model OGD500.001 for the purpose of reporting and interpreting genetic health risks, including the 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants). The 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) is indicated for reporting of the 185delAG and 5382insC variants in the BRCA1 gene and the 6174delT variant in the BRCA2 gene. The report describes if a woman is at increased risk of developing breast and ovarian cancer, and if a man is at increased risk of developing breast cancer or may be at increased risk of developing prostate cancer. The three variants included in this report are most common in people of Ashkenazi Jewish descent and do not represent the majority of the BRCA1/BRCA2 variants in the general population. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.<sup>70</sup>

## Rationale

### 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.<sup>1</sup> 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).<sup>1-4</sup> In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.<sup>5</sup> 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.<sup>2</sup> 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.<sup>6</sup> 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.<sup>7-9</sup>

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.<sup>4</sup> Several other studies have documented the significant influence of family history.<sup>6-10</sup>

In patients with "triple-negative" breast cancer (i.e., 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.<sup>11</sup> 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.<sup>12</sup> *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.<sup>13</sup> 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*).<sup>14</sup>

### **Literature Review**

This review was informed by a 1997 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment.<sup>15</sup>

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 (i.e., 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 (eg, for people without cancer) or the specialty setting (eg, 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;  $p=0.034$ ).<sup>16</sup> 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.<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup> Studies of founder mutations in ethnic populations (eg, 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*.<sup>7,10,20,21</sup> 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).<sup>22</sup> 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.<sup>23</sup> 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.<sup>24</sup> 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%.<sup>25</sup> 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*.<sup>17</sup> Table 1 lists results from several additional studies measuring the presence of *BRCA* variants among patients with ovarian cancer.<sup>26-30</sup> One study noted that variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%).<sup>26</sup> 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.<sup>26</sup>

**Table 1. BRCA Variant Rates in Patients With Ovarian Cancer**

| Study                               | Population  | N                 | BRCA Variant, n (%) |           |
|-------------------------------------|---|-------------------|---------------------|-----------|
|                                     |   |                   | BRCA1               | BRCA2     |
| Harter et al (2017) <sup>30</sup>   | Patients with invasive ovarian cancer across 20 medical centers   | 523               | 81 (15.5)           | 29 (5.5)  |
| Kurian et al (2017) <sup>27</sup>   | Patients with invasive ovarian cancer tested for hereditary cancer risk from a commercial laboratory database | 5020 <sup>a</sup> | 255 (15.5)          | 199 (5.5) |
| Langer et al (2016) <sup>28</sup>   | Patients with ovarian cancer tested for hereditary cancer risk from a commercial laboratory database          | 3088              | 153 (4.9)           | 124 (4.0) |
| Norquist et al (2016) <sup>29</sup> | Patients with invasive ovarian cancer, from 2 phase 3 clinical trials and a gynecologic oncology tissue bank  | 1915              | 182 (9.5)           | 98 (5.1)  |
| Zhang et al (2011) <sup>26</sup>    | Patients with invasive ovarian cancer   | 1342              | 107 (8.0)           | 67 (5.0)  |

<sup>a</sup> 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.<sup>31</sup> 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.<sup>32</sup> 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.<sup>33</sup> Table 2 lists results from several studies measuring the presence of *BRCA* variants among patients with pancreatic adenocarcinoma.<sup>34-39</sup> 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**

| Study                               | Population  | N    | <i>BRCA</i> Variant, n (%) |              |
|-------------------------------------|---|------|----------------------------|--------------|
|                                     |   |      | <i>BRCA1</i>               | <i>BRCA2</i> |
| Hu et al (2018) <sup>39,a</sup>     | Patients with pancreatic adenocarcinoma from a prospective pancreatic cancer registry                         | 3030 | 18 (0.6)                   | 59 (1.9)     |
| Yurgelun et al (2018) <sup>38</sup> | Patients with pancreatic adenocarcinoma from 3 medical centers  | 289  | 3 (1.0)                    | 4 (1.4)      |
| Shindo et al (2017) <sup>37</sup>   | Patients with pancreatic adenocarcinoma from 1 medical center   | 854  | 3 (0.3)                    | 12 (1.4)     |
| Holter et al (2015) <sup>36</sup>   | Patients with pancreatic adenocarcinoma from a large academic health care complex                             | 306  | 3 (1.0)                    | 11 (3.6)     |
| Ferrone et al (2009) <sup>35</sup>  | Jewish patients with pancreatic adenocarcinoma from 1 hospital  | 145  | 2 (1.3)                    | 6 (4.1)      |
| Couch et al (2007) <sup>34</sup>    | Probands from high-risk families identified through pancreatic cancer clinics and a pancreatic tumor registry | 180  |                            | 10 (5.5)     |

<sup>a</sup> 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.<sup>40-42</sup>

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

| Study                                | Population  | N   | <i>BRCA</i> Variant, n (%) |              |
|--------------------------------------|---|-----|----------------------------|--------------|
|                                      |   |     | <i>BRCA1</i>               | <i>BRCA2</i> |
| Abida et al (2017) <sup>42</sup>     | Patients with prostate cancer from 1 clinical practice                              | 221 | 2 (1)                      | 20 (9)       |
| Pritchard et al (2016) <sup>41</sup> | Patients with metastatic prostate cancer from 7 case series across multiple centers | 692 | 6 (0.9)                    | 37 (5.3)     |
| Edwards et al (2003) <sup>40</sup>   | Patients with prostate cancer diagnosed before age 56 from 2 cancer study groups    | 263 |                            | 6 (2.3)      |

### ***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*.<sup>43</sup> 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%.<sup>44</sup> 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.<sup>45-52</sup> 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.<sup>53</sup>

Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90%.<sup>46</sup> Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more<sup>49,50,54</sup> and reduces the risk of breast cancer by approximately 50%.<sup>50</sup> In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.<sup>48</sup> Prophylactic oophorectomy or salpingo-oophorectomy in women with *BRCA1* or *BRCA2* reduced the risk of all-cause mortality by 60% to 77%.<sup>54,55</sup> 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.<sup>56</sup>

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.<sup>57-59</sup> Studies have indicated that the results of genotyping significantly influenced treatment choices.<sup>47,51,52</sup>

In a systematic review for USPSTF, Nelson et al (2014) assessed the efficacy of risk-reducing surgery in *BRCA*-positive women.<sup>60</sup> 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).<sup>53</sup> 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.<sup>61</sup> 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 from Blue Cross Blue Shield Association, input was received for 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) 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.<sup>62</sup> Patients who satisfy any of the testing criteria listed in Table 4 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**

| Recommendations |  |
|-----------------|--|
| 1.              | Individual from a family with a known <i>BRCA1/BRCA2</i> mutation  |
| 2.              | Personal history of breast cancer and ≥1 of the following:   |
| a.              | Diagnosed age ≤45 years  |
| b.              | Diagnosed age ≤ 46 to 50 years AND:  |
|                 | An additional breast cancer primary  |
|                 | ≥1 close blood relative with breast cancer at any age  |
|                 | ≥1 close relative with pancreatic cancer   |
|                 | ≥1 close relative with prostate cancer (Gleason score ≥7), or  |
|                 | Unknown or limited family history  |
| c.              | Diagnosed age ≤60 years with a triple-negative (ER-, PR-, HER2-) breast cancer   |
| d.              | Diagnosed any age AND  |
|                 | ≥2 additional diagnoses of breast cancer at any age in patient and/or in close blood relatives   |
|                 | ≥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                                  |
| 3.              | Personal history of ovarian carcinoma  |
| 4.              | Personal history of male breast cancer   |
| 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 |

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#### Recommendations

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- cancer at any age or breast cancer at or before age 50 or  $\geq 2$  relatives with breast, pancreatic or prostate cancer (any grade) at any age.
6. Personal history of pancreatic cancer
  7. BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis
  8. An individual who does not meet the other criteria but with  $\geq 1$  1st- or 2nd-degree blood relative meeting any of the above criteria
  9. Regardless of family history, some individuals with a BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment
- 

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."<sup>63</sup>

#### **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)."<sup>64</sup>

#### **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.<sup>65</sup> 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."<sup>66</sup> A 2015 update affirmed that multigene panel testing "is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history."<sup>67</sup>

#### **Society of Gynecologic Oncology**

The Society of Gynecologic Oncology (SGO; 2015) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer.<sup>68</sup> 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.<sup>69</sup> 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.”

### **National Society of Genetic Counselors**

The National Society of Genetic Counselors (NSGC) commends the FDA for the approved marketing of 23andMe Personal Genome Service Genetic Health Risk Report for BRCA1/BRCA2 on March 6, 2018 and for recognizing that these tests are limited and should not be used for medical treatment without consulting with a medical professional, such as a genetic counselor. This is the first direct-to-consumer (DTC) test to report on three specific breast cancer gene mutations most common in people of Ashkenazi (Eastern European) Jewish descent.<sup>71</sup>

Genetic counselors can guide, and support patients seeking more information about their genetic health and help interpret test results. The 23andMe test detects only three out of more than 1,000 known BRCA mutations and doesn't rule out other BRCA mutations that increase cancer risk. Consumers who test positive for these mutations need to be retested in a clinical setting under the supervision of a medical professional before moving forward with any medical decisions. Those who test negative, yet have a strong family history of cancer, may be appropriate candidates for testing and should also consult with medical professionals.<sup>71</sup>

Erica Ramos, MS, CGC, NSGC President, states, “Although this test may help to identify people who have a previously undetected BRCA mutation, there are several limitations and the results may be confusing or misleading without appropriate education. Anyone who has a strong personal or family history of breast or ovarian cancer and is interested in finding out more about their individualized risk should consult with a genetic counselor to discuss their genetic testing options, or to discuss their results. Genetic counselors can help them be prepared for what the results may tell them, identify other clinical tests that may be needed based on their history and understand how those results could affect them and their relatives.”<sup>71</sup>

### **U.S. Preventive Services Task Force**

Current U.S. Preventive Services Task Force (USPSTF) recommendations for genetic testing of *BRCA1* and *BRCA2* variants in women state<sup>17</sup>:

“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. (B recommendation)

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* 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 5. Summary of Key Trials**

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

NCT: national clinical trial.

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## Documentation for Clinical Review

### Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Ethnicity/Ancestry
  - Personal and/or family history of cancer (if applicable) including:
    - Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) ((if applicable)
    - Site(s) of cancer
    - Age at diagnosis (including family members)
    - If breast cancer, indicate if bilateral, premenopausal, or triple negative cancer
  - BRCA1/BRCA2 mutation history (if applicable)
- Genetic counseling/professional results (if applicable)
- Laboratory or Pathology reports

### Post service

- Procedure report(s)

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.*

### MN/IE

**The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.**

| Type | Code  | Description   |
|------|-------|---|
| CPT® | 81162 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)         |
|      | 81163 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis ( <b>Code effective 1/1/2019</b> )  |
|      | 81164 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) ( <b>Code effective 1/1/2019</b> ) |

| Type             | Code  | Description   |
|------------------|-------|---|
|                  | 81165 | BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis ( <b>Code effective 1/1/2019</b> )  |
|                  | 81166 | BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) ( <b>Code effective 1/1/2019</b> )   |
|                  | 81167 | BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) ( <b>Code effective 1/1/2019</b> )   |
|                  | 81211 | 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) ( <b>Deleted code effective 1/1/2019</b> ) |
|                  | 81212 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants  |
|                  | 81213 | BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants ( <b>Deleted code effective 1/1/2019</b> )  |
|                  | 81214 | 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) ( <b>Deleted code effective 1/1/2019</b> )                       |
|                  | 81215 | BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant  |
|                  | 81216 | BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis  |
|                  | 81217 | BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant  |
|                  | 81432 | Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53                     |
|                  | 81433 | Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11   |
|                  | 81479 | Unlisted molecular pathology procedure  |
| HCPCS            | None  |   |
| ICD-10 Procedure | None  |   |

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action              | Reason                   |
|----------------|---------------------|--------------------------|
| 10/15/1997     | New Policy Adoption | Medical Policy Committee |

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

| Effective Date | Action   | Reason                   |
|----------------|--|--------------------------|
| 06/01/1999     | BCBSA Medical Policy adoption  | Medical Policy Committee |
| 05/01/2001     | Administrative Review  | Administrative Review    |
| 08/01/2005     | BCBSA Medical Policy adoption  | Medical Policy Committee |
| 10/01/2005     | Administrative Review  | Administrative Review    |
| 01/11/2008     | Policy Revision  | Medical Policy Committee |
| 12/05/2008     | Policy Revision  | Medical Policy Committee |
| 05/06/2009     | Coding Update  | Administrative Review    |
| 07/28/2009     | Criteria Revised   | Medical Policy Committee |
| 11/04/2009     | Coding update  | Administrative Review    |
| 04/02/2010     | Policy revision with position change to clarify BART testing   | Medical Policy Committee |
| 07/15/2010     | Policy Revision with position change adopting 2010 NCCN guidelines   | Medical Policy Committee |
| 09/13/2010     | Coding Update  | Administrative Review    |
| 03/30/2012     | Title change from BRCA1 and BRCA2 Genetic Testing with position change   | Medical Policy Committee |
| 06/13/2012     | Coding Update  | Administrative Review    |
| 08/21/2012     | Administrative Update (Clarification of Policy Guideline)  | Administrative Review    |
| 02/22/2013     | Coding Update  | Administrative Review    |
| 03/29/2013     | Policy revision with position change   | Medical Policy Committee |
| 10/9/2013      | Administrative Update (Clarification of BART testing policy statement)   | Administrative Review    |
| 12/19/2013     | Policy revision with position change   | Medical Policy Committee |
| 03/30/2015     | Administrative Update (Revision and clarification of the Documentation Required section)   | Administrative Review    |
| 08/31/2015     | Policy title change from Genetic Testing for Hereditary Breast and/or Ovarian Cancer Administrative Update (Formatting changes only)                       | Administrative Review    |
| 02/01/2016     | Coding update  | Administrative Review    |
| 01/01/2017     | Policy title change from Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1/BRCA2)<br>Policy revision without position change     | Medical Policy Committee |
| 09/01/2017     | Policy revision without position change  | Medical Policy Committee |
| 01/01/2018     | Policy revision without position change  | Medical Policy Committee |
| 04/01/2018     | Policy revision without position change  | Medical Policy Committee |
| 07/01/2018     | Policy revision without position change  | Medical Policy Committee |
| 01/01/2019     | Policy title change from Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2)<br>Policy statement clarification<br>Coding update | Administrative Review    |

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### **Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*