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

**Policy #** 00047
Original Effective Date: 05/13/2003
Current Effective Date: 05/11/2020

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Testing for CHEK2, PALB and ATM variants in assessment of breast cancer risk is addressed separately in medical policy 00504.*

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

**Patients with Cancer**

Based on review of available data, the Company may consider genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals will be considered when ANY of the following criteria are met:

- Individual from a family with a known *BRCA1* or *BRCA2* variant
- Personal history of breast cancer and one or more of the following:
    - Diagnosed at age ≤45 years
    - Diagnosed 46 to 50 years with:
        - An additional breast cancer primary at any age (e.g. bilateral cancer) [a]
        - ≥1 close relative with breast cancer at any age
        - ≥1 close relative with high grade (Gleason score ≥7) prostate cancer
        - An unknown or limited family history
    - Diagnosed ≤60 years with:

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

**Patients without Cancer**

Based on review of available data, the Company may consider genetic testing for BRCA1 and BRCA2 variants in unaffected individuals to be **eligible for coverage.****

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Patient Selection Criteria

Coverage eligibility for genetic testing for BRCA1 and BRCA2 variants in unaffected individuals will be considered when ANY of the following criteria are met:

- Individual from a family with a known *BRCA1/BRCA2* variant; or
- 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients with Cancer; or
- 3rd-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND ≥2 1st-, 2nd-, or 3rd-degree relatives[b] with breast cancer (≥1 at age ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer; or
- Individual with a family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with BRCA 1/ 2 gene variants with documented positive results on the appropriate familial risk assessment tool (e.g. Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Tyrer- Cuzick Model, and BRCAPRO) who has received comprehensive genetic counseling that included at minimum detailed kindred analysis, risk assessment for potentially harmful BRCA 1/ 2 variants, patient education, discussion of the benefits and harms of testing, interpretation of results, and discussion of management options, when comprehensive genetic counseling resulted in a recommendation for BRCA genetic testing.

*Note: 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).*

[a] Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

[b] For the testing criteria mentioned above, "close relatives" pertain to first-, second-, or third-degree blood relatives on the same side (either maternal or paternal side) of the family.

i. 1st-degree relatives are parents, siblings, and children.
ii. 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.

iii. 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great- grandchildren, and first cousins.

**Table 1. Ontario Family History Assessment Tool [a]**

| Risk Factor | Points |
|---|---|
| Breast and ovarian cancer | |
| Mother | 10 |
| Sibling | 7 |
| Second-/third-degree relative | 5 |
| Breast cancer relatives | |
| Parent | 4 |
| Sibling | 3 |
| Second-/third-degree relative | 2 |
| Male relative (add to above) | 2 |
| Breast cancer characteristics | |
| Onset age, y | |
| 20-29 | 6 |
| 30-39 | 4 |
| 40-49 | 2 |
| Premenopausal/perimenopausal | 2 |
| Bilateral/multifocal | 3 |

| | |
|---|---|
| Ovarian cancer relatives | |
| Mother | 7 |
| Sibling | 4 |
| Second-/third-degree relative | 3 |
| Ovarian cancer onset age, y | |
| <40 | 6 |
| 40-60 | 4 |
| >60 | 2 |
| Prostate cancer onset | |
| Age <50 y | 1 |
| Colon cancer onset | |
| Age <50 y | 1 |
| Family total | |
| Referral [b] | ≥10 |

[a] See Gilpin et al, Oros et al, Panchal et al, Parmigiani et al.
[b] Referral with score of 10 or greater corresponds to doubling of lifetime risk for breast cancer (22%).

**Table 2. Manchester Scoring System [a,b]**

| **Risk Factor (Age at Onset for Relative in Direct Lineage)** | ***BRCA1* Score** | ***BRCA2* Score** |
|---|---|---|
| Female breast cancer, y | | |

| | | |
|---|---|---|
| <30 | 6 | 5 |
| 30-39 | 4 | 4 |
| 40-49 | 3 | 3 |
| 50-59 | 2 | 2 |
| ≥60 | 1 | 1 |
| Male breast cancer, y | | |
| <60 | 5[c] | 8[d] |
| ≥60 | 5[c] | 5[d] |
| Ovarian cancer, y | | |
| <60 | 8 | 5 |
| ≥60 | 5 | 5 |
| Pancreatic cancer | | |
| Any age | 0 | 1 |
| Prostate cancer, y | | |
| <60 | 0 | 2 |
| ≥60 | 0 | 1 |
| Total individual genes | 10 | 10 |
| Total for combined = 15 | | |

[a] See Oros et al, Parmigiani et al, Antoniou et al, Barcenas et al, Evans et al.
[b] A score of 10 in either column or a combined score of 15 for both columns would be equivalent to a 10% chance of identifying a *BRCA1* or *BRCA2* mutation.

[c] If testing for *BRCA2*.
[d] If testing for *BRCA1*.
Abbreviation: *BRCA*, breast cancer susceptibility gene.

**Table 3. Referral Screening Tool [a,b]**

| **History of Breast or Ovarian Cancer in the Family? If Yes, Complete Checklist** | | |
|---|---|---|
| **Risk Factor** | **Breast Cancer at Age ≤50 y** | **Ovarian Cancer at Any Age** |
| Yourself | | |
| Mother | | |
| Sister | | |
| Daughter | | |
| Mother's side | | |
| Grandmother | | |
| Aunt | | |
| Father's side | | |
| Grandmother | | |
| Aunt | | |
| ≥2 cases of breast cancer after age 50 y on same side of family | | |
| Male breast cancer at any age in any relative | | |
| Jewish ancestry | | |

[a] See Bellcross et al.
[b] Referral if 2 or more checks in table.

**Table 4. Pedigree Assessment Tool [a,b]**

| Risk Factor | Score for Every Family Member With Breast or Ovarian Cancer Diagnosis, Including Second-/Third-Degree Relatives |
|---|---|
| Breast cancer at age ≥50 y | 3 |
| Breast cancer at age <50 y | 4 |
| Ovarian cancer at any age | 5 |
| Male breast cancer at any age | 8 |
| Ashkenazi Jewish heritage | 4 |
| Total | |

[a] See Hoskins et al, Teller et al.
[b] Score 8 or greater is the optimal referral threshold.

# When Services Are Considered Not Medically Necessary

Repeated germline BRCA 1 and 2 genetic testing is considered to be **not medically necessary.****

*Note: If BRCA testing done before August 2006 was negative, repeated testing for large deletions and rearrangements in BRCA 1 and 2 may be warranted.*

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# When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for *BRCA*1 and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met to be **investigational**.*

Based on review of available data, the Company considers genetic testing in minors for *BRCA1* and *BRCA2* variants to be **investigational.***

# When Services Are Not Covered

The Company does not consider *BRCA* gene testing to be eligible for coverage if testing is performed primarily for the medical management of persons **not covered**** by Blue Cross and Blue Shield of Louisiana or HMO Louisiana, Inc.

*Note: BRCA* gene testing performed primarily for the medical management of persons *is considered an exclusion in most member contracts.*

# Policy Guidelines

Current U.S. Preventive Services Task Force guidelines recommend screening women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutation. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (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).
- International Breast Cancer Intervention Study instrument (Tyrer-Cuziak)
- brief versions of the BRCAPRO

**Recommended Testing Strategies**

Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for variants in *BRCA1* and *BRCA2*. Recommended strategies are listed below.

- In patients with a known familial *BRCA* variant, targeted testing for the specific variant is recommended.
- In patients with unknown familial *BRCA* variant:
    - Non-Ashkenazi Jewish descent
        - To identify clinically significant variants, National Comprehensive Cancer Network (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 exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* variants (eg, prostate cancer, pancreatic cancer, melanoma).
        - If no familial variant can be identified, 2 possible testing strategies are:
- Full sequencing followed by testing for *common* large genomic rearrangements (deletions, duplications) only if sequencing detects no variant (negative result).
    - More than 90% of *BRCA* variants will be detected by full sequencing.
- Alternatively, simultaneous full sequencing and testing for *common* large genomic rearrangements (also known as comprehensive *BRCA* testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN
    - Comprehensive testing can detect 92.5% of *BRCA*1 or *BRCA2* variants.
        - If comprehensive *BRCA* testing is negative, testing for *uncommon* large genomic rearrangements (eg, BART) may be done.

- Testing for *uncommon* large rearrangements should not be done unless both sequencing and testing for *common* large rearrangements have been performed and are negative.
    - Among patients with negative comprehensive testing, BART identified a deleterious variant (positive result) in less than 1%.
    - Ashkenazi Jewish descent
        - In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first.
        - If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Variant Analysis).

**Comprehensive Variant Analysis**
Comprehensive variant analysis currently includes sequencing the coding regions and intron and exon splice sites, as well as testing to detect common large deletions and rearrangements that can be missed with sequence analysis alone. In addition, before August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing before this time may consider repeat testing for the rearrangements (see Coverage section for criteria).

**High-Risk Ethnic Groups**
Testing of eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations should begin with tests specifically for these variants. For example, founder mutations account for approximately three-quarters of the *BRCA* variants found in Ashkenazi Jewish populations. When testing for founder mutations is negative, comprehensive variant analysis should then be performed.

**Testing Unaffected Individuals**
In unaffected family members of potential *BRCA* variant 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, because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination.

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

**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.

# Background/Overview

**Hereditary Breast and Ovarian Cancer Syndrome**
Several genetic syndromes with an autosomal dominant pattern of inheritance that features breast cancer have been identified. Of these, HBOC and some cases of hereditary site-specific breast cancer have in common causative variants in *BRCA* (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer

occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early-onset breast cancer with or without male cases, but without ovarian cancer. For this evidence review, BCBSA refers collectively to both as *hereditary breast and/or ovarian cancer*.

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

**Clinical Features Suggestive of BRCA Variant**

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30. In several studies, BRCA variants were independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years). In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2*variants is in the 40s. In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* variants. In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants. Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of BRCA variants in the absence of family history in this population.

As in the general population, a family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a *BRCA* variant in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will

have a *BRCA* variant depending on the extent and nature of the family history. Several other studies have documented the significant influence of family history.

In patients with "triple-negative" breast cancer (ie, negative for expression of estrogen, progesterone, and overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of *BRCA* variants. Pathophysiologic research has suggested that the physiologic pathway for the development of triple-negative breast cancer is similar to that for *BRCA*-associated breast cancer. In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, Kandel et al (2006) reported there was a greater than 3-fold increase in the expected rate of *BRCA* variants. *BRCA1* variants were found in 39.1% of patients and *BRCA2* variants in 8.7%. Young et al (2009) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for *BRCA* testing. Six BRCA variants (5 *BRCA1*, 1 *BRCA2*) were found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had BRCA variants (12 in *BRCA1*, 3 in *BRCA2*).

# FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

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.

Numerous *BRCA* tests are available as listed below. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these:

Myriad Genetic Laboratories offers the following tests:

- Comprehensive BRACAnalysis®‡ test includes complete sequencing of *BRCA1* and *BRCA2* and gap polymerase chain reaction for five 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℠‡ suite of tests, which includes: targeted *BRCA1* and *BRCA2* variant analysis; a founder mutation panel for Ashkenazi Jewish patients (three 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 addition to the various individual variant tests which are the focus of this policy, numerous other multigene panel tests exist that include *BRCA1/2* among other genes. Although these multigene panel tests are outside of the scope of this review, among them, it is worth noting that FoundationOne CDx™‡ (F1CDx) is an FDA-approved companion diagnostic for use of Lynparza®‡ (olaparib) and Rubraca®‡ (rucaparib) in accordance with their respective FDA labels in women with ovarian cancer. F1CDx is FDA-approved to assess *BRCA1/2* and other homologous recombination pathway genes (e.g. *ATM, BRIP1, CHEK2, FANCA, FANCL, FANCM, NBN, RAD51C, RAD51D*, and *RAD54L as well as* MSI and DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*). *FoundationOne CDx is also* FDA-approved for determining homologous recombination deficiency based on genomic loss of heterozygosity (LOH) and BRCA mutant status.

# Rationale/Source

**Hereditary Breast and Ovarian Cancer Syndrome**

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

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diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants. Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of BRCA variants in the absence of family history in this population.

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# Supplemental Information

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

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

In response to requests, input was received for 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) while this policy was under review in 2010. Those providing

input were in general agreement with the Policy statements considering testing for genomic rearrangements of *BRCA1* and *BRCA2* as medically necessary and with adding fallopian tube and primary peritoneal cancer as *BRCA*-associated malignancies to assess when obtaining the family history.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

**Breast Cancer and Ovarian Cancer**
Current NCCN(v.32.2019) guidelines on the genetic and familial high-risk assessment of breast and ovarian cancers include criteria for identifying individuals who should be referred for further risk assessment and separate criteria for genetic testing. Patients who satisfy any of the testing criteria listed in Table 5 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. The NCCN recommends if a somatic variant is identified through tumor profiling, then *BRCA1* and *BRCA2* germline testing is recommended.

**Table 5. *BRCA1* and *BRCA2* Testing Criteria for Hereditary Breast and Ovarian Cancer Syndrome**

| **Recommendations** |
|---|
| 1. Individual from a family with a known *BRCA1*/*BRCA2* 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 |

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| **Recommendations** |
|---|
| ≥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 cancer at any age or breast cancer at or before age 50 or ≥2 relatives with breast, pancreatic or prostate cancer (any grade) at any age. |
| 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 ≥1 1st- or 2nd-degree blood relative meeting any of the above criteria |
| 9. Regardless of family history, some individuals with *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.

Additionally, the NCCN Ovarian Cancer guidelines (v2.2019) recommend tumor molecular testing prior to initiation of therapy for persistent/recurrent disease (OV-6) and describe in multiple algorithms that testing should include at least *BRCA1/2* and microsatellite instability or DNA

mismatch repair, and evaluation of homologous recombination deficiency can be considered (OV-6, OV-7, OV-B Principles of Pathology, OV-C Principles of Systemic Therapy).

**Pancreatic Adenocarcinoma**
Current NCCN guidelines for pancreatic adenocarcinoma (v.3.2019) 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."

**Prostate Cancer**
The current NCCN guidelines for prostate cancer are (v.4.2019). For initial risk stratification and staging workup for clinically localized disease, footnote c states: "Family history for known germline variants and genetic testing for germline variants should include *MLH1, MSH2, MSH6, and PMS2* (for Lynch Syndrome)and homologous recombination genes *BRCA1, BRCA2, ATM, PALB2, and CHEK2.* Consider cancer predisposition NGS panel testing, which includes *BRCA1, BRCA2, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, and PMS2."*

Also, in the "Genetic and Molecular Biomarker Analysis" section, germline testing is recommended and footnote ee states "Consider evaluating tumor for alterations in homologous recombination DNA repair such as: BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, and CHEK2."“At present, this information may be used for genetic counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors). If mutations in BRCA2, BRCA1, ATM, CHEK2, or PALB2 are found and/or there is a strong family history of cancer, refer to genetic counseling to assess for the possibility of hereditary breast and ovarian cancer (HBOC)."

**American Society of Clinical Oncology**
The American Society of Clinical Oncology has released statements on genetic and genomic testing for cancer susceptibility since 1996. The Society (2003) recommended that cancer predisposition testing be offered when 3 factors are at play: (1) there is a personal or family history suggesting genetic cancer susceptibility, (2) the test can be adequately interpreted, and (3) results will influence medical management of the patient or family member at hereditary risk of cancer. A 2010 update of this statement recommended that "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials." 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."

**Society of Gynecologic Oncology**
The SGO (2015) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer. The statement included criteria for recommending genetic assessment (counseling with or without testing) to patients who may be genetically predisposed to breast or ovarian cancer. Overall, the SGO and the NCCN recommendations are very similar; the main differences are 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, reaffirmed 2019) published a Practice Bulletin on hereditary breast and ovarian cancer syndrome. The following recommendation was based primarily on consensus and expert opinion (level C): "Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management."

**U.S. Preventive Services Task Force**
Current USPSTF recommendations for genetic testing of *BRCA1* and *BRCA2* variants in women state:

"The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutation with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after

counseling, genetic testing (B recommendation). The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful BRCA1/2 gene mutations. (D recommendation)"

"This recommendation applies to women who are asymptomatic for *BRCA*-related cancer and have unknown *BRCA* mutation status. It includes women who have never been diagnosed with *BRCA*-related cancer, as well as those with a previous breast, ovarian, tubal, or peritoneal cancer diagnosis who have completed treatment and are considered cancer free but have not been previously tested. While this recommendation applies to women, the net benefit estimates are driven by biological sex (ie, male/female) rather than gender identity. Persons should consider their sex at birth to determine which recommendation best applies to them."

Recommended brief familial risk assessment tools included the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), and brief versions of the BRCAPRO.

"In general, these brief familial risk assessment tools include factors associated with increased likelihood of potentially harmful *BRCA1/2* mutations. These include breast cancer diagnosis before age 50 years, bilateral breast cancer, presence of both breast and ovarian cancer in one individual, male family members with breast cancer, multiple cases of breast cancer in the family, 1 or more family members with 2 primary types of *BRCA*-related cancer (such as ovarian cancer), and Ashkenazi Jewish ancestry. The USPSTF recognizes that each risk assessment tool has advantages and limitations and found insufficient evidence to recommend one over another."

"The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful *BRCA1/2* mutations. It also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options. Genetic counseling about *BRCA1/2* mutation testing should be performed by trained health professionals, including suitably trained primary care clinicians. Several professional organizations describe the skills and training necessary to provide comprehensive genetic counseling."

"Testing for *BRCA1/2* mutations should be performed only when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to talk with a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision-making. Clinical practice guidelines recommend that *BRCA1/2* mutation testing begin with a relative with known *BRCA*-related cancer, including male relatives, to determine if a clinically significant mutation is detected in the family before testing individuals without cancer. If an affected family member with a *BRCA*-related cancer is not available, then the relative with the highest probability of mutation should be tested. The type of mutation analysis required depends on family history. Individuals from families with known mutations or from ancestry groups in which certain mutations are more common (eg, Ashkenazi Jewish founder mutations) can be tested for these specific mutations. Because risk assessment is primarily based on family history, it is unclear how women with a limited or unknown family history should be assessed for *BRCA1/2* mutation risk and potential referral to counseling or genetic testing."

"BRCA1/2 Mutation Testing
One good-quality trial (n = 1034) of women and men of Ashkenazi Jewish ancestry evaluated population-based *BRCA1/2* mutation testing vs family history–based testing. Results showed that a strategy of population-based testing for founder mutations detected more *BRCA1/2* mutation carriers than testing persons who met family history criteria. However, no clinical outcomes were reported and, because not all participants had *BRCA1/2* mutation testing, the accuracy of this strategy could not be determined. Genetic testing generally improved risk perception, with increased perceived risk of breast and ovarian cancer risk in *BRCA1/2* mutation carriers and decreased perceived risk in persons testing negative."

**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 6.

**Table 6. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| 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 |
| NCT04090567 | Overcoming PARP Inhibitor Resistance in BRCA Germline Mutation Positive Advanced Breast Cancer | 60 | June 2021 |
| NCT03740165 | A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (KEYLYNK-001/ENGOT-ov43) | 1086 | August 2025 |

NCT: national clinical trial.

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3. *Final Recommendation Statement: BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing*. U.S. Preventive Services Task Force. January 2020. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing1
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# Policy History

Original Effective Date: 05/13/2003
Current Effective Date: 05/11/2020
04/25/2003 Medical Policy Committee review
05/12/2003 Managed Care Advisory Council approval
05/07/2004 Medical Director review

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|---|---|
| 05/18/2004 | Medical Policy Committee review. Format revision. No substance changes to policy. |
| 06/28/2004 | Managed Care Advisory Council approval |
| 04/05/2005 | Medical Director review |
| 04/19/2005 | Medical Policy Committee review. Investigational statements added to address: BRCA testing for unaffected individuals without family history or early age diagnosis as well as the use of BRCA testing in minors. |
| 05/23/2005 | Managed Care Advisory Council approval |
| 06/07/2006 | Medical Director review |
| 06/21/2006 | Medical Policy Committee approval. Format changes, FDA / Governmental, Rational/Source updated in response to literature review. Coverage eligibility unchanged. |
| 05/02/2007 | Medical Director review |
| 05/23/2007 | Medical Policy Committee approval |
| 05/07/2008 | Medical Director review |
| 05/21/2008 | Medical Policy Committee approval. Title changed to match BCBSA. No change to coverage eligibility. |
| 07/02/2009 | Medical Director review |
| 07/22/2009 | Medical Policy Committee approval. No change to coverage eligibility. |
| 07/01/2010 | Medical Policy Committee approval |
| 07/21/2010 | Medical Policy Implementation Committee approval. Two statements were added to the coverage section: one to indicate testing for genomic rearrangements may be considered to be eligible with criteria and a second that testing for CHEK2 mutations is investigational. Fallopian tube cancer and primary peritoneal cancer added to the coverage statements as additional cancers to be assessed in determining family history to assess risk. |
| 07/07/2011 | Medical Policy Committee review |
| 07/20/2011 | Medical Policy Implementation Coverage eligibility unchanged. |
| 04/12/2012 | Medical Policy Committee review |
| 04/25/2012 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 09/06/2012 | Medical Policy Committee review |

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| 09/19/2012 | Medical Policy Implementation Committee approval. Replaced the Patient Selection Criteria for both Cancer-affected Individuals and Unaffected Adults with criteria from the 2012 NCCN Guidelines. Added a *Note* following the Patient Selection Criteria for clarification. |
| 11/01/2012 | Medical Policy Committee review |
| 11/28/2012 | Medical Policy Implementation Committee approval. Removed "and either (1) there are 3 or more family members (1 lineage) affected with breast or ovarian or fallopian tube or primary peritoneal cancer or (2) who have a risk of a BRCA mutation of at least 10%" from that last eligible for coverage statement on testing for genomic rearrangements of the BRCA1 and BRCA 2 genes. |
| 03/04/2013 | Coding updated |
| 04/04/2013 | Medical Policy Committee review |
| 04/24/2013 | Medical Policy Implementation Committee approval. Criteria revised to track BCBSA. |
| 06/05/2014 | Medical Policy Committee review |
| 06/18/2014 | Medical Policy Implementation Committee approval. Policy coverage statement rewritten for clarity and policy was updated with current NCCN guidelines. Added a 4th criteria bullet for patients without cancer regarding BRCA testing. "Including those with a family history of pancreatic cancer" added to investigational statement. |
| 06/04/2015 | Medical Policy Committee review |
| 06/17/2015 | Medical Policy Committee approval. Title changed to match BCBSA. No change to coverage eligibility. |
| 08/03/2015 | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. |
| 01/01/2016 | Coding update |
| 06/02/2016 | Medical Policy Committee review |
| 06/20/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 06/01/2017 | Medical Policy Committee review |
| 06/21/2017 | Medical Policy Implementation Committee approval. Removed *CHEK2* statement and added reference to 00504 which addresses *CHEK2, PALB* and A*TM* testing. |
| 06/07/2018 | Medical Policy Committee review |

06/20/2018 Medical Policy Implementation Committee approval. Replaced "mutation(s)" with "variant(s)" throughout the policy. Created a "When Services Are Eligible for Coverage" section for the first coverage statement, since it stands alone with no criteria. Changed the last three criteria bullets in the "Patients with Cancer" section to as follows:

- Personal history of pancreatic cancer or prostate cancer[c] at any age AND ≥1 1st-, 2nd-, or 3rd-degree relatives[a] with either of the following.
  - Breast cancer ≤50; or
  - Ovarian/fallopian tube/primary peritoneal cancer at any age.
- Personal history of pancreatic cancer or prostate cancer[b] at any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic or prostate cancer[b] at any age.
- For pancreatic cancer, if Ashkenazi Jewish ancestry no additional affected relative is needed.

Added footnotes (a-d) from BCBSA's policy to the end of the "When Services May Be Eligible for Coverage" section.

01/10/2019 Medical Policy Committee review

01/23/2019 Medical Policy Implementation Committee approval. Changed title from "Genetic Testing for Hereditary Breast and/or Ovarian Cancer" to "Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers". Removed the "When Services Are Eligible for Coverage" section. Coverage section with criteria on Patients with Cancer changed to track BCBSA. Added a *Note* after the coverage criteria for Patients without Cancer. After the coverage criteria, replaced the explanation of familial assessment of 1st, 2nd, and 3rd degree relatives with verbiage defining close relatives from NCCN Guidelines. Added a Not Medically Necessary section. Changed investigational statement for when criteria are not met to track BCBSA.

03/07/2019 Medical Policy Committee review

03/20/2019 Medical Policy Implementation Committee approval. Changed "ovarian carcinoma" to "ovarian/fallopian tube/primary peritoneal cancer" throughout the coverage section to be consistent with BCBSA and the NCCN guidelines Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 3.2019 that

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|---|---|
| | footnotes, "Ovarian carcinoma includes fallopian tube and primary peritoneal cancers." |
| 06/17/2019 | Coding update |
| 09/09/2019 | Coding update |
| 03/05/2020 | Medical Policy Committee review |
| 03/11/2020 | Medical Policy Implementation Committee approval. The definition of two breast cancer primaries was added as a footnote [a] from NCCN Guidelines for genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals for two criteria bullets. Removed the last criterion from genetic testing for BRCA1 and BRCA2 variants in unaffected individuals and replaced it with information from the U.S. Preventative Services Task Force regarding individuals with a family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with BRCA 1/ 2 gene mutations. Four familial risk assessment tools tables added at the end of the When Services May Be Eligible for Coverage section. |
| 04/02/2020 | Medical Policy Committee review |
| 04/08/2020 | Medical Policy Implementation Committee approval. Replaced 3rd criteria bullet for Patients without Cancer with information regarding individuals with a family history. Added tables for the Ontario Family History Assessment Tool, the Manchester Scoring System, the Referral Screening Tool, and the Pedigree Assessment Tool to the end of the eligible for coverage section. |
| 06/09/2020 | Coding update |
| 08/17/2020 | Coding update |

Next Scheduled Review Date: 04/2021

# Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 05/11/2020

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|---|---|
| CPT | 0102U, 0103U, 0129U, 0138U, 81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217, 81432, 81433<br>Code added eff 7/1/2020: 0172U |
| HCPCS | No codes |
| ICD-10 Diagnosis | C50.011-C50.029, C50.111-C50.129, C50.211-C50.229, C50.311-C50.329, C50.411-C50.429, C50.511-C50.529, C50.611-C50.629, C50.811-C50.829, C50.911-C50.929, C56.1-C56.9, C79.60-C79.62, C79.81, D05.00-D05.02, D50.10-D50.12, D05.80-D05.82, D05.90-D05.92, D07.30-D07.39, Z80.3, Z80.41, Z80.8-Z80.9, Z85.3, Z85.43 |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.