

BRCA Analysis

MOL.TS.238.A
v2.0.2025

Germline BRCA analysis is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
BRCA1 full duplication/deletion analysis	81166
BRCA1 full sequencing	81165
BRCA1 known familial mutation analysis	81215
BRCA2 full duplication/deletion analysis	81167
BRCA2 full sequencing	81216
BRCA2 known familial mutation analysis	81217
BRCA1/2 full duplication/deletion analysis	81164
BRCA1/2 full sequence analysis	81163
BRCA1/2 full sequencing and duplication/deletion analysis (combined)	81162
BRCA1 and BRCA2 Ashkenazi Jewish founder mutation analysis	81212

Criteria

Requests for BRCA analysis are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
 - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
 - No previous genetic testing that would detect the familial mutation, and
 - Known family mutation in BRCA1/2 identified in 1st, 2nd, or 3rd degree relative(s), AND
- Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Ashkenazi Jewish Founder Mutation Testing

- Genetic Counseling:
 - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
 - No previous full sequence testing, and
 - No previous deletion/duplication analysis, and
 - No previous Ashkenazi founder mutation testing, AND
- Age 18 years or older, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Ashkenazi Jewish descent, and
 - Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, or
 - Male or female breast cancer diagnosis at any age, or
 - Personal history of exocrine pancreatic cancer, or
 - Personal history of a confirmed diagnosis of prostate cancer at any age, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
 - Ashkenazi Jewish descent, and
 - A first or second degree relative who is Ashkenazi Jewish and meets at least one of the following:
 - Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, or
 - Male or female breast cancer diagnosis at any age, or
 - Exocrine pancreatic cancer, or
 - A confirmed diagnosis of prostate cancer at any age, and
 - The affected relative is deceased, unable, or unwilling to be tested[†], or

- Close blood relative (1st, 2nd, or 3rd degree) with a known Ashkenazi Jewish founder mutation in BRCA 1/2 gene, AND
 - Rendering laboratory is a qualified provider of service per the Health Plan policy.
- †Testing of unaffected individuals should only be considered when an affected family member is unavailable for testing due to the significant limitations in interpreting a negative result.

Full Sequence Analysis

- Genetic Counseling:
 - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
 - No previous full sequencing of BRCA1/2, and
 - No known mutation identified by previous BRCA analysis, AND
- Age 18 years or older, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Member meets "Diagnostic Testing for Symptomatic Individuals" criteria for AJ Founder mutation testing and had no previous founder mutation testing, and/or
 - Female with breast cancer diagnosis 50 years of age or younger, and/or
 - Diagnosed with two or more primary breast cancers at any age, and/or
 - Diagnosed at any age with triple negative breast cancer (i.e., estrogen receptor negative (ER-), progesterone receptor negative (PR-), and human epidermal growth factor receptor negative (HER2-) breast cancer), and/or
 - Male with breast cancer at any age, and/or
 - Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, and/or
 - Prostate cancer at any age with metastatic (radiographic evidence of or biopsy-proven disease), intraductal/cribriform histology, high-risk, or very-high-risk group, and/or
 - Exocrine pancreatic cancer, OR
- Personal & Family History Combination
 - Initial breast cancer diagnosis at any age and one or more of the following:
 - Breast cancer in at least 1 close blood relative (first-, second-, or third- degree) occurring at 50 years of age or younger, and/or
 - Epithelial ovarian, fallopian tube, or primary peritoneal cancer in at least 1 close blood relative (first-, second-, or third- degree) at any age, and/or
 - At least three breast cancer diagnoses at any age in patient and close blood relatives (first-, second-, or third- degree on same side of family), and/or
 - Male close blood relative (first- or second-degree) with breast cancer, and/or

- Metastatic (radiographic evidence of or biopsy proven disease) or intraductal/cribriform histology, high- or very-high risk prostate cancer in at least 1 close blood relative (first-, second-, or third- degree) at any age, and/or
- Pancreatic cancer in at least 1 close blood relative (first-, second-, or third-degree), and/or
- A close blood relative (first- or second-degree) with a triple negative breast cancer (ER-, PR-, HER2-) at any age, and/or
- At least two close blood relatives (on the same side of the family) with either breast cancer or a confirmed diagnosis of prostate cancer at any age, and/or
- Personal history of a confirmed diagnosis of prostate cancer at any age with ≥1 close blood relatives (on the same side of the family) with ovarian cancer at any age, pancreatic cancer at any age, metastatic (radiographic evidence of or biopsy proven disease) or intraductal/cribriform prostate cancer at any age, high- or very-high risk group prostate cancer at any age, breast cancer occurring at 50 years of age or younger, triple-negative breast cancer at any age, or male breast cancer, and/or
- Personal history of a confirmed diagnosis of prostate cancer at any age with two or more close blood relatives (on the same side of the family) with breast or prostate cancer (any grade) at any age, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals
 - The member has a first-degree relative who meets any of the "Diagnostic Testing for Symptomatic Individuals" or "Personal & Family History Combination" criteria above, or
 - The member has a second-degree relative who meets any of the "Diagnostic Testing for Symptomatic Individuals" or "Personal & Family History Combination" criteria above, excluding those who meet solely based on one of the following:
 - A single affected relative with pancreatic cancer, or
 - A single affected relative with prostate cancer (metastatic, intraductal/cribriform, or high- or very-high risk group per NCCN), or
 - A single affected relative who meets AJ Founder Mutation "Diagnostic Testing for Symptomatic Individuals" criteria, AND
 - Unaffected member is the most informative person to test and an affected family member cannot proceed with testing. If the member is not the most informative person to test, documentation must be provided by the ordering physician's office clearly documenting that it is impossible to test the most informative family member and describing the reason the unaffected member is being tested at this time, OR
- BRCA 1/2 mutation detected by tumor profiling in the absence of a germline mutation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Deletion/Duplication Analysis

- Genetic Counseling:
 - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
 - No previous BRCA deletion/duplication analysis, and
 - Meets criteria for full sequence analysis of BRCA1/2, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

- Family history terminology used in the above criteria is defined as follows:
 - First-degree relatives: parents, siblings, children
 - Second-degree relatives: aunts, uncles, grandparents, grandchildren, nieces, nephews and half-siblings
 - Third-degree relatives: great-grandparents, great-aunts, great-uncles, and first cousins
 - Relatives "on the same side of the family" are defined as individuals who share a common ancestor and are thus related to each other by blood (e.g., a member's maternal grandmother and maternal grandfather are not considered to be on the same side of the family if they are only related by marriage).
- For information on BRCA genetic testing to determine eligibility for targeted treatment (e.g., BRCAAnalysis CDx), please refer to the guidelines *Pharmacogenomic Testing for Drug Toxicity and Response* or *Somatic Mutation Testing*, as this testing is not addressed here.
- BRCA1/2 testing may be performed as part of a multigene, multisynndrome panel. For information on multigene, multisynndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:

- If BRCA1/2 deletion/duplication analysis will be performed concurrently with BRCA1/2 gene sequencing, CPT code 81162 is likely most appropriate.

What is hereditary breast and ovarian cancer?

Hereditary breast and ovarian cancer (HBOC) is an inherited form of cancer.

Prevalence

About 1 in 400-500 people in the general population has a BRCA1 or BRCA2 mutation. The prevalence of mutations is higher in people of Norwegian, Dutch, Inuit from Ammassalik (Greenland), or Icelandic ethnicity.^{1,2}

The prevalence of BRCA mutations varies among African Americans, Hispanics, Asian Americans, and non-Hispanic whites.²

Ashkenazi Jewish ancestry

About 1 in 40 people of Ashkenazi Jewish ancestry has a BRCA1 or BRCA2 mutation. The majority of the risk in the Ashkenazi Jewish population is associated with three common founder mutations, two of which are in the BRCA1 gene and one in the BRCA2 gene.^{1,3,4} These three mutations account for up to 99% of identified mutations in the Ashkenazi Jewish population.¹

Signs of HBOC

Individuals and/or families with HBOC may have the following histories of cancer or other characteristics:^{1,3,5}

- breast cancer at a young age, typically under age 50
- multiple breast primaries in one individual and/or family members (on the same side of the family)
- triple negative breast cancer (ER-, PR-, HER2-)
- ovarian, fallopian tube, or primary peritoneal cancer
- metastatic (radiographic evidence of or biopsy-proven disease), intraductal/cyribriform histology, high-risk, or very-high-risk group prostate cancer as defined by NCCN
- male breast cancer
- exocrine pancreatic cancer
- multiple cases of breast and/or ovarian cancer in a family or one individual with breast and ovarian cancer
- a confirmed diagnosis of prostate cancer and a family history of ovarian, breast, prostate, or pancreatic cancer
- previously identified germline BRCA1 or BRCA2 mutation in the family, or
- any of the above with Ashkenazi Jewish ancestry.

Cancer Risks

People with a BRCA mutation have an increased risk of various types of cancer.¹ These risks vary based on whether the mutation is in the BRCA1 or BRCA2 gene.

Type of cancer	Risk for malignancy with a BRCA1 mutation	Risk for malignancy with a BRCA2 mutation
Breast cancer	55-72% by age 70	45-69%
Ovarian cancer	39-44%	11-17%
Male breast cancer	1-2%	6-8%
Prostate cancer	21% by age 75	27% by age 70
Pancreatic cancer	1-3%	3-5% by age 70
Melanoma	N/A	Elevated

Note:

The risk for breast and ovarian cancer varies among family members and between families.

Cause

Up to 10% of all breast cancer and 15% of all ovarian cancer is associated with an inherited gene mutation, with BRCA1 and BRCA2 accounting for about 20-25% of all hereditary cases.^{1,2,6,7}

Inheritance

HBOC due to a mutation in BRCA1 or BRCA2 is an autosomal dominant disorder.¹

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

BRCA2 mutations inherited in an autosomal recessive manner (mutations in both copies of the gene) cause Fanconi Anemia. BRCA1 mutations inherited in an autosomal recessive manner usually end in miscarriage, however, rare reports of individuals with Fanconi Anemia due to biallelic mutations in BRCA1 have been reported. For more information on testing for Fanconi Anemia, please refer to the

guideline *Inherited Bone Marrow Failure Syndrome (IBMFS) Testing*, as this testing is not addressed here.

Diagnosis

The diagnosis is established by the identification of a pathogenic mutation in a gene associated with HBOC.

Management

Screening and prevention options are available to specifically address the increased risk of these cancers in a person with a BRCA mutation.¹

Special Considerations

Other inherited cancer syndromes that can include breast cancer are Li-Fraumeni syndrome (TP53), Cowden syndrome (PTEN), Hereditary Diffuse Gastric Cancer (CDH1), and Peutz-Jeghers syndrome (STK11). Additionally, other genes that can increase the risk for breast cancer are ATM, BARD1, CHEK2, NF1, and PALB2.^{1,3,8,9}

Test information

BRCA testing may include known familial mutation analysis, Ashkenazi Jewish founder mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

This test is appropriate for those who have a known BRCA mutation in the family and are not Ashkenazi Jewish.^{3,4}

Ashkenazi Jewish Founder Mutation Testing

Ashkenazi Jewish founder mutation testing includes the three mutations most commonly found in the Ashkenazi Jewish population:

- 185delAG and 5382insC in BRCA1, and
- 6174delT in BRCA2

Testing for these mutations detects up to 99% of mutations in those with Ashkenazi Jewish ancestry.

Founder mutation testing may be appropriate for those with Ashkenazi Jewish ancestry, even with a known familial mutation, since these mutations are common enough that multiple mutations can be found in the same Ashkenazi Jewish individual or family. If the familial mutation is not one of the three Ashkenazi Jewish mutations, the known familial mutation analysis for that mutation should be performed in addition to the founder mutation panel.^{1,3}

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2019) issued a statement regarding BRCA1/2 testing in all individuals with breast cancer:¹¹

- "With the advances in sequencing technologies and increasing access to and expanding indications for genetic testing, it remains critical to ensure that implementation of testing is based on evidence. Currently, there is insufficient evidence to recommend genetic testing for BRCA1/2 alone or in combination with multi-gene panels for all breast cancer patients."

American Society of Breast Surgeons

The American Society of Breast Surgeons (ASBrS, 2019) published a consensus guideline on genetic testing for hereditary breast cancer. They stated the following:¹²

- "Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling

and make recommendations to their patients regarding genetic testing and arrange testing. When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes."

- "Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies."
- "Patients who had genetic testing previously may benefit from updated testing. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing. Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2."
- "Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of "uninformative negative" results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above."

American Society of Clinical Oncology and Society of Surgical Oncology

A 2024 American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) joint guideline for germline testing in individuals with breast cancer stated the following:¹³

- "All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are 65 years or younger at diagnosis should be offered BRCA1/2 testing"
- "All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are older than age 65 should be offered BRCA1/2 testing if:
 - they are candidates for poly(ADP-ribose) polymerase (PARP) inhibitor therapy for early-stage or metastatic disease,
 - they have triple-negative breast cancer,
 - their personal or family history suggests the possibility of a pathogenic variant,
 - they were assigned male sex at birth,
 - they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations""BRCA1/2 testing should be offered to patients with a second primary cancer either in the contralateral or ipsilateral breast"

American Urological Association and American Society for Radiation Oncology

A 2022 American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) joint guideline for clinically localized prostate cancer stated the following:¹⁴

- "Clinicians should perform an assessment of patient and tumor risk factors to guide the decision to offer germline testing that includes mutations known to be associated with aggressive prostate cancer and/or known to have implications for treatment."
- Indications for germline testing for individuals with clinically localized prostate cancer included: a strong personal or family history of related cancers, a known familial mutation, and adverse tumor characteristics. Genes associated with prostate cancer risk included: "ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSh6, NBN, PALB2, PMS2, TP53."

American Urological Association and Society of Urological Oncology

A 2023 American Urological Association (AUA) and Society of Urological Oncology (SUO) joint guideline for advanced prostate cancer stated the following:¹⁵

- "In patients with mHSPC [metastatic hormone-sensitive prostate cancer], clinicians should offer germline testing, and consider somatic testing and genetic counseling."
- "In patients with mCRPC [metastatic castrate-resistant prostate cancer], clinicians should offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, MSI status, tumor mutational burden, and other potential mutations that may inform prognosis and familial cancer risk as well as direct potential targeted therapies."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) evidence and consensus-based guidelines addressed test indications for BRCA testing. These guidelines included recommendations related to unaffected individuals with a family history of cancer, those with a known mutation in the family, those with a personal history of breast cancer, exocrine pancreatic cancer, ovarian cancer, a confirmed diagnosis of prostate cancer, and men with breast cancer. They take into consideration age of diagnosis, tumor pathology, degree of relationship, and Ashkenazi Jewish ancestry.³

These recommendations are Category 2A, defined as "lower-level evidence" with "uniform NCCN consensus that the intervention is appropriate" and are frequently updated.³

Testing unaffected individuals

NCCN stated "[t]he testing of the unaffected individual (or of unaffected family members) is reasonable when no affected family member is available for testing." They cautioned that the significant limitations in interpreting results from unaffected relatives must be discussed.³

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2021) guidelines stated: "[f]or families with a known P/LPV, cascade testing refers to the process of counseling and testing at-risk family members. Relatives who do not carry the variation can avoid unnecessary medical interventions, whereas those who do can pursue surveillance and prevention measures aimed at reducing morbidity and mortality."⁸

U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force (USPSTF, 2019) recommendations addressed women with a personal and/or family history of breast cancer and/or ovarian, tubal, or primary peritoneal cancer. The USPSTF guideline recommended:¹⁰

- When a woman's personal or family history of cancer is consistent with a BRCA1/2 mutation: "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 breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations 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." (Evidence grade: B)
- When a woman's personal or family history is not consistent with a BRCA1/2 mutation: "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." (Evidence grade: D)

- "Genetic risk assessment and BRCA1/2 mutation testing is a multistep process that begins with identifying patients with family or personal histories of breast, ovarian, tubal, or peritoneal cancer; family members with known harmful BRCA1/2 mutations; or ancestry associated with harmful BRCA1/2 mutations. Risk for clinically significant BRCA1/2 mutations can be further evaluated with genetic counseling by suitably trained health care clinicians, followed by genetic testing of selected high-risk individuals and posttest counseling about results."
- "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."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for BRCA analysis will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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