Introduction

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.

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<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
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What is hereditary breast and ovarian cancer

Definition

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

Characteristics of HBOC

HBOC is characterized by any of the following:\footnote{1}{2}

- personal history of
  - breast cancer at a young age, typically under age 50
  - two primary breast cancers
- both breast and ovarian cancer
- triple negative breast cancer (ER-, PR-, HER2-)
- ovarian, fallopian tube, or primary peritoneal cancer, or
- metastatic prostate cancer

- multiple cases of breast or ovarian cancer in a family
- personal or family history of
  - male breast cancer
  - pancreatic cancer with breast or ovarian cancer, or
  - prostate cancer with a Gleason score of at least 7 and a family history of
    ovarian, breast, prostate, or pancreatic cancer

- previously identified BRCA1 or BRCA2 mutation in the family, or
- any of the above with Ashkenazi Jewish ancestry.

Inheritance

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.\(^{1,3-5}\)

BRCA mutations are inherited in an autosomal dominant manner. When a parent has a BRCA mutation, each offspring has a 50% risk of inheriting the mutation.\(^1\)

Prevalence

About 1 in 400 people in the general population has a BRCA1 or BRCA2 mutation. The prevalence of mutations is higher in people of Norwegian, Dutch, or Icelandic ethnicity.\(^1,3\)

The prevalence of BRCA mutations varies among African Americans, Hispanics, Asian Americans, and non-Hispanic whites.\(^3\)

**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.\(^1,6,7\) These three mutations account for 99% of identified mutations in the Ashkenazi Jewish population.\(^1\)

Cancer risks

People with a BRCA mutation have an increased risk of various types of cancer.\(^1\)
<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Risk</th>
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<td>Ovarian cancer</td>
<td>16.5-63%</td>
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<tr>
<td>Male breast cancer</td>
<td>1-9%</td>
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<tr>
<td>Prostate cancer</td>
<td>up to 20%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1-7%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Increased risk with BRCA2</td>
</tr>
</tbody>
</table>

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

**Screening and prevention**

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

**Breast cancer risk and other genes**

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

**Test information**

**Introduction**

BRCA testing may include full gene sequencing, deletion/duplication analysis, known familial mutation analysis, or multigene panel testing.

**Sequence analysis**

Full sequence analysis of BRCA1/2 genes looks at all of the coding regions of the BRCA1/2 genes, and often includes analysis of five common BRCA1/2 gene duplications and deletions.

Full sequence testing is typically appropriate as an initial test for people who meet criteria and do NOT have Ashkenazi Jewish ancestry.

**Deletion/duplication analysis**

Deletion/duplication analysis looks for large rearrangements, duplications, and deletions in the BRCA1/2 genes. Both BRCA1/2 sequencing and large rearrangement
analysis are often performed concurrently as routine laboratory practice when BRCA1/2 analysis is requested.

**Known familial mutation testing**

Known familial mutation testing looks for a specific mutation in either the BRCA1/2 gene previously identified in a family member.

This test is appropriate for those who have a known BRCA mutation in the family and are not Ashkenazi Jewish.

**Note** 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, then known familial mutation analysis for that mutation should be performed in addition to the founder mutation panel.\(^1,6\)

**Ashkenazi Jewish founder mutation testing**

Ashkenazi Jewish founder mutation testing includes the three mutations most commonly found in the Ashkenazi Jewish population: 187delAG and 5385insC in BRCA1 and 6174delT in BRCA2.\(^1\)

**Cancer multigene panels**

BRCA1/2 gene testing is also available in the form of multigene panels for individuals with a personal or family history of cancer suggestive of more than one hereditary cancer syndrome.

**Guidelines and evidence**

**Introduction**

This section includes relevant guidelines and evidence pertaining to BRCA analysis.

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN, 2019)\(^6\) evidence and consensus-based guidelines address test indications for BRCA testing. These recommendations are Category 2A, defined as “lower-level evidence with uniform NCCN consensus” and are frequently updated.

NCCN recommends BRCA analysis in individuals with a personal and/or family history of HBOC-related cancers such as breast cancer (male or female), ovarian cancer, prostate cancer, and pancreatic cancer. Testing recommendations take into
consideration age of diagnosis, tumor pathology, degree of relationship, and Ashkenazi Jewish ancestry.

Testing unaffected individuals

NCCN states “Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.” They caution that the significant limitations in interpreting results from unaffected relatives must be discussed.

U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force (USPSTF, 2019) recommendations address women with a personal and/or family history of breast and/or ovarian cancer.\textsuperscript{10} The USPSTF guideline recommends:\textsuperscript{10}

- When a woman’s personal or family history 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 “There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.”)

- 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 “There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.”)

“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.” \textsuperscript{11}

American College of Medical Genetics and Genomics

The ACMG issued a 2019 statement regarding BRCA1/2 testing in all breast cancer patients:\textsuperscript{12}

- “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
American Society of Breast Surgeons

The American Society of Breast Surgeons (2019) published a consensus guideline on genetic testing for hereditary breast cancer. They state the following:13

- "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."

- "Genetic testing should be made available to all patients with a personal 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."

National Society of Genetic Counselors

The National Society of Genetic Counselors (2013)\textsuperscript{8} guidelines also state that: “[For patients with negative sequencing results], it may be appropriate to request additional analysis to detect large genomic rearrangements in both BRCA1 and BRCA2 genes.”

In non-Ashkenazi Jewish individuals: If no mutation or inconclusive results are reported after sequence analysis, testing for large deletions/duplications in BRCA1/2 should be considered.\textsuperscript{1,7,8}

Criteria

Introduction

Requests for BRCA analysis are reviewed using these criteria.

Scope

\textbf{Note} This guideline does not address BRCA analysis for individuals of Ashkenazi Jewish ancestry. For information on this testing, please see the guideline \textit{BRCA Ashkenazi Jewish Founder Mutation Testing}. This guideline also does not address BRCA Analysis as part of multigene panels. For information on this testing, please see the guideline \textit{Hereditary Cancer Syndrome Multigene Panels}.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy),\textsuperscript{6,8,11,14} AND
- Previous Genetic Testing:
  - No previous full sequence testing or deletion/duplication analysis, and
  - Known family mutation in BRCA1/2 identified in 1st, 2nd, or 3rd degree relative(s), AND
- Age 18 years or older\textsuperscript{15}, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

\textbf{Note} If the familial mutation is not one of the three Ashkenazi Jewish mutations, then known familial mutation analysis for that mutation should be performed in addition to the founder mutation panel.\textsuperscript{1,6}
Full Sequence Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy)\textsuperscript{6,8,11,14}, 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\textsuperscript{15}, AND

- Diagnostic Testing for Symptomatic Individuals: \textsuperscript{6}
  - Non-Ashkenazi Jewish descent, AND: \textsuperscript{1,6}
  - Personal History:
    - Female with breast cancer diagnosis ≤45 years of age, and/or
    - Two breast primary tumors with first diagnosis ≤50 years of age and second diagnosis at any age (ipsilateral or bilateral), and/or
    - Diagnosed ≤60 years of age with estrogen receptor negative, progesterone receptor negative, and HER2 negative (triple negative) breast cancer, and/or
    - Diagnosed ≤50 years of age with a limited family history (NCCN provides this guidance regarding limited family history: “individuals with limited family history, such as fewer than two first- or second-degree female relatives having lived beyond 45 in either lineage, may have an underestimated probability of a familial mutation”), 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
    - Metastatic prostate cancer (radiographic evidence of or biopsy-proven disease), and/or
    - Pancreatic cancer, and/or
    - Diagnosed with three primary breast cancers at any age, OR

  - Personal & Family History Combination: \textsuperscript{6}
    - Diagnosed ≤50 years of age with at least one close blood relative with breast cancer diagnosed at any age, and/or
    - Diagnosed ≤50 years of age with at least one close blood relative with high grade prostate cancer (Gleason score at least 7) diagnosed at any age, and/or
• 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) ≤50 years of age, 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 2 close blood relatives (first-, second-, or third-degree on same side of family) with breast cancer at any age, and/or
  • Male close blood relative (first-, second-, or third-degree) with breast cancer, and/or
  • Metastatic prostate cancer (radiographic evidence of or biopsy proven disease) in at least 1 close blood relative (first-, second-, or third-degree), and/or
  • Pancreatic cancer in at least 1 close blood relative (first-, second-, or third-degree), and/or
  • A close blood relative (first-, second-, or third-degree) with a triple negative breast cancer (ER-, PR-, Her2-) occurring at age 60 or younger, and/or

• Personal history of high-grade prostate cancer (Gleason score at least 7) 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 prostate cancer (radiographic evidence of or biopsy proven disease) at any age, breast cancer <50 years, or male breast cancer, and/or

• Personal history of high-grade prostate cancer (Gleason score at least 7) 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
  o Non-Ashkenazi Jewish descent⁶, and
  o The member has a first or second degree relative who meets any of the “Personal History” or “Personal & Family History Combination” criteria above, and
  o Unaffected member is the most informative person to test. All affected family members are deceased, or all affected family members have been contacted and are unwilling to be tested, OR

• Ashkenazi Jewish individual who is negative for founder mutation testing, and has a high pre-test probability of carrying a BRCA mutation¹⁶,⁸ OR

• BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.
First-degree relatives (parents, siblings, children); second-degree relatives (aunts, uncles, grandparents, grandchildren, nieces, nephews and half-siblings); and third-degree relatives (great-grandparents, great-aunts, great-uncles, and first cousins) on the same side of the family.

Billing and reimbursement considerations

- These criteria may only be applied to a single BRCA sequencing CPT code as defined in the table at the beginning of this guideline.
- If BRCA gene testing will be performed as part of an expanded hereditary cancer syndrome panel, please also see that guideline for guidance.

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.

Billing and reimbursement considerations

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

If BRCA gene testing will be performed as part of an expanded hereditary cancer syndrome panel, please also see that guideline for guidance.

Other Considerations

BRCA genetic testing to determine eligibility for targeted treatment (e.g., PARP inhibitors for ovarian cancer or metastatic HER2-negative breast cancer) is addressed in either the Pharmacogenomic Testing for Drug Toxicity and Response guideline or the Somatic Mutation Testing-Solid Tumors guideline.

References

Introduction

These references are cited in this guideline.


3. NCI Fact Sheet for BRCA1 and BRCA2: Cancer Risk and Genetic Testing (Reviewed 05/17/2019) Available at: http://www.cancer.gov/about-cancer/causes-prevention/genetics/brcac-a-fact-sheet#r1


