BRCA Ashkenazi Jewish Founder Mutation Testing

Introduction

BRCA Ashkenazi Jewish founder mutation testing 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.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA 1 and BRCA 2 Ashkenazi Jewish Founder Mutations</td>
<td>81212</td>
</tr>
</tbody>
</table>

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:\(^1,2\)

- 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 have 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>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>38-87%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>16.5-63%</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>1-9%</td>
</tr>
<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.¹

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, and PALB2.¹,⁶,⁸,⁹

Test information
Introduction
BRCA testing may include Ashkenazi Jewish founder mutation testing, full gene sequencing, deletion/duplication analysis, known familial mutation analysis, or multigene panel testing.

Ashkenazi Jewish founder mutation testing
This test is appropriate for those who meet criteria and have Ashkenazi Jewish ancestry.⁶-⁸
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

Testing for these three most common mutations detects about 98% of mutations in those with Ashkenazi Jewish ancestry.¹,⁶

Other testing options
See the BRCA Analysis guideline for other testing options:

- full sequence testing
- deletion/duplication analysis, or
- known familial mutation.
Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to BRCA Ashkenazi Jewish founder mutation testing.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2019)\(^7\) evidence and consensus-based guidelines include unaffected women with a family history of cancer, those with a known mutation in the family, those with a personal history of breast cancer and/or ovarian cancer, those with a personal history of pancreatic and/or prostate (metastatic or Gleason score at least 7) cancer, and men with breast cancer.

Based on these guidelines, and the recommendations of the National Society of Genetic Counselors (2013)\(^8\) the founder mutation analysis is appropriate for any individual with Ashkenazi Jewish ancestry with a personal history of breast, epithelial ovarian, fallopian tube, primary peritoneal, prostate (Gleason score at least 7), or pancreatic cancer.

These recommendations are Category 2A, defined as "lower-level evidence with uniform NCCN consensus."

U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force (USPSTF, 2013) recommendations address women who do not have a personal history of breast and/or ovarian cancer, but rather have a family history of these cancer types.\(^10,\,11\)

The USPSTF guideline recommends that primary care providers identify women who have a family history of breast, ovarian, fallopian tube, or peritoneal cancer with one of several screening tools. These tools are designed to identify women who may be at an increased risk to carry a BRCA mutation. Women identified as high risk should then be referred for genetic counseling and, if indicated after counseling, BRCA testing.

Women identified as high risk by these screening tools typically have one or more of the following characteristics:\(^10-11\)

- a first or second degree relative with
  - breast cancer before 50 years old
  - ovarian cancer
  - bilateral/multifocal breast cancer, or
  - both breast and ovarian cancers
- a first or second degree male relative with breast cancer
- two or more relatives (first, second, third degree) with
• breast or ovarian cancer or both
• breast, prostate, or pancreatic cancer, or
• presence of Ashkenazi Jewish ancestry with any of the above

Grade B recommendation

The USPSTF considers this a Grade B recommendation: “The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.”

Criteria

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy),\(^7,8,10-12\) AND

• Previous Genetic Testing:
  o No previous full sequence testing, and
  o No previous deletion/duplication analysis, and
  o No previous Ashkenazi Jewish founder mutation testing, AND

• Age 18 years or older\(^{13}\), AND

• Diagnostic Testing for Symptomatic Individuals:\(^7\)
  o 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 pancreatic cancer, or
    • Personal history of high-grade prostate cancer (Gleason score at least 7) at any age, or
    • Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease), OR

• Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  o Ashkenazi Jewish descent, and
  o A first or second degree relative who is Ashkenazi Jewish and meets at least one of the following:\(^7\)
• Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, or
• Male or female breast cancer diagnosis at any age, or
• Pancreatic cancer, or
• High-grade prostate cancer (Gleason score at least 7), and
• The affected relative is deceased, unable, or unwilling to be tested†, or
• Close blood relative (1st, 2nd, or 3rd degree) with a known founder mutation in a BRCA1/2 gene, 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.

†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.

Note Full gene sequencing of BRCA1/2 may be indicated if no founder mutations are detected by 81212 and the individual meets the criteria above. See BRCA Analysis guideline for criteria.

References

Introduction

These references are cited in this guideline.


