Test Specific Guidelines

BRCA Ashkenazi Jewish Founder Mutation Testing

MOL.TS.135.A
v1.0.2023

Introduction

Germline BRCA Ashkenazi Jewish founder mutation testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure code
BRCA 1 and BRCA 2 Ashkenazi Jewish Founder Mutations	81212

What Is Hereditary Breast and Ovarian Cancer?

Definition

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

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, 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 99% of identified mutations in the Ashkenazi Jewish population.[1]

Symptoms

Individuals and/or families with HBOC may have the following histories of cancer:[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/cribriform 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 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 75
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.

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 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 Syndromes*, as this testing is not addressed here.

Diagnosis

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

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 syndrome10417 (TP53), Cowden syndrome10192 (PTEN), Hereditary Diffuse Gastric Cancer10317 (CDH1), and Peutz-Jeghers syndrome10643 (STK11). Additionally, other genes that can increase the risk for breast cancer are ATM, BARD1, CHEK2, NF1, and PALB210690.[1,3,8,9]

Test Information

Introduction

BRCA testing may include Ashkenazi Jewish founder mutation testing.

Ashkenazi Jewish Founder Mutation Testing

This test is appropriate for those who meet criteria and have Ashkenazi Jewish ancestry.[3,4,8]

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 up to 99% of mutations in those with Ashkenazi Jewish ancestry.[1,3]

Guidelines and Evidence

Introduction

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

National Comprehensive Cancer Network and National Society of Genetic Counselors

The National Comprehensive Cancer Network (NCCN, 2022) evidence and consensus-based guidelines included unaffected individuals with a family history of cancer, those with a known mutation in the family, those with a personal history of breast cancer, epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, exocrine pancreatic cancer, a confirmed diagnosis of prostate cancer, and men with breast cancer.[3]

Based on these guidelines, and the recommendations of the National Society of Genetic Counselors (NSGC, 2013), 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, exocrine pancreatic cancer, a confirmed diagnosis of prostate cancer, or male breast cancer.[3,8]

These recommendations are Category 2A, defined as "lower-level evidence with uniform NCCN consensus."[3]

Testing unaffected individuals

NCCN stated "Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing." They cautioned that the significant limitations in interpreting results from unaffected relatives must be discussed.[3]

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 "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 post-test counseling about results."[10]

"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."[10]

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

Introduction

Requests for Ashkenazi Jewish founder mutation testing are reviewed using these criteria.

- 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 Jewish 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 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.

Other Considerations

Testing of BRCA1 and BRCA2 may also include known familial mutation analysis, full sequence analysis, and/or deletion/duplication analysis. For information on additional BRCA1/2 testing, please refer to the guideline *BRCA Analysis*, as this testing is not addressed here.

References

Introduction

These references are cited in this guideline.

1. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. 1998 Sept 4 [Updated 2022 May 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1247/
2. NCI Fact Sheet for BRCA1 and BRCA2: Cancer Risk and Genetic Testing (Reviewed 04/25/2022). Available at: http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#r1
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. V.2.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
4. Rubinstein WS. Hereditary breast cancer in Jews. *Fam Cancer.* 2004; 3(3-4):249-57.
5. Hampel H et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med.* 2015; 17(1):70-87. Available at: https://www.acmg.net/docs/gim2014147a.pdf
6. van der Groep P, van der Wall E, van Diest, P. Pathology of hereditary breast cancer. *Cell Oncol.* 2011; 34:71-88.
7. Walsh T, King MC. Ten genes for inherited breast cancer. *Cancer Cell.* 2007;11:103-5.
8. Berliner JL, Fay AM, Cummings SA, Burnett B, Tillmanns T. NSGC Practice Guideline: Risk assessment and genetic counseling for hereditary breast and ovarian cancer. *J Genet Counsel.* 2013; 22:155-63.
9. Kleibl Z, Kristensen VJ. Women at high risk of breast cancer: Molecular characteristics, clinical presentation, and management. *Breast.* 2016; 28:136-144.
10. U.S. Preventive Services Task Force (USPSTF). Risk assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: recommendation statement. Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing?ds=1&s=genetic counseling

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924