Test Specific Guidelines

BRCA Analysis

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Introduction

Germline BRCA analysis 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.

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 Deletion/Duplication Analysis (Combined)	81162

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]

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/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%

Type of cancer	Risk for malignancy with a BRCA1 mutation	Risk for malignancy with a BRCA2 mutation
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 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 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 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 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.

Note **Ashkenazi Jewish founder mutation analysis includes three mutations most commonly found in the Ashkenazi Jewish population. 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.[1,3]**

For information on founder mutation testing in Ashkenazi Jewish individuals, please refer to the guideline ***BRCA Ashkenazi Jewish Founder Mutation Testing***, as this testing is not addressed here.

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.

Full sequence testing is typically appropriate as an initial test for people who meet criteria and do NOT have Ashkenazi Jewish ancestry.[1,3]

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

Introduction

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

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:[10]

- "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:[11]

- "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. 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."**

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) evidence and consensus-based guidelines addressed test indications for BRCA testing. These recommendations are Category 2A, defined as "lower-level evidence with uniform NCCN consensus" and are frequently updated.[3]

NCCN recommended 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 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.

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2013) guidelines stated: "[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." [8] 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.[1,4,8]

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:[12]

- **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 posttest counseling about results."**

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 BRCA analysis are reviewed using these 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.**

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 year or older, AND**
- **Ancestry:**
  - **Member is of non-Ashkenazi Jewish descent, or**
  - **Member is of Ashkenazi Jewish descent and is negative for founder mutation testing, AND**
- **Diagnostic Testing for Symptomatic Individuals:**

- Female with breast cancer diagnosis 45 years of age or younger, and/or
- Multiple primary breast tumors (synchronous or metachronous) with at least one diagnosed at 50 years of age or younger, and/or
- Diagnosed at any age with estrogen receptor negative, progesterone receptor negative, and HER2 negative (triple negative) breast cancer, and/or
- Diagnosed at 50 years of age or younger with an unknown or 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
- 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, and/or
- Diagnosed with three or more primary breast cancers at any age, OR

- Personal & Family History Combination
  - Diagnosed at 50 years of age or younger with at least 1 close blood relative (first-, second-, or third- degree) with breast cancer, ovarian cancer, pancreatic cancer, and/or a confirmed diagnosis of prostate cancer, 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) 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, breast cancer occurring at 50 years of age or younger, 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 or second degree relative who meets any of the "Personal History" or "Personal & Family History Combination" criteria above, with the exception of an affected relative with pancreatic or prostate cancer. A member will meet criteria if the affected relative with pancreatic cancer or prostate cancer (metastatic, intraductal/cribriform, or high- or very-high-risk group per NCCN) is a first-degree relative. If the relative with prostate or pancreatic cancer is a second-degree relative, additional family history is needed to support testing of the member, and
  - 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

- 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.

** 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.

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

For information on BRCA genetic testing to determine eligibility for targeted treatment (e.g., PARP inhibitors for ovarian cancer or metastatic HER2-negative breast cancer), please refer to the guidelines *Pharmacogenomic Testing for Drug Toxicity and Response* or *Somatic Mutation Testing-Solid Tumors*, as this testing is not addressed here.

BRCA1/2 testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

For information on founder mutation testing in Ashkenazi Jewish individuals, please refer the guideline *BRCA Ashkenazi Jewish Founder Mutation Testing*, as this testing is not addressed here.

References

Introduction

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