Hereditary Breast and Ovarian Cancer

Indications for Ordering

- Numerous professional guidelines are available for hereditary breast and ovarian cancer testing
  - Ordering indications below are suggestions based on National Comprehensive Cancer Network (NCCN) guidelines for BRCA1- and BRCA2-associated hereditary breast and ovarian cancer (HBOC) syndrome
- For any individual with a family member who has a known pathogenic variant previously identified in 1 of the genes on the Breast and Ovarian Hereditary Cancer Panel, order the Familial Mutation, Targeted Sequencing test

Based on personal AND family history, testing is indicated for

- Women with any of the following
  - Breast cancer diagnosed by age 45
  - Ovarian cancer
  - 2 primary breast cancers, with 1 diagnosed by age 50
  - Breast cancer diagnosed by age 50, with 1 or more family members with either pancreatic or prostate cancer
  - Triple negative breast cancer diagnosed by age 60
  - Breast cancer at any age with 1 or more family members with breast cancer diagnosed by age 50
  - Breast cancer diagnosed at any age with 2 or more family members from the same side of the family with breast cancer at any age
  - Breast cancer diagnosed at any age with 1 or more family members with ovarian cancer
  - Breast cancer diagnosed at any age with 2 or more family members from the same side of the family with pancreatic or prostate cancer
  - Breast cancer diagnosed at any age and male family member with breast cancer
  - Breast or pancreatic cancer at any age and Ashkenazi Jewish ancestry
  - Pancreatic cancer or prostate cancer at any age with 1 or more family members with breast cancer by age 50 or ovarian cancer at any age

- Men with any of the following
  - Breast cancer at any age
  - Pancreatic cancer or prostate cancer at any age with 1 or more family members with breast cancer by age 50 or ovarian cancer at any age
  - Pancreatic cancer or prostate cancer at any age with 2 or more family members from the same side of the family with breast, pancreatic, and/or prostate cancer at any age

Based on family history ONLY, testing is indicated for an asymptomatic patient with

- First- or second-degree family member meeting any of the criteria above
- Third-degree family member who has breast and/or ovarian cancer and 2 or more family members with breast cancer (at least 1 diagnosed by age 50) and/or ovarian cancer

Test Description

Breast and Ovarian Hereditary Cancer Panel

- Targeted capture of all coding exons and intron/exon junctions of the genes listed in the table below, including the PTEN promoter region, followed by massively parallel sequencing
- Sanger sequencing of CHEK2 c.1100delC variant
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array for the genes listed in the table below

BRCA1 and BRCA2 testing only

- Bidirectional sequencing of the entire coding regions and intron-exon boundaries of the BRCA1 and BRCA2 genes
- Deletion/duplication analysis by multiplex ligation-dependent probe amplification (MLPA) for the BRCA1 and BRCA2 genes
**Tests to Consider**

**Primary tests**

**Breast and Ovarian Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 20 Genes 2012026**
- Preferred first-tier genetic test to diagnose a hereditary cancer syndrome related to breast and ovarian cancer if a known familial variant has NOT been previously identified
- When a relative has a previously identified pathogenic variant, see Familial Mutation, Targeted Sequencing
- Highest detection rate for a hereditary syndrome related to breast and/or ovarian cancer, but also highest likelihood of identifying variants of uncertain significance

**Breast and Ovarian Hereditary Cancer Syndrome (BRCA1 and BRCA2) Sequencing and Deletion/Duplication 2011949**
- Preferred first-tier genetic test to confirm HBOC syndrome (BRCA1 and BRCA2 genes only)
- Up to 99% sensitivity for BRCA1 and BRCA2 variants
- 20-60% sensitivity for hereditary breast and ovarian cancers, in general
- When a relative has a previously identified pathogenic BRCA1 or BRCA2 gene variant, see Familial Mutation, Targeted Sequencing

**Breast and Ovarian Hereditary Cancer Syndrome (BRCA1 and BRCA2) Sequencing 2011954**
- Acceptable first-tier genetic test to confirm HBOC syndrome (BRCA1 and BRCA2 genes only)
- Up to ~90% sensitivity for BRCA1 and BRCA2 variants
- 20-60% sensitivity for hereditary breast and ovarian cancers, in general
- When a relative has a previously identified pathogenic BRCA1 or BRCA2 gene variant, see Familial Mutation, Targeted Sequencing

**Related tests**

**Familial Mutation, Targeted Sequencing 2001961**
- Useful when a pathogenic familial variant identifiable by sequencing is known

**Disease Overview**

**HBOC syndrome**

**Prevalence** – 1/500 individuals from general population or 1/40 Ashkenazi Jews have a BRCA1 or BRCA2 pathogenic variant
- BRCA1 and BRCA2 pathogenic variants are believed to cause 20-60% of hereditary breast and ovarian cancers, in general
- 5-10% of all breast cancers and 10-15% of all ovarian cancers are caused by BRCA1 or BRCA2 variants

**Age of onset**
- Sporadic breast cancer typically occurs after menopause and/or after age 50
- Breast cancer commonly occurs before menopause and/or before age 50 in carriers of BRCA1 and BRCA2 pathogenic variants

**Symptoms**
- BRCA1 pathogenic variant carriers are at increased risk for hereditary breast and ovarian cancers
  - May also be at increased risk for fallopian, peritoneal, cervical, uterine, pancreatic, and colorectal cancers
- BRCA2 pathogenic variant carriers are at increased risk for hereditary breast and ovarian cancers
  - May also be at increased risk for pancreatic, stomach, gallbladder, bile duct, and melanoma cancers
- Men with BRCA1 pathogenic variants are at increased risk for breast cancer and possibly pancreatic, prostate, and testicular cancers
- Men with BRCA2 pathogenic variants are at increased risk for breast, pancreatic, and prostate cancers
- See table below for full gene list and associated cancer risks

**Genetics**

**Genes** – see table

**Penetrance** – cumulative cancer risks for female pathogenic variant carriers include
- Breast cancer – 57% for BRCA1 and 49% for BRCA2 by age 70
- Ovarian cancer – 40% for BRCA1 and 18% for BRCA2 by age 70

**Test Interpretation**

**Clinical sensitivity**
- Although actual value is unknown, sensitivity of HBOC 20-gene panel is at least 20-60%
- BRCA1 and BRCA2 sequencing and deletion/duplication testing alone detects 20-60% of hereditary breast and ovarian cancers, in general (Pruthi, 2010; Meindl, 2011)
  - Up to 90% of BRCA1 and BRCA2 variants are detectable by sequencing
  - ~10% of BRCA1 and BRCA2 variants are detectable by large deletion/duplication analysis

**Test results**
- Positive
  - 1 pathogenic variant identified in a gene with autosomal dominant inheritance
    - Confirms a diagnosis of gene-specific risk/predisposition for associated hereditary cancer(s)
    - If the pathogenic variant is identified in BRCA1 or BRCA2, this confirms a diagnosis of HBOC syndrome
  - 2 pathogenic variants located on opposite chromosomes detected in the autosomal recessively inherited gene MUTYH
    - Confirms a diagnosis of MUTYH-associated polyposis (MAP) syndrome
  - 1 pathogenic variant detected in the autosomal recessively inherited gene MUTYH
    - Confirms carrier status for MAP syndrome

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• Negative
  o No pathogenic variants detected in any of the genes tested
    ▪ Reduces the likelihood of, but does not exclude, a hereditary cancer syndrome diagnosis
• Inconclusive
  o Variants of uncertain clinical significance may be identified

Limitations
• The following will not be determined or evaluated
  o Deep intronic and regulatory variants
  o Breakpoints for large deletions/duplications
  o Sequence changes in EPCAM gene
  o Exons 11-15 of CHEK2 gene will not be evaluated, with the exception of the c.1100delC variant
  o Deletions/duplications
    ▪ Exon 1 in CDH1, MSH2, and RAD51D genes
    ▪ Exons 4, 6, and 7 in STK11 gene
    ▪ Exon 8 in PTEN gene
    ▪ Exon 12 in ATM gene
• Small deletions or insertions may not be detected
• Diagnostic errors can occur due to rare sequence variations

References

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>NM #</th>
<th>OMIM #</th>
<th>Inheritance</th>
<th>Associated Cancer/Syndrome</th>
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<td>ATM</td>
<td>Ataxia telangiectasia mutated (includes complementation groups A, C and D)</td>
<td>000051</td>
<td>607585</td>
<td>AD, AR</td>
<td>Breast, possible increased risk for colorectal (AD) Ataxia telangiectasia (AR)</td>
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<td>BARD1</td>
<td>BRCA1-associated RING domain gene 1</td>
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<td>BRCA1</td>
<td>Breast cancer 1</td>
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<td>Breast cancer 2</td>
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<td>600185</td>
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<td>BRCA1 interacting protein C-terminal, helicase 1</td>
<td>032043</td>
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<td>Cadherin 1, E-cadherin (epithelial)</td>
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<td>EPCAM</td>
<td>Epithelial cell adhesion molecule</td>
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<td>185535</td>
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<td>Multiple endocrine neoplasia 1</td>
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<td>613733</td>
<td>AD</td>
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<td>MutL homologue 1, colorectal cancer, nonpolyposis type 2 (E. coli)</td>
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<td>AD, AR</td>
<td>Ovarian, colorectal, endometrial, gastric, bladder, kidney; Lynch syndrome (AD) Constitutional mismatch repair deficiency (AR)</td>
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<tr>
<td>Gene Symbol</td>
<td>Gene Name</td>
<td>NM #</td>
<td>OMIM #</td>
<td>Inheritance</td>
<td>Associated Cancer/Syndrome</td>
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<td>MutY homologue (<em>E. coli</em>)</td>
<td>001128425</td>
<td>604933</td>
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<td>Colorectal; MUTYH-associated polyposis (MAP) (AR) Possible increased risk for gastric, breast, duodenal, endometrium (AD)</td>
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<td>NBN</td>
<td>Nibrin (NBS1)</td>
<td>002485</td>
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<td>Breast, possible increased risk for ovarian (AD) Nijmegen breakage syndrome (AR)</td>
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<td>PALB2</td>
<td>Partner and localizer of BRCA2</td>
<td>024675</td>
<td>610335</td>
<td>AD, AR</td>
<td>Breast, pancreatic, possible increased risk for ovarian (AD) Fanconi anemia, complementation group N (AR)</td>
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<td>Phosphatase and tensin homolog</td>
<td>000314</td>
<td>601728</td>
<td>AD</td>
<td>Breast, thyroid, endometrial, colorectal; PTEN hamartoma tumor syndrome/Cowden syndrome</td>
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<td>RAD51 homolog (<em>S. cerevisiae</em>)</td>
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<td>602774</td>
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</table>

AD = autosomal dominant; AR = autosomal recessive