

# Hereditary Breast and Ovarian Cancer

## Indications for Ordering

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- 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
  - 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
  - Pathogenic *BRCA1* or *BRCA2* variant detected by tumor profiling
- 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

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### 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

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### 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

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### 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

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**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

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### 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

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

#### Limitations

- The following will not be determined or evaluated
  - Deep intronic and regulatory variants
  - Breakpoints for large deletions/duplications
  - Sequence changes in *EPCAM* gene
  - Exons 11-15 of *CHEK2* gene will not be evaluated, with the exception of the c.1100delC variant
  - 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

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- Pruthi S, Gostout BS, et al. Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian cancer. *Mayo Clin Proc.* 2010;85(12):1111-1120
- Walsh T, Casadei S, et al. Mutations in 12 genes for inherited ovarian cancer, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci USA.* 2011;108(44):18032-18037

Gene Symbol	Gene Name	NM #	OMIM #	Inheritance	Associated Cancer/Syndrome
<i>ATM</i>	Ataxia telangiectasia mutated (includes complementation groups A, C and D)	000051	607585	AD, AR	Breast, possible increased risk for colorectal (AD) Ataxia telangiectasia (AR)
<i>BARD1</i>	BRCA1-associated RING domain gene 1	000465	601593	AD	Breast, neuroblastoma
<i>BRCA1</i>	Breast cancer 1	007294	113705	AD	Breast, ovarian, fallopian, peritoneal, pancreatic, prostate; HBOC syndrome
<i>BRCA2</i>	Breast cancer 2	000059	600185	AD, AR	Breast, ovarian, fallopian, peritoneal, pancreatic, prostate, gallbladder, gastric, melanoma; HBOC syndrome (AD) Fanconi anemia, complementation group J (AR)
<i>BRIP1</i>	BRCA1 interacting protein C-terminal, helicase 1	032043	605882	AD, AR	Ovarian, possible increased risk for breast (AD) Fanconi anemia, complementation group J (AR)
<i>CDH1</i>	Cadherin 1, E-cadherin (epithelial)	004360	192090	AD	Gastric, breast, prostate
<i>CHEK2</i>	CHK2 checkpoint homologue ( <i>S. pombe</i> RAD53)	007194	604373	AD	Breast, colorectal, prostate
<i>EPCAM</i>	Epithelial cell adhesion molecule	002354	185535	AD	Colorectal, ovarian; Lynch syndrome
<i>MEN1</i>	Multiple endocrine neoplasia 1	130799	613733	AD	Glucagonomas, gastrinomas, VIPomas, thymic, bronchial, gastric, breast; multiple endocrine neoplasia type 1 (MEN1)
<i>MLH1</i>	MutL homologue 1, colorectal cancer, nonpolyposis type 2 ( <i>E. coli</i> )	000249	120436	AD, AR	Ovarian, colorectal, endometrial, gastric, bladder, kidney; Lynch syndrome (AD) Constitutional mismatch repair deficiency (AR)

Gene Symbol	Gene Name	NM #	OMIM #	Inheritance	Associated Cancer/Syndrome
<i>MSH2</i>	MutS homologue 2, colorectal cancer, nonpolyposis type 1 ( <i>E. coli</i> )	000251	609309	AD, AR	Ovarian, colorectal, endometrium, gastric, bladder, kidney; Lynch syndrome (AD) Constitutional mismatch repair deficiency (AR)
<i>MSH6</i>	MutS ( <i>E.coli</i> ) homologue 6	000179	600678	AD, AR	Ovarian, colorectal, endometrium, gastric, bladder, kidney; Lynch syndrome (AD) Constitutional mismatch repair deficiency (AR)
<i>MUTYH</i>	MutY homologue ( <i>E. coli</i> )	001128425	604933	AD, AR	Colorectal; <i>MUTYH</i> -associated polyposis (MAP) (AR) Possible increased risk for gastric, breast, duodenal, endometrium (AD)
<i>NBN</i>	Nibrin (NBS1)	002485	602667	AD, AR	Breast, possible increased risk for ovarian (AD) Nijmegen breakage syndrome (AR)
<i>PALB2</i>	Partner and localizer of BRCA2	024675	610335	AD, AR	Breast, pancreatic, possible increased risk for ovarian (AD) Fanconi anemia, complementation group N (AR)
<i>PTEN</i>	Phosphatase and tensin homolog	000314	601728	AD	Breast, thyroid, endometrial, colorectal; PTEN hamartoma tumor syndrome/Cowden syndrome
<i>RAD51C</i>	RAD51 homolog ( <i>S. cerevisiae</i> )	058216	602774	AD, AR	Ovarian, possible increased risk for breast (AD) Fanconi anemia, complementation group O (AR)
<i>RAD51D</i>	RAD51D homolog D ( <i>S. cerevisiae</i> )	002878	602954	AD	Ovarian, possible increased risk for breast
<i>STK11</i>	Serine/threonine kinase 11 (LKB1)	000455	602216	AD	Breast, colorectal, stomach, pancreatic, ovarian; Peutz-Jeghers syndrome
<i>TP53</i>	Tumor protein 53	000546	191170	AD	Breast, ovarian, brain, soft tissue and osteosarcomas, gastrointestinal, leukemia, lymphoma, adrenocortical carcinoma; Li-Fraumeni syndrome

AD = autosomal dominant; AR = autosomal recessive