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
  - 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

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

- 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

- Ford D, Easton DF, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1998;62:676-689
- Lalloo F, Evans DG. Familial breast cancer. Clin Genet. 2012;82:105-114
- Meindl A, Ditsch N, et al. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch Arztebl Int. 2011;108(19):323-330
- National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian (version 2.2017). https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection. Accessed Jan 2017
- National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (version 1.2017). https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection. Accessed June 2017
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- 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
ATM	Ataxia telangiectasia mutated (includes complementation groups A, C and D)	000051	607585	AD, AR	Breast, possible increased risk for colorectal (AD) Ataxia telangiectasia (AR)
BARD1	BRCA1-associated RING domain gene 1	000465	601593	AD	Breast, neuroblastoma
BRCA1	Breast cancer 1	007294	113705	AD	Breast, ovarian, fallopian, peritoneal, pancreatic, prostate; HBOC syndrome
BRCA2	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)
BRIP1	BRCA1 interacting protein C-terminal, helicase 1	032043	605882	AD, AR	Ovarian, possible increased risk for breast (AD) Fanconi anemia, complementation group J (AR)
CDH1	Cadherin 1, E-cadherin (epithelial)	004360	192090	AD	Gastric, breast, prostate
CHEK2	CHK2 checkpoint homologue (*S. pombe* RAD53)	007194	604373	AD	Breast, colorectal, prostate
EPCAM	Epithelial cell adhesion molecule	002354	185535	AD	Colorectal, ovarian; Lynch syndrome
MEN1	Multiple endocrine neoplasia 1	130799	613733	AD	Glucagonomas, gastrinomas, VIPomas, thymic, bronchial, gastric, breast; multiple endocrine neoplasia type 1 (MEN1)
MLH1	MutL homologue 1, colorectal cancer, nonpolyposis type 2 (*E. coli*)	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
MSH2	MutS homologue 2, colorectal cancer, nonpolyposis type 1 (*E. coli*)	000251	609309	AD, AR	Ovarian, colorectal, endometrium, gastric, bladder, kidney; Lynch syndrome (AD) Constitutional mismatch repair deficiency (AR)
MSH6	MutS (E.coli) homologue 6	000179	600678	AD, AR	Ovarian, colorectal, endometrium, gastric, bladder, kidney; Lynch syndrome (AD) Constitutional mismatch repair deficiency (AR)
MUTYH	MutY homologue (*E. coli*)	001128425	604933	AD, AR	Colorectal; *MUTYH*-associated polyposis (MAP) (AR) Possible increased risk for gastric, breast, duodenal, endometrium (AD)
NBN	Nibrin (NBS1)	002485	602667	AD, AR	Breast, possible increased risk for ovarian (AD) Nijmegen breakage syndrome (AR)
PALB2	Partner and localizer of BRCA2	024675	610335	AD, AR	Breast, pancreatic, possible increased risk for ovarian (AD) Fanconi anemia, complementation group N (AR)
PTEN	Phosphatase and tensin homolog	000314	601728	AD	Breast, thyroid, endometrial, colorectal; PTEN hamartoma tumor syndrome/Cowden syndrome
RAD51C	RAD51 homolog (*S. cerevisiae*)	058216	602774	AD, AR	Ovarian, possible increased risk for breast (AD) Fanconi anemia, complementation group O (AR)
RAD51D	RAD51D homolog D (*S. cerevisiae*)	002878	602954	AD	Ovarian, possible increased risk for breast
STK11	Serine/threonine kinase 11 (LKB1)	000455	602216	AD	Breast, colorectal, stomach, pancreatic, ovarian; Peutz-Jeghers syndrome
TP53	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					