Breast and Ovarian Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 20 Genes

Indications for Ordering

- Numerous professional guidelines are available for hereditary breast and ovarian cancer (HBOC) testing
  - Ordering indications below are suggestions based on National Cancer Institute recommendations
  - Should be combined with healthcare provider's clinical judgment
- For any individual with a family member with a known pathogenic variant previously identified in one of the genes on the Breast and Ovarian Hereditary Cancer Panel, order Familial Mutation, Targeted Sequencing

Based on symptoms

- For women with any of the following
  - Breast cancer diagnosed by age 50
  - Ovarian cancer
  - Two primary breast cancers
  - Breast cancer diagnosed by age 50 with one or more family members with breast cancer
  - Triple negative breast cancer diagnosed by age 60
  - Breast cancer at any age with one or more family members with breast cancer diagnosed by age 50
  - Breast cancer diagnosed at any age with two or more family members from the same side diagnosed with breast cancer at any age
  - Breast cancer at any age with one or more family members with ovarian cancer
  - Breast cancer diagnosed at any age with two or more family members with pancreatic or prostate cancer
  - Breast cancer diagnosed at any age and male family member with breast cancer
  - Breast cancer at any age and Ashkenazi Jewish ancestry
- For men with any of the following
  - Breast cancer at any age
  - Pancreatic cancer or prostate cancer at any age with two or more family members with breast, ovarian, pancreatic, and/or prostate cancer at any age

Based on family history (in asymptomatic patient)

- For women with no Ashkenazi Jewish ancestry and family history of any of the following on the same side of the family
  - One first- or second-degree relative with breast cancer at age 45 or younger
  - Two first-degree relatives diagnosed with breast cancer, one diagnosed at age 50 or younger
  - Two or more first-, second-, or third-degree relatives diagnosed with breast cancer
  - Any first-, second-, or third-degree relative with ovarian cancer
  - A first-degree relative with bilateral breast cancer
  - Breast cancer diagnosed in a male relative

Based on Ashkenazi Jewish ancestry and family history of any of the following

- First-degree relative diagnosed with breast or ovarian cancer
- Two second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer

Test Description

- Targeted capture of all coding exons and intron/exon junctions, 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

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, including HBOC, if a known familial variant has NOT been previously identified
- When a relative has been previously tested, see Familial Mutation, Targeted Sequencing
- Highest detection rate for HBOC syndrome but also highest likelihood of identifying variants of unknown significance

Breast and Ovarian Hereditary Cancer Syndrome (*BRCA1* and *BRCA2*) Sequencing and Deletion/Duplication 2011949

- Acceptable first-tier genetic test to confirm HBOC syndrome
- ~20-60% sensitivity for HBOC syndrome
  - Only the *BRCA1* and *BRCA2* genes are assayed
- When a relative has been previously tested, 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
- Up to ~90% sensitivity for *BRCA1* and *BRCA2* variants
- When a relative has been previously tested, 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* variant

- *BRCA1 and BRCA2* variants are believed to cause 20-60% of hereditary breast cancer
- 5-10% of all breast cancers and 10-15% of ovarian cancers are caused by *BRCA1* or *BRCA2* variants

Age of onset

- Sporadic breast cancer usually occurs after age 50
- Breast cancer commonly occurs before age 50 in *BRCA1* and *BRCA2* variant carriers

Symptoms

- *BRCA1* variant carriers are at increased risk for HBOC
  - May also be at increased risk for fallopian, peritoneal, cervical, uterine, pancreatic, and colorectal cancers
- *BRCA2* variant carriers are at increased risk for HBOC
  - May also be at increased risk for pancreatic, stomach, gallbladder, bile duct, and melanoma cancers
- Men with *BRCA1* variants are at increased risk for breast cancer and possibly pancreatic, prostate, and testicular cancers
- Men with *BRCA2* variants are at increased risk for breast, pancreatic, and prostate cancers

Diagnostic issues

- Diagnostic testing may indicate predisposition for developing HBOC and other associated cancers
  - Optimizes screening/medical management
- Allows asymptomatic family members to learn who is at increased risk
- Prevention of primary manifestations for *BRCA1* and *BRCA2* gene variant carriers
  - Prophylactic mastectomy and/or oophorectomy and chemoprevention using tamoxifen
- Breast cancer screening combines
  - Monthly breast self-examinations
  - Annual or semiannual clinical breast examinations
  - Annual mammography
  - Breast MRI
- Ovarian cancer screening combines
  - Annual or semiannual pelvic examinations
  - Transvaginal ultrasound
  - Measurement of CA-125 concentration
- Prostate cancer screening involves annual digital rectal exam and prostate-specific antigen testing

Genetics

Genes – see table

Penetrance – female variant carriers have cumulative cancer risks

- For breast cancer – 57% for *BRCA1* and 49% for *BRCA2* by age 70
- For ovarian cancer – 40% for *BRCA1* and 18% for *BRCA2* by age 70

Variants

- 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 Interpretation

Clinical sensitivity

- Unknown for HBOC 20-gene panel
- *BRCA1* and *BRCA2* sequencing and deletion/duplication testing alone detects 20-60% of HBOC (Pruthi, 2010; Meindl, 2011)

Test results

- Positive
  - One pathogenic variant identified in a gene with autosomal dominant inheritance
    - Confirms a diagnosis of HBOC syndrome
    - Individuals with a pathogenic dominant germline variant have a 50% chance of passing the variant on to their offspring
  - Two pathogenic variants located on opposite chromosomes detected in an autosomal recessively inherited gene
    - Confirms a diagnosis of HBOC syndrome
  - One pathogenic variant detected in an autosomal recessively inherited gene
    - Confirms carrier status for HBOC syndrome
- Negative
  - No pathogenic variants detected in any of the genes tested
    - Reduces the likelihood of, but does not exclude, a diagnosis of HBOC syndrome
      - Not all variants in the tested genes are identified
      - Not all predisposing genes are interrogated
- Inconclusive
  - Variants of unknown 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
- 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	Cancer Association
ATM	Ataxia telangiectasia mutated (includes complementation groups A, C and D)	000051	607585	AD	Breast
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
BRCA2	Breast cancer 2	000059	600185	AD	Breast, ovarian, fallopian, peritoneal, pancreatic, prostate, gallbladder, gastric, melanoma
BRIP1	BRCA1 interacting protein C-terminal, helicase 1	032043	605882	AD	Breast, ovarian
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
MEN1	Multiple endocrine neoplasia 1	130799	613733	AD	Glucagonomas, gastrinomas, VIPomas, thymic, bronchial, gastric, breast
MLH1	MutL homologue 1, colorectal cancer, nonpolyposis type 2 (*E. coli*)	000249	120436	AD	Ovarian, colorectal, endometrial, bladder, kidney
MSH2	MutS homologue 2, colorectal cancer, nonpolyposis type 1 (*E. coli*)	000251	609309	AD	Ovarian, colorectal, endometrium, bladder, kidney
MSH6	MutS (E.coli) homologue 6	000179	600678	AD	Ovarian, colorectal , endometrium, bladder, kidney

Gene Symbol	Gene Name	NM #	OMIM #	Inheritance	Cancer Association
MUTYH	MutY homologue (*E. coli*)	001128425	604933	AR, AD	Colorectal (AR), gastric, breast, duodenal, endometrium (AD)
NBN	Nibrin (NBS1)	002485	602667	AD	Breast, ovarian
PALB2	Partner and localizer of BRCA2	024675	610335	AD	Breast, pancreatic
PTEN	Phosphatase and tensin homolog	000314	601728	AD	Thyroid, breast, endometrial
RAD51C	RAD51 homolog (*S. cerevisiae*)	058216	602774	AD	Breast, ovarian
RAD51D	RAD51D homolog D (*S. cerevisiae*)	002878	602954	AD	Breast, ovarian
STK11	Serine/threonine kinase 11 (LKB1)	000455	602216	AD	Colorectal, pancreatic, breast, ovarian
TP53	Tumor protein 53	000546	191170	AD	Breast, ovarian, brain, soft tissue and osteosarcomas, gastrointestinal, leukemia, lymphoma, adrenocortical carcinoma
AD = autosomal dominant; AR = autosomal recessive					