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Hereditary Breast and Ovarian Cancer

Pathogenic variants in multiple genes have been implicated in hereditary breast and/or ovarian cancer (HBOC). Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50) and multiple, multifocal, and/or similar cancers in a single individual or in a closely related family member(s). Pathogenic variants in the genes analyzed by this panel cause variable phenotypes and cancer risks, including nonbreast/nonovarian cancers. Pathogenic variants in the *BRCA1* and *BRCA2* genes are associated with HBOC syndrome.

DISEASE OVERVIEW

Associated Disorder

***BRCA1*- and *BRCA2*-associated HBOC syndrome**

- Individuals with a pathogenic *BRCA1* or *BRCA2* variant are at increased risk for breast, ovarian, fallopian, peritoneal, pancreatic, prostate, melanoma, and other cancers.

Etiology

At least 5-10% of all breast cancers and 10-15% of all ovarian cancers are associated with a hereditary cause.

Prevalence

- 1/400 individuals from general population or 1/40 Ashkenazi Jews have a *BRCA1* or *BRCA2* pathogenic variant.
- Prevalence of pathogenic variants in the additional genes on this panel is largely unknown.

Inheritance

- All genes tested on the HBOC panel are autosomal dominant with the exception of the *MUTYH* gene, which is autosomal recessive but may also have autosomal dominant risks that are not well defined.
- Some genes are associated with autosomal recessive childhood cancer predisposition or other syndromes.

TEST DESCRIPTION

See Genes Tested table for genes included in the panel.

Clinical Sensitivity

Variable, dependent on phenotype/condition

- *BRCA1* and *BRCA2* sequencing and deletion/duplication testing alone detects 20-60% of HBOCs, in general (Pruthi, 2010; Meindl, 2011).
  - >80% of *BRCA1* and *BRCA2* variants are detectable by sequencing.
  - ~10% of *BRCA1* and *BRCA2* variants are detectable by large deletion/duplication analysis.

TESTING STRATEGY

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low with methodology used for germline assays.
- Individuals with hematological malignancy and/or a previous allogenic bone marrow transplant should not undergo molecular genetic testing on a peripheral blood specimen.

TESTS TO CONSIDER

Hereditary Breast and Ovarian Cancer Panel, Sequencing and Deletion/Duplication 2012026
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Indication for testing:

- Recommended test to confirm a diagnosis of hereditary breast and/or ovarian cancer in individuals with a personal or family history of breast and/or ovarian cancer.
- When a relative has a previously identified pathogenic sequence variant, see Familial Mutation, Targeted Sequencing (2001961).

Breast and Ovarian Hereditary Cancer Syndrome (BRCA1 and BRCA2) Sequencing and Deletion/Duplication 2011949
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Indication for testing:

- Recommended test to confirm hereditary breast and ovarian cancer (HBOC) syndrome (*BRCA1* and *BRCA2* genes only).
- When a relative has a previously identified pathogenic sequence variant, see Familial Mutation, Targeted Sequencing (2001961).

Breast and Ovarian Hereditary Cancer Syndrome (BRCA1 and BRCA2) Sequencing 2011954
Method: Polymerase Chain Reaction/ Sequencing

Indication for testing:

- Acceptable test to confirm HBOC syndrome (*BRCA1* and *BRCA2* genes only).
- When a relative has a previously identified pathogenic sequence variant, see Familial Mutation, Targeted Sequencing (2001961).

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

- Testing of cultured fibroblasts is required for accurate interpretation of test results.
- When a relative has a previously identified pathogenic variant, see Familial Mutation, Targeted Sequencing (2001961).

Indication for testing:

- Recommended test for a known familial sequence variant previously identified in a family member.
- A copy of the family member's test result documenting the familial variant is required.

See Related Tests

Limitations

- A negative result does not exclude a heritable form of cancer.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *NF1, RECQL*
  - Sequence variants in *EPCAM*
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *CHEK2* (NM_001349956) 4; (NM_001005735) 3; (NM_007194) 10,12,13,14,15
    - *RECQL* (NM_002907) 14, 15
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:

Gene	Exon(s)
BARD1	(NM_000465) 1
BRCA1	(NM_007300) 13
CDH1	(NM_004360) 1
CHEK2	(NM_001005735) 3; (NM_007194) 11, 12, 14, 15
MRE11	(NM_005591) 2
MSH2	(NM_000251) 1; (NM_001258281) 2
MSH6	(NM_000179) 10
MUTYH	(NM_001128425) 1
PALB2	(NM_024675) 1
PTEN	(NM_000314) 8, 9; (NM_001304717) 1
RAD51D	(NM_002878) 1
TP53	(NM_001126113) 10; (NM_001126114) 1

Analytical Sensitivity

- For Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) of *BRCA1* and *BRCA2*: 99%.
- For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ATM	607585	Associated cancer(s)/tumor(s): breast, ovarian,[a] colorectal [a]	AD
		Ataxia-telangiectasia (AT) Associated cancer(s)/tumor(s): leukemia and lymphoma	AR
BARD1	601593	Associated cancer(s)/tumor(s): breast [a]	AD
BRCA1	113705	Hereditary breast and ovarian cancer (HBOC) syndrome Associated cancer(s)/tumor(s): breast, ovarian, prostate, pancreas, melanoma	AD
		Fanconi anemia, complementation group S	AR
BRCA2	600185	Hereditary breast and ovarian cancer (HBOC) syndrome Associated cancer(s)/tumor(s): breast, ovarian, prostate, pancreas, melanoma	AD
		Fanconi anemia, complementation group D1	AR
BRIP1	605882	Associated cancer(s)/tumor(s): ovarian, breast [a]	AD
		Fanconi anemia, complementation group J	AR
CDH1	192090	Hereditary diffuse gastric cancer (HDGC) Associated cancer(s)/tumor(s): diffuse gastric, lobular breast	AD
CHEK2	604373	Associated cancer(s)/tumor(s): breast, colorectal,[a] prostate,[a] thyroid [a]	AD
DICER1	606241	*DICER1*-related disorders Associated cancer(s)/tumor(s): pleuropulmonary blastoma, ovarian sex cord-stromal tumors, cystic nephroma, thyroid	AD
EPCAM	185535	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
MLH1	120436	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
MRE11/MRE11A	600814	Associated cancer(s)/tumor(s): breast [a]	AD
		Ataxia-telangiectasia-like disorder	AR
MSH2	609309	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
MSH6	600678	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
MUTYH	604933	Associated cancer(s)/tumor(s): breast [a]	AD
		MUTYH-associated polyposis (MAP) Associated cancer(s)/tumor(s): colon, duodenal	AR
NBN	602667	Associated cancer(s)/tumor(s): breast	AD
		Nijmegan breakage syndrome (NBS)	AR
NF1	613113	Neurofibromatosis type 1 (NF1) Associated cancer(s)/tumor(s): breast, neurofibromas, gliomas, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumor (GIST), leukemia	AD
PALB2	610355	Associated cancer(s)/tumor(s): breast, pancreatic [a]	AD
		Fanconi anemia, complementation group N	AR
PMS2	600259	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD

Gene	MIM Number	Disorder	Inheritance
		Constitutional mismatch repair deficiency (CMMRD)	AR
PTEN	601728	Cowden syndrome/*PTEN* hamartoma tumor syndrome Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colon, renal cell carcinoma	AD
RAD51C	602774	Associated cancer(s)/tumor(s): ovarian	AD
		Fanconi anemia, complementation group O	AR
RAD51D	602954	Associated cancer(s)/tumor(s): ovarian	AD
RECQL	600537	Associated cancer(s)/tumor(s): breast [a]	AD
STK11	602216	Peutz-Jeghers syndrome (PJS) Associated cancer(s)/tumor(s): breast, colon, stomach, small intestine, pancreas, ovary, testes, lung	AD
TP53	191170	Li-Fraumeni syndrome (LFS) Associated cancer(s)/tumor(s): soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast, adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma	AD

[a] Association is suggested but not well-established at this time.

AD, autosomal dominant; AR, autosomal recessive

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RELATED TESTS

Breast and Ovarian Hereditary Cancer Syndrome (BRCA1 and BRCA2) Sequencing and Deletion/Duplication 2011949
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Hereditary Cancer Panel, Sequencing and Deletion/Duplication 2012032
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

HNPCC/Lynch Syndrome (MLH1) Sequencing and Deletion/Duplication 0051650
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (MSH2) Sequencing and Deletion/Duplication 0051654
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (MSH6) Sequencing and Deletion/Duplication 0051656
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (PMS2) Sequencing and Deletion/Duplication 0051737
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Li-Fraumeni (TP53) Sequencing and Deletion/Duplication 2009313
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

MUTYH-Associated Polyposis (MUTYH) 2 Mutations 2004911
Method: Polymerase Chain Reaction/Sequencing

Neurofibromatosis Type 1 (NF1) Sequencing and Deletion/Duplication 2007154
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Peutz-Jeghers Syndrome (STK11) Sequencing and Deletion/Duplication 2008398
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

PTEN-Related Disorders (PTEN) Sequencing and Deletion/Duplication 2002470
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

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