Hereditary Breast and Ovarian Cancer Panel

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 cancer onset (typically before age 50) and multiple, multifocal, and/or similar cancers in a single individual or in a closely related family member(s). The HBOC panel includes analysis of several genes associated with hereditary breast and/or ovarian cancer that 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 Disorders

- *BRCA1* and *BRCA2*-associated HBOC syndrome[1,2]
  - Caused by a single pathogenic *BRCA1* or *BRCA2* variant
  - Individuals are at increased risk for breast, ovarian, fallopian tube, peritoneal, pancreatic, prostate, melanoma, and other cancers
- Lynch syndrome[3]
  - Caused by a single pathogenic variant in one of the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or *EPCAM* exon 9 deletions
  - Individuals are at an increased risk for colorectal, uterine, ovarian, and other cancers
- Other associated disorders on this panel include: Cowden syndrome, Li-Fraumeni syndrome (LFS), Peutz-Jeghers syndrome (PJS), and others. Please see Genes Tested table for more information

Etiology

At least 5-10% of all breast cancers and 10-15% of all ovarian cancers are associated with a hereditary cause.[4,5,6]

Prevalence

- 1/400 individuals from general population or 1/40 Ashkenazi Jews have a *BRCA1* or *BRCA2* pathogenic variant[7,8]
- Lynch syndrome occurs in approximately 1/440 individuals in the general population[9]
- 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 currently not well defined
- Some genes are associated with a predisposition to autosomal recessive childhood cancer or other syndromes

Test Description

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:

- Multigene panel to confirm a hereditary cause of breast and/or ovarian cancer in individuals with a complex 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)

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

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

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[1,4,10]
  - >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 as sensitivity for mosaic variants is low with the methodology used for germline assays
- Individuals with a hematological malignancy and/or a previous allogenic bone marrow transplant should not undergo molecular genetic testing on a peripheral blood specimen
  - Testing of cultured fibroblasts is required for accurate interpretation of test results for these individuals
- When a relative has a previously identified pathogenic variant, order Familial Mutation, Targeted Sequencing (2001961).

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

Gene	Exon(s)
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

- Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) of *PMS2*: 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, pancreas, ovarian, colorectal[a]	AD
		Ataxia-telangiectasia Associated cancer(s)/tumor(s): leukemia and lymphoma	AR
BARD1	601593	Associated cancer(s)/tumor(s): breast[a]	AD
BRCA1	113705	HBOC syndrome Associated cancer(s)/tumor(s): breast, ovarian, fallopian tube, peritoneal, pancreatic, prostate	AD
		Fanconi anemia, complementation group S	AR
BRCA2	600185	HBOC syndrome Associated cancer(s)/tumor(s): breast, ovarian, fallopian tube, peritoneal, pancreatic,	AD

		prostate, melanoma	

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

AD, autosomal dominant; AR, autosomal recessive; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; GIST, gastrointestinal stromal tumor; HDGC, hereditary diffuse gastric cancer; HNPCC, hereditary nonpolyposis colorectal cancer; MAP, MUTYH-associated polyposis; NBS, Nijmegen breakage syndrome; NF1, neurofibromatosis type 1

Gene	MIM Number	Disorder	Inheritance
		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	HDGC Associated cancer(s)/tumor(s): diffuse gastric, lobular breast	AD
CHEK2	604373	Associated cancer(s)/tumor(s): breast, colorectal, prostate, 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/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, pancreas, ovarian,[a] breast,[a] and others	AD
MLH1	120436	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast,[a] and others	AD
		CMMRD	AR
MRE11/MRE11A	600814	Associated cancer(s)/tumor(s): breast[a]	AD
		Ataxia-telangiectasia-like disorder	AR
MSH2	609309	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast,[a] and others	AD
		CMMRD	AR
MSH6	600678	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast,[a] and others	AD
		CMMRD	AR
MUTYH	604933	Associated cancer(s)/tumor(s): breast,[a] colorectal[a]	AD
		MAP Associated cancer(s)/tumor(s): colorectal adenomas and cancer, duodenal adenomas and cancer	AR
NBN	602667	Associated cancer(s)/tumor(s): breast, ovarian[a]	AD

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

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Gene	MIM Number	Disorder	Inheritance
		NBS	AR
NF1	613113	NF1 Associated cancer(s)/tumor(s): breast, neurofibromas, gliomas, malignant peripheral nerve sheath tumors, GIST, leukemia	AD
PALB2	610355	Associated cancer(s)/tumor(s): breast, ovarian, pancreas[a]	AD
		Fanconi anemia, complementation group N	AR
PMS2	600259	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian,[a] breast,[a] and others	AD
		CMMRD	AR
PTEN	601728	Cowden syndrome/*PTEN* hamartoma tumor syndrome Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colorectal, renal cell carcinoma	AD
RAD51C	602774	Associated cancer(s)/tumor(s): ovarian, breast[a]	AD
		Fanconi anemia, complementation group O	AR
RAD51D	602954	Associated cancer(s)/tumor(s): ovarian, breast[a]	AD
RECQL	600537	Associated cancer(s)/tumor(s): breast[a]	AD
STK11	602216	PJS Associated cancer(s)/tumor(s): Peutz-Jeghers-type hamartomatous polyps, breast, colorectal, stomach, small intestine, pancreas, ovarian, testes, lung	AD
TP53	191170	LFS Associated cancer(s)/tumor(s): soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast, colorectal, pancreas,[a] adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma	AD

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

AD, autosomal dominant; AR, autosomal recessive; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; GIST, gastrointestinal stromal tumor; HDGC, hereditary diffuse gastric cancer; HNPCC, hereditary nonpolyposis colorectal cancer; MAP, MUTYH-associated polyposis; NBS, Nijmegen breakage syndrome; NF1, neurofibromatosis type 1

References

1. Petrucelli N, Daly MB, Pal T. *BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Dec 2016; Accessed: Jun 2020]

2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology, genetic/familial high-risk assessment: breast, ovarian, and pancreatic. Version 2.2021. [Last updated: Nov 2020; Accessed: Feb 2021]

3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology, genetic/familial high-risk assessment: colorectal, Version 1.2020. [Updated: Jul 2020; Accessed: Feb 2021]

4. Pruthi S, Gostout BS, Lindor NM. Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian cancer. Mayo Clin Proc. 2010;85(12):1111-1120. PubMed

5. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncol. 2017;3(9):1190-1196. PubM

6. Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001;68(3):700-710. PubMed

7. Whittemore AS, Gong G, John EM, et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiol Biomarkers Prev. 2004;13(12):2078-2083. PubMed

8. King MC, Marks JH, Mandell JB, et al. Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*. Science. 2003;302(5645):643-646. PubMed

9. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome, JAMA. 2006;296(12):1479-1487. PubMed

10. Meindl A, Ditsch N, Kast K, et al. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch Arztebl Int. 2011;108(19):323-330. PubMed

Additional Resources

Doros L, Schultz KA, Stewart DR, et al. *DICER1*-related disorders. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Apr 2020; Accessed: Jun 2020]

Ford D, Easton DF, Stratton M, 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(3):676-689. PubMed

Friedman JM. Neurofibromatosis 1. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Last revision: Jun 2019; Accessed: Jun 2020]

Lalloo F, Evans DG. Familial breast cancer. Clin Genet. 2012;82(2):105-114. PubMed

Walsh T, Casadei S, Lee MK , et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011;108(44):18032-18037. PubMed

Related Information

Breast Cancer Biomarkers
Ovarian Cancer

Related Tests

BRCA1 and BRCA2-Associated HBOC Syndrome Panel, Sequencing and Deletion/Duplication 3001855

Method: Massively Parallel 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 0090212

Li-Fraumeni (TP53) Sequencing and Deletion/Duplication 2009313

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Neurofibromatosis Type 1 (NF1) Sequencing and Deletion/Duplication (Temporary Referral as of 12/7/20) 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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Content Review February 2021 | Last Update February 2021