BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer Syndrome

Pathogenic variants in the *BRCA1* and *BRCA2* genes are associated with hereditary breast and ovarian cancer (HBOC) syndrome. *BRCA1*- and *BRCA2*-associated HBOC syndrome is often characterized by early age of cancer onset (typically before 50 years of age) and multiple, multifocal, and/or similar cancers in a single individual or in a closely related family member(s). Individuals with a single germline *BRCA1* or *BRCA2* pathogenic variant have an increased risk for breast (female and male), ovarian, fallopian tube, peritoneal, pancreatic, prostate, melanoma, and other cancers. Analysis of the *BRCA1* and *BRCA2* genes is offered through ARUP's *BRCA1* and *BRCA2*-Associated HBOC Syndrome Panel. For a more comprehensive test for hereditary causes of breast and/or ovarian cancer, please see the Hereditary Breast and Ovarian Cancer Panel, which includes analysis of several genes, including *BRCA1* and *BRCA2*.

Tests to Consider

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

Method: Massively Parallel Sequencing/Multiplex Ligation-dependent Probe Amplification

- Germline analysis of the *BRCA1* and *BRCA2* genes in individuals with a suspected diagnosis of HBOC syndrome
- 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

- 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

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

- Use to assess for large deletion/duplication previously identified in a family member
- A copy of a relative's lab report is REQUIRED

See Related Tests

Disease Overview

Associated Disorder

BRCA1- and *BRCA2*-associated HBOC syndrome

- Caused by a single germline *BRCA1* or *BRCA2* pathogenic variant[1]
- Individuals are at increased risk for the following cancers (combined estimated risks for *BRCA1* and *BRCA2* listed below)[1]:
  - Breast (female): 38-87%
  - Breast (male): 1.2-8.9%
  - Ovarian (including fallopian tube and peritoneal): 16.5-63%
  - Pancreatic: 1-7%
  - Prostate: 8.6-20%
  - Melanoma: elevated for *BRCA2* only

Etiology

At least 5-10% of all breast cancers and 10-15% of all ovarian cancers are associated with a hereditary cause.[2,3,4]

Prevalence

One in 400 individuals from the general population or 1 in 40 Ashkenazi Jewish individuals have a *BRCA1* or *BRCA2* pathogenic variant.[5,6]

Inheritance

- Single pathogenic variants in the *BRCA1* and *BRCA2* genes are inherited in an autosomal dominant manner and are associated with HBOC syndrome.
- *BRCA1* and *BRCA2* pathogenic variants are also associated with autosomal recessive Fanconi anemia.

Test Description

Genes Tested

- *BRCA1* (NM_007294) and *BRCA2* (NM_000059)

- See Genes Tested table for more information.

Clinical Sensitivity

BRCA1 and *BRCA2* sequencing and deletion/duplication testing detects 20-60% of hereditary breast and/or ovarian cancers, in general.[1,2,7]

- >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 hematologic malignancy and/or a previous allogeneic bone marrow transplantation should not undergo molecular genetic testing on a peripheral blood specimen.
  - 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.

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
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Analytical Sensitivity

- Analytical sensitivity for multiplex ligation-dependent probe amplification (MLPA) is 99%.
  - Approximately 99% for single nucleotide variants (SNVs) and >93% for insertions/duplications/deletions from 1-10 base pairs in size
  - Variants >10 base pairs may be detected, but analytical sensitivity may be reduced.

Genes Tested

Gene	MIM Number	Disorder	Inheritance
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, prostate, melanoma	AD
		Fanconi anemia, complementation group D1	AR

AD, autosomal dominant; AR, autosomal recessive

References

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6. 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

7. 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

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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

Hereditary Breast and Ovarian Cancer Panel, Sequencing and Deletion/Duplication 2012026

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Hereditary Cancer Panel, Sequencing and Deletion/Duplication 2012032

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

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