Hereditary Breast Cancer Panels (Including BRCA1 and BRCA2)

Pathogenic germline variants in multiple genes have been implicated in hereditary breast cancer. Hereditary cancer syndromes are often characterized by an 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). Pathogenic variants in the *BRCA1* and *BRCA2* genes are associated with the most common cause of hereditary breast cancer, known as *BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer (HBOC) syndrome. Other inherited causes of hereditary breast cancer have been identified. Additional screening, and in some cases, risk-reducing options have been recommended for individuals with pathogenic variants in moderate to high-risk hereditary breast cancer genes. Expanded testing for hereditary causes of breast and/or gynecological cancers is also available. For more information, refer to the ARUP Hereditary Cancer Panel Comparison table or visit the Laboratory Test Directory.

Disease Overview

BRCA1- and BRCA2-Associated HBOC Syndrome

BRCA1- and *BRCA2*-associated HBOC syndrome is caused by a single germline *BRCA1* or *BRCA2* pathogenic variant and results in an increased lifetime risk of certain cancers.[1]

Lifetime Cancer Risk by Type

Cancer Type	Cancer Risk by Gene	
	BRCA1	*BRCA2*
Breast cancer (female)	55-72% by 70 yrs of age	45-69%
Breast cancer (male)	1-2%	6-8%
Ovarian cancer (including fallopian tube and peritoneal)	39-44%	11-17%

Source: Petrucelli, 2022[1]

Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

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

Method: Massively Parallel Sequencing

- Germline analysis of the *BRCA1* and *BRCA2* genes in individuals with a suspected diagnosis of HBOC syndrome
- Testing minors for adult-onset conditions is not recommended. Testing will not be performed on minors without prior approval. For additional information, please contact an ARUP genetic counselor at 800-242-2787.

Hereditary Breast Cancer High-Risk Panel, Sequencing and Deletion/Duplication 3005632

Method: Massively Parallel Sequencing/Sequencing

- Germline analysis of high lifetime risk (>40%) hereditary breast cancer genes (including *BRCA1* and *BRCA2*) for individuals with personal or family history of hereditary breast or other related cancers
- Testing minors for adult-onset conditions is not recommended. Testing will not be performed on minors without prior approval. For additional information, please contact an ARUP genetic counselor.

Cancer Type	Cancer Risk by Gene	
	BRCA1	*BRCA2*
Pancreatic cancer	1-3%	3-5% by 70 yrs of age
Prostate cancer	29% by 85 yrs of age	60% by 85 yrs of age
Melanoma	1.6% (same as general population)	Elevated risk

Source: Petrucelli, 2022[1]

Others

See the Genes Tested table for more information about the other syndromes included in the Hereditary Breast Cancer High-Risk Panel and the Hereditary Breast Cancer Guidelines-Based Panel.

Hereditary Breast Cancer Guidelines-Based Panel, Sequencing and Deletion/Duplication 3005654

Method: Massively Parallel Sequencing/Sequencing

- Germline analysis of moderate and high lifetime risk (>15%) hereditary breast cancer genes (including *BRCA1* and *BRCA2*) for individuals with personal or family history of hereditary breast or other related cancers
- Testing minors for adult-onset conditions is not recommended. Testing will not be performed on minors without prior approval. For additional information, please contact an ARUP genetic counselor.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Genetics

Genes Tested by Panel

Genetic Markers Included in ARUP Breast Cancer Panel Tests			
Gene	*BRCA1* and *BRCA2*-Associated HBOC Syndrome Panel, Sequencing and Deletion/Duplication 3001855	Hereditary Breast Cancer High-Risk Panel, Sequencing and Deletion/Duplication 3005632	Hereditary Breast Cancer Guidelines-Based Panel, Sequencing and Deletion/Duplication 3005654
BRCA1	✓	✓	✓
BRCA2	✓	✓	✓
CDH1		✓	✓
PALB2		✓	✓
PTEN		✓	✓
TP53		✓	✓
ATM			✓
BARD1			✓

Gene	*BRCA1* and *BRCA2*-Associated HBOC Syndrome Panel, Sequencing and Deletion/Duplication 3001855	Hereditary Breast Cancer High-Risk Panel, Sequencing and Deletion/Duplication 3005632	Hereditary Breast Cancer Guidelines-Based Panel, Sequencing and Deletion/Duplication 3005654
CDH1			✓
CHEK2			✓
NF1			✓
STK11			✓

See Genes Tested table for more information regarding the genes included in all three panels.

Etiology

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

Prevalence

BRCA1 and *BRCA2* genes

- One in 400 individuals from the general population or 1 in 40 Ashkenazi Jewish individuals have a *BRCA1* or *BRCA2* pathogenic variant.[4,5]

Inheritance

- Autosomal dominant for all genes on the three described panels
- Additionally, some genes are associated with autosomal recessive childhood cancer predisposition or other syndromes.

BRCA1 and *BRCA2* Pathogenic Founder Variants

- The following three founder variants are estimated to make up 99% of pathogenic variants in individuals of Ashkenazi Jewish descent[1]:
  - *BRCA1* c.68_69delAG (also known as 185delAG)
  - *BRCA1* c.5266dupC (also known as 5382insC)
  - *BRCA2* c.5946delT (also known as 6174delT)
- Additional founder variants have been identified in other populations, including African, Amish, Ammassalik (Greenlandic), and Icelandic populations.[1]

Test Interpretation

Contraindications for Ordering

- These tests should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low with the 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, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for the detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.
- Bidirectional Sanger sequencing is performed on the following gene and exon:
  - *PTEN* (NM_000314) 9

Clinical Sensitivity

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

- Greater than 98% for *BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer syndrome[1]
  - *BRCA1* variants:
    - Approximately 87-89% are detectable by sequencing
    - Approximately 11-13% detectable by deletion/duplication analysis
  - *BRCA2* variants:
    - Approximately 97-98% are detectable by sequencing
    - Approximately 2-3% are detectable by deletion/duplication analysis

Hereditary Breast Cancer High-Risk Panel, Sequencing and Deletion/Duplication (3005632) and Hereditary Breast Cancer Guidelines-Based Panel, Sequencing and Deletion/Duplication (3005654)

- *BRCA1* and *BRCA2* sequencing and deletion/duplication testing detects approximately 20-60% of hereditary breast and/or ovarian cancers, in general.[2,6]
- Clinical sensitivity of additional genes is largely unknown.

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8% (90.3-99.8%) [2 exons or larger] 62.5% (38.3-82.6%) [single exon]	>99.9
Exon-level[c] duplications	83.3% (56.4-96.4%) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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

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 exons are not sequenced due to technical limitations of the assay:
    - *BRCA1* (NM_007300) 13
    - *CHEK2* (NM_001005735) 3; (NM_001349956) 4
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than 3 exons in size
  - Deletions/duplications in the following exons:
    - *BRCA1* (NM_007294, NM_007299, NM_007300) 2; (NM_007298) 1
    - *CDH1* (NM_001317185) 10
    - *CHEK2* (NM_007194) 11-15; (NM_001005735) 3,12-16; (NM_001257387) 12-16; (NM_001349956) 4,10-14; (NM_145862) 10-14;
    - *PTEN* (NM_000314, NM_001304718) 9; (NM_001304717) 1,10
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes and/or repetitive or homologous regions
  - Low-level somatic variants

Genes Tested

The following genes are included on one or more of the panels described in this document. For a list of genes tested by each panel, see the Genes Tested by Panel section.

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

Gene	MIM Number	Disorder	Inheritance
ATM	607585	Breast, colorectal,[a] ovarian, pancreas, prostate	AD
		Ataxia-telangiectasia	AR
BARD1	601593	Breast	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, prostate, melanoma	AD
		Fanconi anemia, complementation group D1	AR
CDH1	192090	HDGC Diffuse gastric, lobular breast	AD
CHEK2	604373	Breast, colorectal, prostate, thyroid[a]	AD
NF1	613113	NF1 Breast, GIST, gliomas, leukemia, malignant peripheral nerve sheath tumors, neurofibromas, pheochromocytoma	AD
PALB2	610355	Breast, ovarian, pancreas, prostate	AD
		Fanconi anemia, complementation group N	AR
PTEN	601728	Cowden syndrome/PTEN hamartoma tumor syndrome Breast, colorectal, endometrial, Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma), melanoma,[a] renal cell carcinoma, thyroid, and others	AD

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

AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; HDGC, hereditary diffuse gastric cancer; LFS, Li-Fraumeni syndrome; NF1, neurofibromatosis type 1; PJS, Peutz-Jeghers syndrome

Gene	MIM Number	Disorder	Inheritance
STK11	602216	PJS Breast, cervix, colorectal, endometrial, lung, ovarian (sex cord with annular tubules), pancreas, Peutz-Jeghers-type hamartomatous polyps, small intestine, stomach, testes	AD
TP53	191170	LFS Adrenocortical carcinoma, breast, choroid plexus carcinoma, CNS, colorectal, melanoma,[a] osteosarcoma, pancreas, prostate, renal, rhabdomyosarcoma, soft tissue sarcoma, stomach, thyroid, and others	AD

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

AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; HDGC, hereditary diffuse gastric cancer; LFS, Li-Fraumeni syndrome; NF1, neurofibromatosis type 1; PJS, Peutz-Jeghers syndrome

References

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6. 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.

Related Information

Breast Cancer Biomarkers
Hereditary Cancer Germline Genetic Testing
Ovarian Cancer Biomarkers