Hereditary Breast and Gynecologic Cancers Panel

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Pathogenic germline variants in multiple genes have been implicated in hereditary breast, ovarian, and endometrial cancers. Hereditary cancer predisposition is often characterized by an early age of cancer onset (typically before age 50) and multiple, multifocal, and/or related cancers in a single individual or in a closely related family member(s). This test includes analysis of several genes associated with hereditary breast and/or gynecologic cancer(s) that cause variable phenotypes and cancer risks, including nonbreast/nongynecologic cancers. See Genes Tested table below for more details regarding the genes and syndromes included on the Hereditary Breast and Gynecological Cancers Panel. Genes included on this panel are also included in other ARUP hereditary cancer tests. For more information, refer to the ARUP Hereditary Cancer Panel Comparison table.

Featured ARUP Testing

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

Hereditary Breast and Gynecological Cancers Panel, Sequencing and Deletion/Duplication 2012026

Method: Massively Parallel Sequencing/Sequencing/Multiplex Ligation-Dependent Probe Amplification (MLPA)

- Multigene panel to confirm a hereditary cause of breast and/or gynecologic cancer(s) in individuals with a complex personal or family history of breast, ovarian, or endometrial cancer
- Testing minors for adult-onset conditions is not recommended and will not be performed on minors without prior approval; for additional information, please contact an ARUP genetic counselor (800-242-2787).

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.

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
  - Additional BRCA1 and BRCA2 testing is available; refer to the Laboratory Test Directory
- 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
  - Additional Lynch syndrome panel testing is available; refer to the Laboratory Test Directory
- Disorders assessed on this panel also include Cowden syndrome, Li-Fraumeni syndrome (LFS), Peutz-Jeghers syndrome (PJS), and others. Please see Genes Tested table for more information.

Genetics

Genes

See the Genes Tested table for genes included in the panel.

Etiology

Approximately 5-10% of all breast cancers, 10-15% of ovarian cancers, and 5% of endometrial cancers are associated with a hereditary cause.[4,5,6,7]

Prevalence

- 1/400 individuals from general population or 1/40 Ashkenazi Jewish individuals have a *BRCA1* or *BRCA2* pathogenic variant[8,9]
- Lynch syndrome occurs in approximately 1/279 individuals in the general population[10]

Inheritance

- Autosomal dominant
- Some genes are also associated with a predisposition to autosomal recessive childhood cancer or other syndromes.
- See the Genes Tested table for additional details.

Test Description

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 hematologic malignancy and/or a previous allogeneic 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.

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 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.
- Long-range PCR followed by nested Sanger sequencing is performed on the following gene and exons:
  - *PMS2* (NM_000535) 11, 12, 13, 14, 15
- Bidirectional Sanger sequencing is performed on the following genes and exons:
  - *MSH2* (NM_000251) 5
  - *PMS2* (NM_000535) 7
  - *PTEN* (NM_000314) 9
- Multiplex ligation-dependent probe amplification (MLPA) is performed on the following gene to call exon-level deletions and duplications:
  - *PMS2* (NM_000535)

Clinical Sensitivity

Variable, dependent on phenotype/condition

- *BRCA1* and *BRCA2* sequencing and deletion/duplication testing alone detects 20-60% of hereditary breast and ovarian cancers, in general.[1,4,11]
- The majority of inherited endometrial cancers are thought to be caused by Lynch syndrome.

Analytic Sensitivity

- Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) of *PMS2*: 99%
- For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%)
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]	>99.9

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by MLPA unless otherwise indicated.

[b]Variants greater than 10 bp may be detected, but the analytic 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

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%)
	62.5 (38.3-82.6) [single exon]	
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9
Exon-level deletions/duplications (MLPA)	>99	>99.9

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by MLPA unless otherwise indicated.

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

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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:
    - *BRCA1* (NM_007300) 13
    - *CHEK2* (NM_001005735) 3; (NM_001349956) 4
    - *RECQL* (NM_002907) 14, 15; (NM_032941) 15, 16
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement
  - Some variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
  - Low-level somatic variants
  - Deletions/duplications in the following exons:

Gene	Exon(s)
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
RECQL	(NM_002907) 14-15; (NM_032941) 15-16

Genes Tested

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[a]	AD
BRCA1	113705	HBOC syndrome Breast, fallopian tube, melanoma, ovarian, pancreatic, peritoneal, prostate	AD
		Fanconi anemia, complementation group S	AR
BRCA2	600185	HBOC syndrome Breast, fallopian tube, melanoma, ovarian, pancreatic, peritoneal, prostate	AD
		Fanconi anemia, complementation group D1	AR
BRIP1	605882	Breast,[a] ovarian	AD
		Fanconi anemia, complementation group J	AR
CDH1	192090	HDGC Diffuse gastric, lobular breast	AD
CHEK2	604373	Breast, colorectal, prostate, thyroid[a]	AD
DICER1	606241	*DICER1*-related disorders CNS, cystic nephroma, ovarian sex cord-stromal tumors, pleuropulmonary blastoma, thyroid	AD
EPCAM (Exon 9 deletions/duplications only)	185535	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
MLH1	120436	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MSH2	609309	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MSH6	600678	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	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; HBOC, hereditary breast and ovarian cancer; HDGC, hereditary diffuse gastric cancer; HNPCC, hereditary nonpolyposis colorectal cancer; LFS, Li-Fraumeni syndrome; NBS, Nijmegan breakage syndrome; NF1, neurofibromatosis type 1; PJS, Peutz-Jeghers syndrome; RTPS, rhabdoid tumor predisposition syndrome; SCCOHT, small-cell carcinoma of the ovary—hypercalcemic type

Gene	MIM Number	Disorder	Inheritance
		CMMRD	AR
NBN	602667	Breast,[a] ovarian,[a] prostate[a]	AD
		NBS	AR
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
PMS2	600259	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	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
RAD51C	602774	Breast, ovarian	AD
		Fanconi anemia, complementation group O	AR
RAD51D	602954	Breast, ovarian, prostate	AD
RECQL	600537	Breast[a]	AD
SMARCA4	603254	Coffin-Siris syndrome, RTPS Rhabdoid tumors located in CNS, kidney, ovary (SCCOHT), and others	AD
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

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Related Information

Breast Cancer Biomarkers
Hereditary Cancer Germline Genetic Testing
Ovarian Cancer Biomarkers

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