

# Hereditary Cancer Panel

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Pathogenic germline variants in multiple genes have been implicated in hereditary cancer. Hereditary cancer predisposition is often characterized by 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). See [Genes Tested](#) table below for more details regarding the genes and syndromes included on the Hereditary Cancer 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.

## Genetics

### Genes

Refer to the [Genes Tested](#) table for genes included in the panel.

### Etiology

Approximately 5-10% of cancer is associated with a hereditary cause.<sup>1</sup>

### Inheritance

- All genes tested on this panel are autosomal dominant except for the following:

Gene	Inheritance Pattern
<i>SDHAF2</i>	Autosomal dominant with paternal parent-of-origin effect
<i>SDHD</i>	Autosomal dominant with paternal parent-of-origin effect
<i>MAX</i>	Autosomal dominant with possible paternal parent-of-origin effect
<i>MUTYH</i>	Autosomal recessive but may also have autosomal dominant risks that are not well-defined
<i>MLH3</i>	Autosomal recessive
<i>MSH3</i>	Autosomal recessive
<i>NTHL1</i>	Autosomal recessive
<i>TERT</i>	Both autosomal dominant and autosomal recessive

- Some genes are associated with autosomal recessive childhood cancer predisposition or other syndromes.
- Refer to the [Genes Tested](#) table for additional details.

## Test Interpretation

### 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

## Featured ARUP Testing

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

### [Hereditary Cancer Panel, Sequencing and Deletion/Duplication 2012032](#)

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

- Recommended test to confirm a diagnosis of a hereditary cancer syndrome in individuals with personal or family history consistent with features of more than one cancer syndrome
- Testing minors for adult-onset conditions is not recommended and testing 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.

- Individuals with hematological malignancy and/or a previous allogenic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen.
  - Testing of cultured fibroblasts is required for accurate interpretation of test results.

## 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 polymerase chain reaction (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

## Analytic Sensitivity

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

<sup>a</sup>PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

<sup>b</sup>Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

<sup>c</sup>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.
- Deletions/duplications within *PMS2* exons 12-15 may not be distinguishable from the *PMS2CL* pseudogene and may be reported as inconclusive.

- 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
  - Sequence variants in *EPCAM*
  - The following exons are not sequenced due to technical limitations of the assay:
    - *APC* (NM\_001354896) 12; (NM\_001354898, NM\_001354904) 2; (NM\_001354900) 11
    - *BRCA1* (NM\_007300) 13
    - *CHEK2* (NM\_001005735) 3; (NM\_001349956) 4
    - *FLCN* (NM\_001353229) 7
    - *MEN1* (NM\_001370251) 8
    - *MITF* (NM\_001354607) 2
    - *PDGFRA* (NM\_001347827) 17; (NM\_001347828) 2; (NM\_001347830) 1
    - *RECQL* (NM\_002907) 14,15; (NM\_032941) 15,16
    - *SDHA* (NM\_004168) 14; (NM\_001294332) 13; (NM\_001330758) 12
    - *SDHC* (NM\_001035511) partial exon 5 (Chr1:161332225-161332330); (NM\_001278172) partial exon 4 (Chr1:161332225-161332330)
    - *SDHD* (NM\_001276506) 4
    - *VHL* (NM\_001354723) 2
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - 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
  - The following regions may have reduced sequencing sensitivity due to technical limitations of the assay:
    - *RB1* (NM\_000321) exon 22
    - *SUFU* (NM\_016169, NM\_001178133) exon 1
  - Deletions/duplications in the following exons:

Gene	Exon(s)
<i>APC</i>	(NM_001354896) 12; (NM_001354898, NM_001354904) 2; (NM_001354900) 11
<i>BMPR1A</i>	(NM_004329) 12-13
<i>BRCA1</i>	(NM_007294, NM_007299, NM_007300) 2; (NM_007298) 1
<i>CDH1</i>	(NM_001317185) 10
<i>CDKN2A</i>	(NM_000077, NM_001195132, NM_001363763, NM_058195) 2
<i>CHEK2</i>	(NM_007194) 11-15; (NM_001005735) 3,12-16; (NM_001257387) 12-16; (NM_001349956) 4,10-14; (NM_145862) 10-14
<i>CTNNA1</i>	(NM_001290307) 19; (NM_001324002, NM_001324004) 13; (NM_001324003) 15; (NM_001324005) 16
<i>FLCN</i>	(NM_001353229) 7
<i>MEN1</i>	(NM_001370251) 8
<i>MITF</i>	(NM_001354607) 2
<i>MLH3</i>	(NM_001040108) 7-8; (NM_014381) 7
<i>PDGFRA</i>	(NM_001347827) 17; (NM_001347828) 2; (NM_001347830) 1

Gene	Exon(s)
<i>PTEN</i>	(NM_000314, NM_001304718) 9; (NM_001304717) 1,10
<i>RB1</i>	(NM_000321) 22
<i>RECQL</i>	(NM_002907) 14-15; (NM_032941) 15-16
<i>SDHA</i>	(NM_004168) 1,10-15; (NM_001294332) 1,9-14; (NM_001330758) 1,10-13
<i>SDHD</i>	(NM_001276506) 4
<i>SMARCE1</i>	(NM_003079) 7,10-11
<i>VHL</i>	(NM_001354723) 2

## 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/Associated Cancer(s)/Tumor(s)	Inheritance
<i>ALK</i>	105590	<i>ALK</i> -related neuroblastic tumor susceptibility Ganglioneuroblastoma, ganglioneuroma, neuroblastoma	AD
<i>APC</i>	611731	FAP AFAP GAPPS Colorectal adenomas and cancer, duodenal adenomas and cancer, gastric fundic gland polyps, medulloblastoma, osteomas, pancreatic, thyroid, and others	AD
<i>ATM</i>	607585	Breast, colorectal, <sup>a</sup> ovarian, pancreatic, prostate Ataxia-telangiectasia	AD AR
<i>AXIN2</i>	604025	ODCRCS Colorectal, <sup>a</sup> polyposis	AD
<i>BAP1</i>	603089	<i>BAP1</i> -TPDS <i>BAP1</i> -inactivated melanocytic tumors, basal cell carcinoma, cutaneous melanoma, malignant mesothelioma, renal cell carcinoma, uveal melanoma	AD
<i>BARD1</i>	601593	Breast	AD
<i>BMPR1A</i>	601299	JPS Colorectal, juvenile polyps, small intestine, stomach	AD
<i>BRCA1</i>	113705	HBOC syndrome Breast, fallopian tube, ovarian, pancreatic, peritoneal, prostate Fanconi anemia, complementation group S	AD AR
<i>BRCA2</i>	600185	HBOC syndrome Breast, fallopian tube, melanoma, ovarian, pancreatic, peritoneal, prostate Fanconi anemia, complementation group D1	AD AR

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
<i>BRIP1</i>	605882	Breast, <sup>a</sup> ovarian	AD
		Fanconi anemia, complementation group J	AR
<i>CDC73</i>	607393	<i>CDC73</i> -related disorders Hyperparathyroidism-jaw tumor syndrome Hyperparathyroidism/parathyroid carcinoma, kidney lesions/tumors	AD
<i>CDH1</i>	192090	HDGC Diffuse gastric, lobular breast	AD
<i>CDK4</i>	123829	Cutaneous melanoma, pancreatic <sup>a</sup>	AD
<i>CDKN1B</i>	600778	MEN Type 4 Gastrinoma, GEP, nonendocrine. parathyroid, pituitary	AD
<i>CDKN2A</i>	600160	FAMMM-PC syndrome (also known as melanoma-pancreatic cancer syndrome) Cutaneous melanoma, pancreatic	AD
<i>CHEK2</i>	604373	Breast, colorectal, prostate, thyroid <sup>a</sup>	AD
<i>CTNNA1</i>	116805	Breast, <sup>a</sup> stomach	AD
<i>DICER1</i>	606241	<i>DICER1</i> -related disorders Pleuropulmonary blastoma, ovarian sex cord-stromal tumors, cystic nephroma, thyroid	AD
<i>EGFR</i>	131550	Lung	AD
<i>EPCAM</i> (Exon 9 deletion/duplications only)	185535	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreatic, prostate, renal pelvis and/or ureter, stomach, and others	AD
<i>FH</i>	136850	<i>FH</i> tumor predisposition syndrome/HLRCC Cutaneous and uterine leiomyomata, papillary type 2 renal cancer, paraganglioma, pheochromocytoma	AD
		Fumarase deficiency	AR
<i>FLCN</i>	607273	BHDS Fibrofolliculomas, pulmonary cysts/history of pneumothorax, renal cancer	AD
<i>HOXB13</i>	604607	Prostate	AD
<i>HRAS</i>	190020	Costello syndrome Neuroblastoma, rhabdomyosarcoma, transitional cell carcinoma of the bladder	AD
<i>KIT</i>	164920	GIST	AD
<i>LZTR1</i>	600574	Schwannomatosis	AD
		Noonan syndrome	AR
<i>MAX</i>	154950	HPP syndromes Paraganglioma, pheochromocytoma	AD <sup>b</sup>
<i>MC1R</i>	155555	Cutaneous melanoma <sup>a</sup>	AD

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
<i>MEN1</i>	613733	MEN type 1 Adrenocortical, carcinoid, GEP, neuroendocrine tumors, meningioma, parathyroid, pituitary, thyroid	AD
<i>MET</i>	164860	HPRCC Papillary type 1 renal cancer	AD
<i>MITF</i>	156845	Waardenburg syndrome type II Cutaneous melanoma	
<i>MLH1</i>	120436	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
<i>MLH3</i>	604395	<i>MLH3</i> -associated polyposis Breast, <sup>a</sup> colorectal, <sup>a</sup> polyposis	AD
<i>MSH2</i>	609309	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
<i>MSH3</i>	600887	Colorectal, <sup>a</sup> polyposis	AR
<i>MSH6</i>	600678	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
<i>MUTYH</i>	604933	Breast, <sup>a</sup> colorectal <sup>a</sup>	AD
		MAP Colorectal adenomas and cancer, duodenal adenomas and cancer	AR
<i>NBN</i>	602667	Breast, <sup>a</sup> ovarian, <sup>a</sup> prostate <sup>a</sup>	AD
		NBS	AR
<i>NF1</i>	613113	NF1 Breast, GIST, gliomas, leukemia, malignant peripheral nerve sheath tumors, neurofibromas, pheochromocytoma	AD
<i>NF2</i>	607379	NF2 Astrocytoma, ependymoma, meningioma, schwannoma	AD
<i>NTHL1</i>	602656	Colorectal, <sup>a</sup> polyposis	AR
<i>PALB2</i>	610355	Breast, ovarian, pancreas, prostate	AD
		Fanconi anemia, complementation group N	AR
<i>PDGFRA</i>	173490	GIST, inflammatory fibroid polyp, fibroid tumor	AD
<i>PMS2</i>	600259	Lynch syndrome/HNPCC	AD

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
		Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	
		CMMRD	AR
<i>POLD1</i>	174761	PPAP Colorectal, <sup>a</sup> polyposis	AD
<i>POLE</i>	174762	PPAP Colorectal, <sup>a</sup> polyposis	AD
<i>POT1</i>	606478	<i>POT1</i> tumor predisposition syndrome Angiosarcoma, chronic lymphocytic leukemia, cutaneous melanoma, glioma	AD
<i>PRKAR1A</i>	188830	Carney complex Endocrine tumor or overactivity, myxoma, schwannoma	AD
<i>PTCH1</i>	601309	NBCCS/Gorlin syndrome Basal cell carcinoma, cardiac and ovarian fibromas, medulloblastoma	AD
<i>PTEN</i>	601728	Cowden syndrome/ <i>PTEN</i> hamartoma tumor syndrome Breast, colorectal, endometrial, Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma), melanoma a, renal cell carcinoma, thyroid, and others	AD
<i>RAD51C</i>	602774	Breast, ovarian	AD
		Fanconi anemia, complementation group O	AR
<i>RAD51D</i>	602954	Breast, ovarian, prostate	AD
<i>RB1</i>	614041	Hereditary retinoblastoma Melanoma, <sup>a</sup> osteosarcoma, pinealoblastoma, retinoblastoma, retinoma, soft tissue sarcoma	AD
<i>RECQL</i>	600537	Breast <sup>a</sup>	AD
<i>RET</i>	164761	MEN2 Medullary thyroid carcinoma, parathyroid adenoma or hyperplasia, pheochromocytoma	AD
<i>SDHA</i>	600857	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
<i>SDHAF2</i>	613019	HPP syndromes Paraganglioma	AD <sup>c</sup>
<i>SDHB</i>	185470	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
<i>SDHC</i>	602413	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
<i>SDHD</i>	602690	HPP syndromes	AD <sup>c</sup>

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
		GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	
<i>SMAD4</i>	600993	JPS, HHT syndrome Colorectal, juvenile polyps, small intestine, stomach	AD
<i>SMARCA4</i>	603254	Coffin-Siris syndrome, RTPS Rhabdoid tumors located in CNS, kidney, ovary (SCCOHT), and others	AD
<i>SMARCB1</i>	601607	Coffin-Siris syndrome, RTPS Associated cancer(s)/tumor(s): Associated cancer(s)/tumor(s): rhabdoid tumors located in: CNS, kidney, and others; schwannomatosis	AD
<i>SMARCE1</i>	603111	Coffin-Siris syndrome Meningioma	AD
<i>STK11</i>	602216	PJS Breast, cervix, colorectal, endometrial, lung, ovarian (sex cord with annular tubules), pancreas, Peutz-Jeghers-type hamartomatous polyps, small intestine, stomach, testes	AD
<i>SUFU</i>	607035	NBCCS/Gorlin syndrome Basal cell carcinoma, cardiac and ovarian fibromas, medulloblastoma	AD
<i>TERT</i>	187270	Dyskeratosis congenita Acute myelogenous leukemia, melanoma, <sup>a</sup> pulmonary fibrosis	AD and AR
<i>TMEM127</i>	613403	HPP syndromes Paraganglioma, pheochromocytoma, renal clear cell carcinoma	AD
<i>TP53</i>	191170	LFS Adrenocortical carcinoma, breast, choroid plexus carcinoma, CNS, colorectal, melanoma, osteosarcoma, pancreas, prostate, renal, rhabdomyosarcoma, soft tissue sarcoma, stomach, thyroid, and others	AD
<i>TSC1</i>	605284	TSC Cardiac rhabdomyoma, fibromas, renal angiomyolipoma, retinal and other hamartomas, SEGA, and others	AD
<i>TSC2</i>	191092	TSC Cardiac rhabdomyoma, fibromas, renal angiomyolipoma, retinal and other hamartomas, SEGA, and others	AD
<i>VHL</i>	608537	VHL syndrome Endolymphatic sac tumors, epididymal and broad ligament cystadenomas, hemangioblastoma, neuroendocrine tumors, pheochromocytoma, renal cell carcinoma, retinal angioma	AD
<i>WT1</i>	607102	<i>WT1</i> disorder Gonadoblastoma, Wilms tumor	AD

<sup>a</sup>Association is suggested but not well-established at this time.

<sup>b</sup>Possible paternal parent-of-origin effect.

<sup>c</sup>Paternal parent-of-origin effect.



Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
AD, autosomal dominant; AFAP, attenuated familial adenomatous polyposis; AR, autosomal recessive; BAP1-TPDS, BAP1 tumor predisposition syndrome; BHDS, Birt-Hogg-Dube syndrome; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; DDS, Denys-Drash syndrome; FAMM-PC, familial atypical multiple mole melanoma-pancreatic carcinoma; FAP, familial adenomatous polyposis; FCTCS, Familial cutaneous telangiectasia and cancer syndrome; GAPPs, gastric adenocarcinoma and proximal polyposis of the stomach; GEP, gastro-entero-pancreatic; GIST, gastrointestinal stromal tumor; HBOC, hereditary breast and ovarian cancer; HDGC, hereditary diffuse gastric cancer; HHT, hereditary hemorrhagic telangiectasia; HLRCC, hereditary leiomyomatosis and renal cell cancer; HNPCC, hereditary nonpolyposis colorectal cancer; HPP, hereditary paraganglioma-pheochromocytoma; HPRCC, hereditary papillary renal cell carcinoma; JPS, juvenile polyposis syndrome; LFS, Li-Fraumeni syndrome; MAP, MUTYH-associated polyposis; MEN, multiple endocrine neoplasia; NBCCS, nevoid basal cell carcinoma syndrome; NBS, Nijmegen breakage syndrome; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; ODCRCS, oligodontia-colorectal cancer syndrome; PJS, Peutz-Jeghers syndrome; PPAP, polymerase proofreading-associated polyposis; RTPS, rhabdoid tumor predisposition syndrome; SEGA, subependymal giant cell astrocytoma, TSC, tuberous sclerosis complex; VHL, Von Hippel-Lindau			

## References

- National Cancer Institute. [Genetic testing for inherited cancer susceptibility syndromes](#). Reviewed March 2019; accessed May 2022.

## Related Information

[Breast Cancer Biomarkers](#)  
[Colorectal \(Colon\) Cancer](#)  
[Hereditary Cancer Germline Genetic Testing](#)  
[Neuroblastoma](#)  
[Ovarian Cancer Biomarkers](#)

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