Hereditary Cancer Panel

Last Literature Review: May 2022 Last Update: September 2023

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.[1]

Inheritance

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

Gene	Inheritance Pattern
SDHAF2	Autosomal dominant with paternal parent-of-origin effect
SDHD	Autosomal dominant with paternal parent-of-origin effect
MAX	Autosomal dominant with possible paternal parent-of-origin effect
MUTYH	Autosomal recessive but may also have autosomal dominant risks that are not well-defined
MLH3	Autosomal recessive
MSH3	Autosomal recessive
NTHL1	Autosomal recessive
TERT	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[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] 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
Exon-level deletions/duplications (MLPA)	>99	>99

[a]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.

[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
- 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)
APC	(NM_001354896) 12; (NM_001354898, NM_001354904) 2; (NM_001354900) 11
BMPR1A	(NM_004329) 12-13
BRCA1	(NM_007294, NM_007299, NM_007300) 2; (NM_007298) 1
CDH1	(NM_001317185) 10
CDKN2A	(NM_000077, NM_001195132, NM_001363763, NM_058195) 2
CHEK2	(NM_007194) 11-15; (NM_001005735) 3,12-16; (NM_001257387) 12-16; (NM_001349956) 4,10-14; (NM_145862) 10-14
CTNNA1	(NM_001290307) 19; (NM_001324002, NM_001324004) 13; (NM_001324003) 15; (NM_001324005) 16
FLCN	(NM_001353229) 7
MEN1	(NM_001370251) 8
MITF	(NM_001354607) 2
MLH3	(NM_001040108) 7-8; (NM_014381) 7
PDGFRA	(NM_001347827) 17; (NM_001347828) 2; (NM_001347830) 1
PTEN	(NM_000314, NM_001304718) 9; (NM_001304717) 1,10
RB1	(NM_000321) 22
RECQL	(NM_002907) 14-15; (NM_032941) 15-16

Gene	Exon(s)
SDHA	(NM_004168) 1,10-15; (NM_001294332) 1,9-14; (NM_001330758) 1,10-13
SDHD	(NM_001276506) 4
SMARCE1	(NM_003079) 7,10-11
VHL	(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
ALK	105590	*ALK*-related neuroblastic tumor susceptibility Ganglioneuroblastoma, ganglioneuroma, neuroblastoma	AD
APC	611731	FAP AFAP GAPPS Colorectal adenomas and cancer, duodenal adenomas and cancer, gastric fundic gland polyps, medulloblastoma, osteomas, pancreatic, thyroid, and others	AD
ATM	607585	Breast, colorectal,[a] ovarian, pancreatic, prostate	AD
		Ataxia-telangiectasia	AR
AXIN2	604025	ODCRCS Colorectal,[a] polyposis	AD
BAP1	603089	*BAP1*-TPDS *BAP1*-inactivated melanocytic tumors, basal cell carcinoma, cutaneous melanoma, malignant mesothelioma, renal cell carcinoma, uveal melanoma	AD
BARD1	601593	Breast	AD
BMPR1A	601299	JPS Colorectal, juvenile polyps, small intestine, stomach	AD
BRCA1	113705	HBOC syndrome Breast, fallopian tube, ovarian, pancreatic, peritoneal, prostate	AD
		Fanconi anemia, complementation group S	AR

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

[b]Possible paternal parent-of-origin effect.

[c]Paternal parent-of-origin effect.

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, Nijmegan 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

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
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
CDC73	607393	*CDC73*-related disorders Hyperparathyroidism-jaw tumor syndrome Hyperparathyroidism/parathyroid carcinoma, kidney lesions/tumors	AD
CDH1	192090	HDGC Diffuse gastric, lobular breast	AD
CDK4	123829	Cutaneous melanoma, pancreatic[a]	AD
CDKN1B	600778	MEN Type 4 Gastrinoma, GEP, nonendocrine. parathyroid, pituitary	AD
CDKN2A	600160	FAMMM-PC syndrome (also known as melanoma-pancreatic cancer syndrome) Cutaneous melanoma, pancreatic	AD
CHEK2	604373	Breast, colorectal, prostate, thyroid [a]	AD
CTNNA1	116805	Breast,[a] stomach	AD
DICER1	606241	*DICER1*-related disorders Pleuropulmonary blastoma, ovarian sex cord-stromal tumors, cystic nephroma, thyroid	AD
EGFR	131550	Lung	AD
EPCAM (Exon 9 deletion/duplications only)	185535	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreatic, prostate, renal pelvis and/or ureter, stomach, and others	AD
FH	136850	*FH* tumor predisposition syndrome/HLRCC Cutaneous and uterine leiomyomata, papillary type 2 renal cancer, paraganglioma, pheochromocytoma	AD
		Fumarase deficiency	AR
FLCN	607273	BHDS Fibrofolliculomas, pulmonary cysts/history of pneumothorax, renal cancer	AD

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Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
HOXB13	604607	Prostate	AD
HRAS	190020	Costello syndrome	AD
		Neuroblastoma, rhabdomyosarcoma, transitional cell carcinoma of the bladder	
KIT	164920	GIST	AD
LZTR1	600574	Schwannomatosis	AD
		Noonan syndrome	AR
MAX	154950	HPP syndromes	AD[b]
		Paraganglioma, pheochromocytoma	
MC1R	155555	Cutaneous melanoma[a]	AD
MEN1	613733	MEN type 1	AD
		Adrenocortical, carcinoid, GEP, neuroendocrine tumors, meningioma, parathyroid, pituitary, thyroid	
MET	164860	HPRCC	AD
		Papillary type 1 renal cancer	
MITF	156845	Waardenburg syndrome type II	
		Cutaneous melanoma	
MLH1	120436	Lynch syndrome/HNPCC	AD
		Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	
		CMMRD	AR
MLH3	604395	*MLH3*-associated polyposis	AD
		Breast,[a] colorectal,[a] polyposis	
MSH2	609309	Lynch syndrome/HNPCC	AD
		Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	
		CMMRD	AR
MSH3	600887	Colorectal,[a] polyposis	AR
MSH6	600678	Lynch syndrome/HNPCC	AD
		Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	

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Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
		CMMRD	AR
MUTYH	604933	Breast,[a] colorectal[a]	AD
		MAP Colorectal adenomas and cancer, duodenal adenomas and cancer	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
NF2	607379	NF2 Astrocytoma, ependymoma, meningioma, schwannoma	AD
NTHL1	602656	Colorectal,[a] polyposis	AR
PALB2	610355	Breast, ovarian, pancreas, prostate	AD
		Fanconi anemia, complementation group N	AR
PDGFRA	173490	GIST, inflammatory fibroid polyp, fibroid tumor	AD
PMS2	600259	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
POLD1	174761	PPAP Colorectal,[a] polyposis	AD
POLE	174762	PPAP Colorectal,[a] polyposis	AD
POT1	606478	*POT1* tumor predisposition syndrome Angiosarcoma, chronic lymphocytic leukemia, cutaneous melanoma, glioma	AD
PRKAR1A	188830	Carney complex Endocrine tumor or overactivity, myxoma, schwannoma	AD
PTCH1	601309	NBCCS/Gorlin syndrome	AD

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Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
		Basal cell carcinoma, cardiac and ovarian fibromas, medulloblastoma	
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
RB1	614041	Hereditary retinoblastoma Melanoma,[a] osteosarcoma, pinealoblastoma, retinoblastoma, retinoma, soft tissue sarcoma	AD
RECQL	600537	Breast[a]	AD
RET	164761	MEN2 Medullary thyroid carcinoma, parathyroid adenoma or hyperplasia, pheochromocytoma	AD
SDHA	600857	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHAF2	613019	HPP syndromes Paraganglioma	AD[c]
SDHB	185470	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHC	602413	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHD	602690	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD[c]
SMAD4	600993	JPS, HHT syndrome Colorectal, juvenile polyps, small intestine, stomach	AD
SMARCA4	603254	Coffin-Siris syndrome, RTPS Rhabdoid tumors located in CNS, kidney, ovary (SCCOHT), and others	AD
SMARCB1	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
SMARCE1	603111	Coffin-Siris syndrome	AD

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[b]Possible paternal parent-of-origin effect.

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Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
		Meningioma	
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
SUFU	607035	NBCCS/Gorlin syndrome Basal cell carcinoma, cardiac and ovarian fibromas, medulloblastoma	AD
TERT	187270	Dyskeratosis congenita Acute myelogenous leukemia, melanoma,[a] pulmonary fibrosis	AD and AR
TMEM127	613403	HPP syndromes Paraganglioma, pheochromocytoma, renal clear cell carcinoma	AD
TP53	191170	LFS Adrenocortical carcinoma, breast, choroid plexus carcinoma, CNS, colorectal, melanoma, osteosarcoma, pancreas, prostate, renal, rhabdomyosarcoma, soft tissue sarcoma, stomach, thyroid, and others	AD
TSC1	605284	TSC Cardiac rhabdomyoma, fibromas, renal angiomyolipoma, retinal and other hamartomas, SEGA, and others	AD
TSC2	191092	TSC Cardiac rhabdomyoma, fibromas, renal angiomyolipoma, retinal and other hamartomas, SEGA, and others	AD
VHL	608537	VHL syndrome Endolymphatic sac tumors, epididymal and broad ligament cystadenomas, hemangioblastoma, neuroendocrine tumors, pheochromocytoma, renal cell carcinoma, retinal angioma	AD
WT1	607102	*WT1* disorder Gonadoblastoma, Wilms tumor	AD

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References

1. 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