

Hereditary Renal Cancer Panel

Pathogenic variants in multiple genes have been implicated in hereditary renal cancer. Hereditary cancer predisposition is often characterized by early age of onset (typically before 50 years) and multiple, multifocal, and/or similar cancers in a single individual or in a closely related family member(s). Pathogenic variants in the genes analyzed by this panel cause variable phenotypes and cancer risks, including nonrenal cancers.

Disease Overview

Etiology

Approximately 5% of renal cancers are associated with a hereditary cause.

Inheritance

- All genes tested on the Hereditary Renal Cancer Panel are autosomal dominant with the exception of the *SDHD* gene, which is autosomal dominant with paternal parent-of-origin effect.
- Some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.
- See [table below](#) for additional details.

Test Description

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

Clinical Sensitivity

Variable, dependent on phenotype/condition

Testing Strategy

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy as sensitivity for mosaic variants is low with methodology used for germline assays
- Individuals with hematological malignancy and/or a previous allogeneic 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.
- When a relative has a previously identified pathogenic variant, see [Familial Mutation, Targeted Sequencing \(2001961\)](#).

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 *SMARCA4* and *WT1*
 - Noncoding transcripts
 - The following exons are not sequenced due to technical limitations of the assay:
 - *SDHC* (NM_001035511) 5
 - *SDHD* (NM_001276506) 4

Tests to Consider

[Hereditary Renal Cancer Panel, Sequencing and Deletion/Duplication 2010214](#)

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

Indication for testing:

- Recommended test to confirm a diagnosis of a hereditary renal cancer syndrome in individuals with a personal or family history of renal cancer.
- 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

Indication for testing:

- Recommended test if there is 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.

See [Related Tests](#)

- The following may not be detected:
 - Deletions/duplications/insertions of any size by massively parallel sequencing
 - Deletions/duplications less than 1kb in the targeted genes by array
 - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
 - Low-level somatic variants
 - Single exon deletions/duplications in the following exons:
 - *BAP1* (NM_004656) 1
 - *FH* (NM_000143) 1
 - *FLCN* (NM_144997) 8
 - *MSH2* (NM_000251) 1; (NM_001258281) 2
 - *MSH6* (NM_000179) 10
 - *PTEN* (NM_000314) 8, 9; (NM_001304717) 1
 - *SDHD* (NM_001276506) 4
 - *SMARCB1* (NM_003073) 5
 - *TP53* (NM_001126113) 10; (NM_001126114) 10
 - *TSC2* (NM_000548) 17, 29, 41
 - *VHL* (NM_000551) 1

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate ^a (%)	Analytical Sensitivity (PPA) 95% Credibility Region ^a (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

^aGenes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

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

Genes Tested

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
<i>BAP1</i>	603089	BAP1-TPDS Associated cancer(s)/tumor(s): <i>BAP1</i> -inactivated melanocytic tumors, uveal melanoma, malignant mesothelioma, cutaneous melanoma, renal cell carcinoma, basal cell carcinoma	AD
<i>DICER1</i>	606241	<i>DICER1</i> -related disorders Associated cancer(s)/tumor(s): pleuropulmonary blastoma, ovarian sex cord-stromal tumors, cystic nephroma, thyroid	AD
<i>FH</i>	136850	HLRCC Associated cancer(s)/tumor(s): papillary type 2 renal cancer, cutaneous and uterine leiomyomata	AD
		Fumarase deficiency	AR
<i>FLCN</i>	607273	BHDS Associated cancer(s)/tumor(s): renal	AD

^aPaternal parent-of-origin effect

AD, autosomal dominant; 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; GIST, gastrointestinal stromal tumor; HLRCC, hereditary leiomyomatosis and renal cell cancer; HNPCC, hereditary nonpolyposis colorectal cancer; HPRCC, hereditary papillary renal cell carcinoma; LFS, Li-Fraumeni syndrome; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
<i>MET</i>	164860	HPRCC Associated cancer(s)/tumor(s): papillary type 1 renal cancer	AD
<i>MLH1</i>	120436	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast, ^a and others	AD
		CMMRD	AR
<i>MSH2</i>	609309	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast, ^a and others	AD
		CMMRD	AR
<i>MSH6</i>	600678	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast, ^a and others	AD
		CMMRD	AR
<i>PMS2</i>	600259	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, ^a breast, ^a and others	AD
		CMMRD	AR
<i>PTEN</i>	601728	Cowden syndrome/ <i>PTEN</i> hamartoma tumor syndrome Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colorectal, renal cell carcinoma	AD
<i>SDHB</i>	185470	Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma	AD
<i>SDHC</i>	602413	Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma	AD
<i>SDHD</i>	602690	Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma	AD ^a
<i>SMARCA4</i>	603254	Rhabdoid tumor predisposition syndrome Associated cancer(s)/tumor(s): rhabdoid tumor	AD
<i>SMARCB1</i>	601607	Rhabdoid tumor predisposition syndrome Associated cancer(s)/tumor(s): rhabdoid tumor	AD
<i>TP53</i>	191170	LFS Associated cancer(s)/tumor(s): soft tissue sarcoma, osteosarcoma, CNS tumor, breast, colorectal, pancreas, ^a adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma	AD
<i>TSC1</i>	605284	TSC Associated cancer(s)/tumor(s): cardiac rhabdomyoma, retinal and other hamartomas, renal angiomyolipoma, SEGA, fibromas	AD
<i>TSC2</i>	191092	TSC Associated cancer(s)/tumor(s): cardiac rhabdomyoma, retinal and other hamartomas, renal angiomyolipoma, SEGA, fibromas	AD
<i>VHL</i>	608537	VHL syndrome Associated cancer(s)/tumor(s): hemangioblastoma, retinal angioma, renal cell carcinoma, pheochromocytoma, neuroendocrine tumors, endolymphatic sac tumors, epididymal and broad ligament cystadenomas	AD
<i>WT1</i>	607102	<i>WT1</i> -related Wilms tumor, WAGR syndrome, DDS, Frasier syndrome Associated cancer(s)/tumor(s): Wilms tumor	AD

^aPaternal parent-of-origin effect

AD, autosomal dominant; 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; GIST, gastrointestinal stromal tumor; HLRCC, hereditary leiomyomatosis and renal cell cancer; HNPCC, hereditary nonpolyposis colorectal cancer; HPRCC, hereditary papillary renal cell carcinoma; LFS, Li-Fraumeni syndrome; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau

Additional Resources

Carlo MI, Mukherjee S, Mandelker D, et al. [Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma](#). *JAMA Oncol*. 2018;4(9):1228-1235.

Dome JS, Huff V. [Wilms tumor predisposition](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Oct 2016; Accessed: Feb 2020]

Kamihara J, Schultz KA, Rana HQ. [FH tumor predisposition syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Apr 2020; Accessed: Jul 2020]

Larsen Haidle J, Howe JR. [Juvenile polyposis syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last update: Mar 2017; Accessed: Jul 2021]

National Comprehensive Cancer Network. [NCCN Clinical Practice Guidelines in Oncology: genetic/familial high-risk assessment—breast, ovarian, and pancreatic](#). Version 2.2021. [Updated: Nov 2020; Accessed: Aug 2021]

National Comprehensive Cancer Network. [NCCN Clinical Practice Guidelines in Oncology: genetic/familial high-risk assessment—colorectal](#). Version 1.2020. [Updated: Jul 2020; Accessed: Feb 2021]

Nemes K, Bens S, Bourdeaut F, et al. [Rhabdoid tumor predisposition syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Initial Posting: Dec 2017; Accessed: Feb 2020]

Northrup H, Koenig MK, Pearson DA, et al. [Tuberous sclerosis complex](#). In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2022. [Revised: Dec 2021; Accessed: Feb 2022]

Pilarski R, Rai K, Cebulla C, et al. [BAP1 tumor predisposition syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Initial Posting: Oct 2016; Accessed: Feb 2020]

Sattler EC, Steinlein OK. [Birt-Hogg-Dubé syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Jan 2020; Accessed: Feb 2020]

van Leeuwen RS, Ahmad S, Links TP, et al. [Von Hippel-Lindau syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last update: Sep 2018; Accessed: Apr 2020]

Related Tests

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

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray/Sequencing/Multiplex Ligation-dependent Probe Amplification

[Glucose-6-Phosphate Dehydrogenase Deficiency \(G6PD\) Sequencing 3004457](#)

Method: Massively Parallel Sequencing

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Content Review February 2021 | Last Update February 2022