# 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 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.
- 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

## 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

- 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

- 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 |

[a]Genes 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 |
|---|---|---|---|
| ***BAP1*** | 603089 | BAP1-TPDS<br>Associated cancer(s)/tumor(s): *BAP1*-inactivated melanocytic tumors, uveal melanoma, malignant mesothelioma, cutaneous melanoma, renal cell carcinoma, basal cell carcinoma | AD |

[a]Paternal 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, Denyis-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 |
|---|---|---|---|
| *DICER1* | 606241 | *DICER1*-related disorders<br>Associated cancer(s)/tumor(s): pleuropulmonary blastoma, ovarian sex cord-stromal tumors, cystic nephroma, thyroid | AD |
| *FH* | 136850 | HLRCC<br>Associated cancer(s)/tumor(s): papillary type 2 renal cancer, cutaneous and uterine leiomyomata | AD |
| | | Fumarase deficiency | AR |
| *FLCN* | 607273 | BHDS<br>Associated cancer(s)/tumor(s): renal | AD |
| *MET* | 164860 | HPRCC<br>Associated cancer(s)/tumor(s): papillary type 1 renal cancer | AD |
| *MLH1* | 120436 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast,[a] and others | AD |
| | | CMMRD | AR |
| *MSH2* | 609309 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast,[a] and others | AD |
| | | CMMRD | AR |
| *MSH6* | 600678 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast,[a] and others | AD |
| | | CMMRD | AR |
| *PMS2* | 600259 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian,[a] breast,[a] and others | AD |
| | | CMMRD | AR |
| *PTEN* | 601728 | Cowden syndrome/*PTEN* hamartoma tumor syndrome<br>Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colorectal, renal cell carcinoma | AD |
| *SDHB* | 185470 | Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma | AD |
| *SDHC* | 602413 | Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma | AD |
| *SDHD* | 602690 | Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma | AD[a] |
| *SMARCA4* | 603254 | Rhabdoid tumor predisposition syndrome<br>Associated cancer(s)/tumor(s): rhabdoid tumor | AD |

[a]Paternal parent-of-origin effect

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| Gene | MIM Number | Disorder/Associated Cancer(s)/Tumor(s) | Inheritance |
|---|---|---|---|
| *SMARCB1* | 601607 | Rhabdoid tumor predisposition syndrome<br>Associated cancer(s)/tumor(s): rhabdoid tumor | AD |
| *TP53* | 191170 | LFS<br>Associated cancer(s)/tumor(s): soft tissue sarcoma, osteosarcoma, CNS tumor, breast, colorectal, pancreas,[a] adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma | AD |
| *TSC1* | 605284 | TSC<br>Associated cancer(s)/tumor(s): cardiac rhabdomyoma, retinal and other hamartomas, renal angiomyolipoma, SEGA, fibromas | AD |
| *TSC2* | 191092 | TSC<br>Associated cancer(s)/tumor(s): cardiac rhabdomyoma, retinal and other hamartomas, renal angiomyolipoma, SEGA, fibromas | AD |
| *VHL* | 608537 | VHL syndrome<br>Associated cancer(s)/tumor(s): hemangioblastoma, retinal angioma, renal cell carcinoma, pheochromocytoma, neuroendocrine tumors, endolymphatic sac tumors, epididymal and broad ligament cystadenomas | AD |
| *WT1* | 607102 | *WT1*-telated Wilms tumor, WAGR syndrome, DDS, Frasier syndrome<br>Associated cancer(s)/tumor(s): Wilms tumor | AD |

[a]Paternal parent-of-origin effect

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## Additional Resources


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## Related Tests

Hereditary Cancer Panel, Sequencing and Deletion/Duplication 2012032

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

Hereditary Paraganglioma-Pheochromocytoma (SDHB, SDHC, and SDHD) Sequencing and Deletion/Duplication Panel 2007167

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (MLH1) Sequencing and Deletion/Duplication 0051650

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (MSH2) Sequencing and Deletion/Duplication 0051654

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (MSH6) Sequencing and Deletion/Duplication 0051656

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (PMS2) Sequencing and Deletion/Duplication 0051737

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Li-Fraumeni (TP53) Sequencing and Deletion/Duplication 2009313

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

PTEN-Related Disorders (PTEN) Sequencing and Deletion/Duplication 2002470

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

von Hippel-Lindau (VHL) Sequencing and Deletion/Duplication 2002965

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

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