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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
  - 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

[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* tumor predisposition syndrome (BAP1-TPDS) Associated cancer(s)/tumor(s): uveal melanoma, malignant mesothelioma, cutaneous melanoma, renal cell carcinoma, basal cell carcinoma	AD
DICER1	606241	*DICER1*-related disorders Associated cancer(s)/tumor(s): pleuropulmonary blastoma, ovarian sex cord-stromal tumors, cystic nephroma, thyroid	AD
FH	136850	Hereditary leiomyomatosis and renal cell cancer (HLRCC) Associated cancer(s)/tumor(s): papillary type 2 renal cancer, cutaneous and uterine leiomyomata	AD
		Fumarase Deficiency	AR
FLCN	607273	Birth-Hogg-Dube syndrome (BHDS) Associated cancer(s)/tumor(s): renal	AD
MET	164860	Hereditary papillary renal cell carcinoma (HPRCC) Associated cancer(s)/tumor(s): papillary type 1 renal cancer	AD
MLH1	120436	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
MSH2	609309	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
MSH6	600678	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
PMS2	600259	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
PTEN	601728	Cowden syndrome/*PTEN* hamartoma tumor syndrome Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colon, 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 Associated cancer(s)/tumor(s): rhabdoid tumor	AD
SMARCB1	601607	Rhabdoid tumor predisposition syndrome Associated cancer(s)/tumor(s): rhabdoid tumor	AD
TP53	191170	Li-Fraumeni syndrome (LFS) Associated cancer(s)/tumor(s): soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast, adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma	AD
TSC1	605284	Tuberous sclerosis complex (TSC) Associated cancer(s)/tumor(s): cardiac rhabdomyoma, retinal and other hamartomas, renal angiomyolipoma, subependymal giant cell astrocytoma (SEGA), fibromas	AD
TSC2	191092	Tuberous sclerosis complex (TSC) Associated cancer(s)/tumor(s): cardiac rhabdomyoma, retinal and other hamartomas, renal angiomyolipoma, subependymal giant cell astrocytoma (SEGA), fibromas	AD
VHL	608537	Von Hippel-Lindau (VHL) syndrome Associated cancer(s)/tumor(s): hemangioblasoma, 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; Denys-Drash syndrome (DDS); Frasier syndrome Associated cancer(s)/tumor(s): Wilms tumor	AD

[a]Paternal parent-of-origin effect

AD, autosomal dominant; AR, autosomal recessive

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RELATED TESTS

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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