Renal Hereditary Cancer Panel

Indications for Ordering

Confirm diagnosis of hereditary renal cancer in individuals with personal or family history of renal cancer

Test Description

- Targeted capture of all coding exons and intron/exon junctions followed by massively parallel sequencing
  - Reported variants are confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary test

Renal Hereditary Cancer Panel, Sequencing and Deletion/ Duplication, 15 Genes 2010214

- Preferred test to confirm a diagnosis of hereditary renal cancer syndrome
- Analysis of specific genes included in this panel may be available individually at ARUP
  - For test availability and further information, see ARUP's Genetics site (www.aruplab.com/genetics)

Related test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence

- >65,000 new cases of renal cancer per year in the U.S.
- 3-4% of renal cancers are hereditary
  - Most renal cancers are not caused by germline variants
- Individuals with a germline variant associated with a hereditary renal cancer syndrome
  - Are at increased risk for renal cancer
  - May be at risk for other types of cancers

Symptoms

- Common signs of a hereditary renal cancer syndrome
  - Early onset of renal cancer or disease (<45 years)
  - Multifocal or bilateral renal tumors
  - Multiple renal tumors in a single individual
  - Family history of renal cancer or related cancers
- See table for common hereditary renal cancer syndromes and associated clinical features

Genetics

Genes – see table for genes analyzed and for gene-specific information

Test Interpretation

Results

- Positive – one pathogenic variant detected in one of the genes analyzed
  - Confirms diagnosis of hereditary renal cancer syndrome
  - Predicts increased risk for renal cancer in an asymptomatic individual
- Negative – no pathogenic variants detected in any of the genes analyzed
  - Reduces, but does not exclude, the risk of a hereditary form of renal cancer in an individual
- Inconclusive – variants of unknown clinical significance may be identified

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
  - Variants in genes not included on the panel
  - Deep intronic and regulatory region variants
  - Breakpoints for large deletions/duplications
  - Deletions/duplications may not be detected in
    - Exon 1 in *BAP1* and *MSH2* genes
    - Exons 1 and 9 in *FH* gene
    - Exon 8 in *FLCN* and *PTEN* genes
    - Exons 7, 17, 23, 25, 29, 32, and 41 in *TSC2* gene
- 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 or buccal specimen is required for accurate interpretation of test results
- Lack of a detectable gene variant does not exclude a diagnosis of hereditary renal cancer syndrome
  - Not all predisposing genes are analyzed

Gene Symbol	Gene Name	NM #	OMIM #	Inh.	Associated Syndromes/Phenotypes	Associated Renal Cancers	Other Clinical Features/Tumors	Disorder Incidence
BAP1	BRCA1-associated protein-1	004329	603089	AD	Tumor predisposition syndrome; malignant mesothelioma	Renal cell carcinoma	Breast, ovarian, pancreatic, and lung cancer; malignant mesothelioma; melanoma	Rare
FH	Fumarate hydratase	000143	136850	AD	Hereditary leiomyomatosis and renal cell cancer (HLRCC)	Type 2 papillary renal cancer	Cutaneous and uterine leiomyomas or fibroids	Rare
FLCN	Folliculin	144997	607273	AD	Birt-Hogg-Dubé (BHD) syndrome	Renal cell carcinoma	Cutaneous fibrofolliculomas; pulmonary cysts	Rare
MET	Met proto oncogene	001127500	164860	AD	Hereditary papillary renal carcinoma (HPRC)	Type 1 papillary renal cancer		Rare
MLH1	MutL homologue 1, colon cancer, nonpolyposis type 2	000249	120436	AD	Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC)	Renal pelvis and ureter cancer	Colon, endometrial, ovarian, stomach, small bowel, hepatobiliary tract, pancreatic, and CNS cancer	1/440
MSH2	MutS homologue 2, colon cancer, nonpolyposis type 1	000251	609309					
MSH6	MutS homologue 6	000179	600678					
PTEN	Phosphatase and tensin homolog	000314	601728	AD	*PTEN* hamartoma tumor syndrome; Cowden syndrome (CS); Bannayan-Riley-Ruvalcaba syndrome (BRRS); Proteus syndrome (PS); Proteus-like syndrome (PLS)	Renal cell carcinoma	Breast, endometrial, thyroid, CNS, colon, and skin cancer; macrocephaly; mucocutaneous lesions; benign breast, thyroid, and endometrial disease; GI polyps; developmental delay; tissue overgrowth	1/200,000
SDHB	Succinate dehydrogenase complex, subunit B, iron sulfur	003000	185470	AD	Hereditary paraganglioma-pheochromocytoma (PGL/PCC)	Renal cell carcinoma	Paraganglioma; pheochromocytoma; GI stromal tumors (GISTs); thyroid cancer	Rare
SDHC	Succinate dehydrogenase complex, subunit C, integral membrane protein	003001	602413	AD				
SDHD	Succinate dehydrogenase complex, subunit D, integral membrane protein	003002	602690	AD*				
TP53	Tumor protein p53	000546	191170	AD	Li-Fraumeni syndrome (LFS)	Renal cell carcinoma	Breast, brain, colon, and adrenocortical cancer; leukemia; osteosarcoma	1/5,000-20,000
TSC1	Tuberous sclerosis 1, hamartin	000368	605284	AD	Tuberous sclerosis complex (TSC)	Renal cell carcinoma; angiomyolipoma	Hamartomas in heart, brain, and eyes; cutaneous lesions; seizures; renal disease; intellectual disability	1/5,800
TSC2	Tuberous sclerosis 2, tuberin	000548	191092					
VHL	Von Hippel-Lindau syndrome	000551	608537	AD	Von Hippel-Lindau (VHL)	Renal cell carcinoma; renal cysts	Retinal angioma; hemangioblastoma; pheochromocytoma; neuroendocrine tumors	1/36,000

Inh. = Inheritance; AD = autosomal dominant
* = parent-of-origin effects