Hereditary Renal Cancer Panel, Sequencing and Deletion/Duplication

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
  o Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants
• Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array

Tests to Consider
Primary test
Hereditary Renal Cancer Panel, Sequencing and Deletion/Duplication 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
  o 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
  o Most renal cancers are not caused by germline variants
• Individuals with a germline variant associated with a hereditary renal cancer syndrome
  o Are at increased risk for renal cancer
  o May be at risk for other types of cancers

Symptoms
• Common signs of a hereditary renal cancer syndrome
  o Early onset of renal cancer or disease (<45 years)
  o Multifocal or bilateral renal tumors
  o Multiple renal tumors in a single individual
  o 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
  o Confirms diagnosis of hereditary renal cancer syndrome
  o Predicts increased risk for renal cancer in an asymptomatic individual
• Negative – no pathogenic variants detected in any of the genes analyzed
  o 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
  o Variants in genes not included on the panel
  o Deep intronic and regulatory region variants
  o Breakpoints for large deletions/duplications
  o 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
  o 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
  o Not all predisposing genes are analyzed
<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>OMIM #</th>
<th>Inh.</th>
<th>Associated Syndromes/Phenotypes</th>
<th>Associated Renal Cancers</th>
<th>Other Clinical Features/Tumors</th>
<th>Disorder Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAP1</td>
<td>BRCA1-associated protein-1</td>
<td>603089</td>
<td>AD</td>
<td>Tumor predisposition syndrome; malignant mesothelioma</td>
<td>Renal cell carcinoma</td>
<td>Breast, ovarian, pancreatic, and lung cancer; malignant mesothelioma; melanoma</td>
<td>Rare</td>
</tr>
<tr>
<td>FH</td>
<td>Fumarate hydratase</td>
<td>00143</td>
<td>AD</td>
<td>Hereditary leiomyomatosis and renal cell cancer (HLRCC)</td>
<td>Type 2 papillary renal cancer</td>
<td>Cutaneous and uterine leiomyomas or fibroids</td>
<td>Rare</td>
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<tr>
<td>FLCN</td>
<td>Folliculin</td>
<td>004329</td>
<td>AD</td>
<td>Bil-Roug-Dubé (BHD) syndrome</td>
<td>Renal cell carcinoma</td>
<td>Cutaneous fibrofolliculomas; pulmonary cysts</td>
<td>Rare</td>
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<tr>
<td>MET</td>
<td>Met proto oncogene</td>
<td>00112750</td>
<td>AD</td>
<td>Hereditary papillary renal carcinoma (HPRC)</td>
<td>Type 1 papillary renal cancer</td>
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<td>Rare</td>
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<tr>
<td>MLH1</td>
<td>MutL homologue 1, colon cancer, nonpolyposis type 2</td>
<td>000249</td>
<td>AD</td>
<td>Lynch syndrome/heritable non-polyposis colorectal cancer (HNPPC)</td>
<td>Renal pelvis and ureter cancer</td>
<td>Colon, endometrial, ovarian, stomach, small bowel, hepatobiliary tract, pancreatic, and CNS cancer</td>
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<td>MSH2</td>
<td>MutS homologue 2, colon cancer, nonpolyposis type 1</td>
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<td>MSH6</td>
<td>MutS homologue 6</td>
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<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
<td>000314</td>
<td>AD</td>
<td>PTEN hamartoma tumor syndrome; Cowden syndrome (CS); Bannayan-Riley-Ruvalcaba syndrome (BRRS); Proteus syndrome (PS); Proteus-like syndrome (PLS)</td>
<td>Renal cell carcinoma</td>
<td>Breast, endometrial, thyroid, CNS, colon, and skin cancer; macrocephaly; mucocutaneous lesions; benign breast, thyroid, and endometrial disease; GI polyps; developmental delay; tissue overgrowth</td>
<td>1/200,000</td>
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<td>SDHB</td>
<td>Succinate dehydrogenase complex, subunit B, iron sulfur</td>
<td>003000</td>
<td>AD</td>
<td>Hereditary paraganglioma- pheochromocytoma (PGL/PCC)</td>
<td>Renal cell carcinoma</td>
<td>Paraganglioma; pheochromocytoma; GI stromal tumors (GISTS); thyroid cancer</td>
<td>Rare</td>
</tr>
<tr>
<td>SDHC</td>
<td>Succinate dehydrogenase complex, subunit C, integral membrane protein</td>
<td>003001</td>
<td>AD</td>
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<tr>
<td>SDHD</td>
<td>Succinate dehydrogenase complex, subunit D, integral membrane protein</td>
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<td>TPS3</td>
<td>Tumor protein p53</td>
<td>000548</td>
<td>AD</td>
<td>Li-Fraumeni syndrome (LFS)</td>
<td>Renal cell carcinoma</td>
<td>Breast, brain, colon, and adrenocortical cancer; leukemia; osteosarcoma</td>
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<td>TSC1</td>
<td>Tuberous sclerosis 1, hamartin</td>
<td>000368</td>
<td>AD</td>
<td>Tuberous sclerosis complex (TSC)</td>
<td>Renal cell carcinoma; angiomyolipoma</td>
<td>Hamartomas in heart, brain, and eyes; cutaneous lesions; seizures; renal disease; intellectual disability</td>
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<td>TSC2</td>
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<td>VHL</td>
<td>Von Hippel-Lindau syndrome</td>
<td>000551</td>
<td>AD</td>
<td>Von Hippel-Lindau (VHL)</td>
<td>Renal cell carcinoma; renal cysts</td>
<td>Retinal angiomia; hemangiblastoma; pheochromocytoma; neuroendocrine tumors</td>
<td>1/36,000</td>
</tr>
</tbody>
</table>

*Parent-of-origin effects
AD, autosomal dominant; Inh., inheritance

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