Endocrine Hereditary Cancer Panel

Indications for Ordering

Confirm suspected hereditary endocrine cancer in individual with personal or family history of endocrine cancer

Test Description

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

Tests to Consider

Primary test

Endocrine Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 13 Genes 2010193
- Preferred test for individuals at high risk for hereditary endocrine cancer
- 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 mutation identifiable by sequencing is known

Disease Overview

Incidence

- Endocrine cancer – 5.25/100,000
  - Most endocrine cancers are not hereditary or caused by germline mutations
  - Individuals with a pathogenic germline mutation have a 50% risk of passing the mutation on to their offspring

Diagnostic issues

Genetic testing should be offered to individuals with
- Medullary thyroid carcinoma
- Parathyroid carcinoma
- Malignant pheochromocytoma/paraganglioma
- Pheochromocytoma/paraganglioma AND
  - <40 years
  - Multiple cancers OR
    - Family history of pheochromocytoma/paraganglioma
- Follicular thyroid cancer AND
  - Personal or family history of breast or endometrial cancer
- Cribriform-morular variant of papillary thyroid cancer
- Two or more
  - Pituitary adenoma
  - Gastrointestinal or pancreatic endocrine tumors
  - Gastric, thymic, or bronchial carcinoid tumors
  - Primary hyperparathyroidism
  - Adrenocortical adenoma, lipoma, angiofibroma, or collagenoma

Genetics

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

Inheritance – autosomal dominant for all genes in panel

Test Interpretation

Results

- Positive – one pathogenic gene mutation detected
  - Confirms diagnosis of a hereditary endocrine cancer in symptomatic individual
  - Predicts increased risk for endocrine cancer in asymptomatic individual
- Negative – no pathogenic mutation detected
  - Reduces, but does not exclude, the risk of a hereditary form of endocrine cancer in individual
- Inconclusive – variants of unknown clinical significance may be identified

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
  - Mutations in genes not included on the panel
  - Deep intronic and regulatory region mutations
  - Structural and numerical chromosomal abnormalities
  - Breakpoints for large deletions/duplications
    - Exon 1 in RET gene
    - Exon 8 in PTEN gene
    - Exons 4, 6, and 7 in STK11 gene
- Lack of a detectable gene mutation does not exclude a diagnosis of hereditary endocrine cancer
- Not all predisposing genes are analyzed
<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>NM #</th>
<th>OMIM #</th>
<th>Associated Syndromes</th>
<th>Associated Tumor/Cancer Risks</th>
<th>Penetrance</th>
<th>Incidence of Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN1B</td>
<td>Cyclin-dependent kinase inhibitor 1B</td>
<td>004064</td>
<td>600778</td>
<td>Multiple endocrine neoplasia, type IV (MEN4)</td>
<td>Parathyroid and pituitary</td>
<td>Unknown</td>
<td>Unknown</td>
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<tr>
<td>MAX</td>
<td>MYC-associated factor X</td>
<td>002382</td>
<td>154950</td>
<td>Hereditary paraganglioma-pheochromocytoma (PGL/PCC)</td>
<td>Pheochromocytoma (often bilateral)</td>
<td>Unknown</td>
<td>Rare</td>
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<tr>
<td>MEN1</td>
<td>Multiple endocrine neoplasia 1</td>
<td>130799</td>
<td>613733</td>
<td>Multiple endocrine neoplasia 1 (MEN1)</td>
<td>Parathyroid, pituitary, pancreatic islet cell, and medullary thyroid cancer (MTC); facial angiofibroma; meningioma; leiomyoma; collagenoma; ependymoma</td>
<td>95% by 40 yrs</td>
<td>1/30,000</td>
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<tr>
<td>PSEN1</td>
<td>Phosphatase and tensin homologue</td>
<td>000314</td>
<td>601728</td>
<td>PSEN1 hamartoma tumor, Cowden (CS), Bannayan-Riley-Ruvalcaba (BRRS), Proteus (PS), and Proteus-Like (PLS)</td>
<td>Cerebellar, breast, endometrial, nonmedullary thyroid, and genitourinary cancer; hemangioma; lipoma; intestinal hamartomas</td>
<td>99% by 30 yrs for Cowden syndrome</td>
<td>1/200,000</td>
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<tr>
<td>RET</td>
<td>Ret proto-oncogene</td>
<td>020975</td>
<td>164761</td>
<td>Multiple endocrine neoplasia 2 (MEN2)</td>
<td>MTC; pheochromocytoma; parathyroid adenoma</td>
<td>100% for MTC</td>
<td>1/35,000 for MEN2</td>
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<tr>
<td>SDHAF2</td>
<td>Succinate dehydrogenase complex assembly factor 2</td>
<td>017841</td>
<td>613019</td>
<td>Hereditary paraganglioma-pheochromocytoma (PGL/PCC)</td>
<td>Paragangiomas; pheochromocytomas</td>
<td>Incomplete, but high</td>
<td>Rare</td>
</tr>
<tr>
<td>SDHB</td>
<td>Succinate dehydrogenase complex, subunit B, iron sulfur</td>
<td>003000</td>
<td>185470</td>
<td>Gastrointestinal stromal tumors; paragangiomas; pheochromocytomas</td>
<td>Gastrointestinal stromal tumors; paragangiomas</td>
<td>Incomplete, but high</td>
<td>Rare</td>
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<tr>
<td>SDHC</td>
<td>Succinate dehydrogenase complex, subunit C, integral membrane protein</td>
<td>003001</td>
<td>602413</td>
<td>Gastrointestinal stromal tumors; paragangiomas</td>
<td>Gastrointestinal stromal tumors; paragangiomas</td>
<td>Incomplete, but high</td>
<td>Rare</td>
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<tr>
<td>SDHD</td>
<td>Succinate dehydrogenase complex, subunit D, integral membrane protein</td>
<td>003002</td>
<td>602690</td>
<td>Paragangiomas; pheochromocytomas</td>
<td>Paragangiomas; pheochromocytomas</td>
<td>Incomplete, but high</td>
<td>Rare</td>
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<tr>
<td>STK11</td>
<td>Serine threonine kinase 11</td>
<td>000455</td>
<td>602216</td>
<td>Peutz-Jeghers (PJS)</td>
<td>Colorectal, gastric, pancreatic, breast, ovarian, sex cord, and cervical cancer; hamartomatous and adenomatous GI polyps</td>
<td>100%</td>
<td>1/25,000-280,000</td>
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<tr>
<td>TMEM127</td>
<td>Transmembrane protein 127</td>
<td>017849</td>
<td>613403</td>
<td>Hereditary paraganglioma-pheochromocytoma (PGL/PCC)</td>
<td>Pheochromocytomas (often bilateral)</td>
<td>Incomplete, but high</td>
<td>Rare</td>
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<td>TP53</td>
<td>Tumor protein p53</td>
<td>000546</td>
<td>191170</td>
<td>Li-Fraumeni (LFS)</td>
<td>Breast, brain, pancreatic, hepatocellular, nasopharyngeal, basal cell, and adrenocortical carcinomas; leukemia; sarcoma; osteosarcoma; glioma</td>
<td>50% by 30 yrs; 90% by 60 yrs</td>
<td>1/5,000-20,000</td>
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<td>VHL</td>
<td>Von Hippel Lindau syndrome</td>
<td>000551</td>
<td>608537</td>
<td>Von Hippel-Lindau (VHL)</td>
<td>Pheochromocytomas; CNS, retinal, adrenal, lung, and liver hemangioblastomas; renal, endolymphatic sac, and pancreatic cancer</td>
<td>100% by 65 yrs</td>
<td>1/36,000</td>
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