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
  - Deletions/duplications may not be detected in
    - 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

Gene Symbol	Gene Name	NM #	OMIM #	Associated Syndromes	Associated Tumor/Cancer Risks	Penetrance	Incidence of Disorder
CDKN1B	Cyclin-dependent kinase inhibitor 1B	004064	600778	Multiple endocrine neoplasia, type IV (MEN4)	Parathyroid and pituitary	Unknown	Unknown
MAX	MYC-associated factor X	002382	154950	Hereditary paraganglioma-pheochromocytoma (PGL/PCC)	Pheochromocytoma (often bilateral)	Unknown	Rare
MEN1	Multiple endocrine neoplasia 1	130799	613733	Multiple endocrine neoplasia 1 (MEN1)	Parathyroid, pituitary, pancreatic islet cell, and medullary thyroid cancer (MTC); facial angiofibroma; meningioma; leiomyoma; collagenoma; ependymoma	95% by 40 yrs	1/30,000
PTEN	Phosphatase and tensin homologue	000314	601728	*PTEN* hamartoma tumor, Cowden (CS), Bannayan-Riley-Ruvalcaba (BRRS), Proteus (PS), and Proteus-Like (PLS)	Cerebellar, breast, endometrial, nonmedullary thyroid, and genitourinary cancer; hemangioma; lipoma; intestinal hamartomas	99% by 30 yrs for Cowden syndrome	1/200,000
RET	Ret proto-oncogene	020975	164761	Multiple endocrine neoplasia 2 (MEN2)	MTC; pheochromocytoma; parathyroid adenoma	100% for MTC	1/35,000 for MEN2
SDHAF2	Succinate dehydrogenase complex assembly factor 2	017841	613019	Hereditary paraganglioma-pheochromocytoma (PGL/PCC)	Paragangliomas; pheochromocytomas	Incomplete, but high	Rare
SDHB	Succinate dehydrogenase complex, subunit B, iron sulfur	003000	185470		Gastrointestinal stromal tumors; paragangliomas; pheochromocytomas	Incomplete, but high	Rare
SDHC	Succinate dehydrogenase complex, subunit C, integral membrane protein	003001	602413		Gastrointestinal stromal tumors; paragangliomas	Incomplete, but high	Rare
SDHD	Succinate dehydrogenase complex, subunit D, integral membrane protein	003002	602690		Paragangliomas; pheochromocytomas	Incomplete, but high	Rare
STK11	Serine threonine kinase 11	000455	602216	Peutz-Jeghers (PJS)	Colorectal, gastric, pancreatic, breast, ovarian, sex cord, and cervical cancer; hamartomatous and adenomatous GI polyps	100%	1/25,000-280,000
TMEM127	Transmembrane protein 127	017849	613403	Hereditary paraganglioma-pheochromocytoma (PGL/PCC)	Pheochromocytomas (often bilateral)	Incomplete, but high	Rare
TP53	Tumor protein p53	000546	191170	Li-Fraumeni (LFS)	Breast, brain, pancreatic, hepatocellular, nasopharyngeal, basal cell, and adrenocortical carcinomas; leukemia; sarcoma; osteosarcoma; glioma	50% by 30 yrs; 90% by 60 yrs	1/5,000-20,000
VHL	Von Hippel Lindau syndrome	000551	608537	Von Hippel-Lindau (VHL)	Pheochromocytomas; CNS, retinal, adrenal, lung, and liver hemangioblastomas; renal, endolymphatic sac, and pancreatic cancer	100% by 65 yrs	1/36,000