Central Nervous System Hereditary Cancer Panel

Indications for Ordering

Confirm suspected hereditary central nervous system (CNS) cancer in individual with personal or family history of hereditary cancer

Contraindications for ordering

Primary CNS tumors are much less common than metastatic CNS tumors

- This test is not indicated for individuals with suspected metastatic tumors
- This test will not detect pathogenic *PHOX2B* polyalanine expansions causative for congenital hypoventilation syndrome

Test Description

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

Tests to consider

Primary test

Central Nervous System Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 15 Genes 2010188

- Preferred test for individuals suspected to have a hereditary CNS 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 variant identifiable by sequencing is known

Disease Overview

Incidence

- 63,000 primary CNS tumors are diagnosed annually in the U.S.
  - ~24,000 malignant
  - ~39,000 benign
- 1/160 individuals will develop a malignant CNS cancer in his/her lifetime
- CNS cancers represent
  - <1% of all primary cancer diagnoses in adults
  - 20-25% of all primary cancer diagnoses in children
- Most common CNS tumors
  - Gliomas – 50%
  - Meningiomas – 21%
  - Pituitary adenomas – 15%
  - Nerve sheath tumors – 8%
- See table for common hereditary CNS cancer syndromes and associated clinical features

Symptoms

- Headache, emesis, papilledema
  - Typically caused by increased intracranial pressure due to increased intracranial hypertension or tumor expansion
- Executive dysfunction
  - Degree and severity depend on tumor location and damage to surrounding brain structures
- Abnormal fatigue, tremors
- Epileptic seizures

Genetics

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

Inheritance – autosomal dominant for all genes in panel

Test Interpretation

Clinical sensitivity – 5% of primary CNS tumors are caused by germline pathogenic variants

Results

- Positive – detection of a pathogenic gene variant in a symptomatic individual
  - Confirms diagnosis of a hereditary CNS cancer
    - Aids in recurrence risk counseling
    - Individuals with a pathogenic gene variant have a 50% risk of passing the variant on to their offspring
- Negative – no pathogenic variants detected in the genes analyzed
  - Reduces, but does not exclude, the risk of a hereditary form of CNS 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
  - Pathogenic variants in genes not included on the panel
  - Deep intronic and regulatory region pathogenic variants
  - Breakpoints for large deletions/duplications
  - Large deletions/duplications in
    - Exon 1 of *BAP1* and *MSH2* genes
    - Exons 7 and 13 in *NF2* gene
    - Exon 8 in *PTEN* gene
    - Exon 5 in *SMARCB1* gene
    - Exons 4, 6, and 7 in *STK11* gene
- Polyalanine repeats of the *PHOX2B* gene are not analyzed
- 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 pathogenic gene variant does not exclude a diagnosis of hereditary CNS cancer syndrome
  - Not all predisposing genes are analyzed

Gene Symbol	Gene Description	NM #	OMIM #	Associated Syndromes/Tumors (Cancer Risk)	Penetrance	Incidence of Disorder
ALK	Anaplastic lymphoma receptor tyrosine kinase	004304	105590	Neuroblastoma; ganglioneuroblastoma; ganglioneuroma (typically infancy to early childhood)	Unknown	Rare
APC	Adenomatous polyposis coli	Ex1b: 001127511 Ex1a-15: 001127510	611731	Adenomatous polyposis coli; colon (100%); small bowel (4-12%); CNS medulloblastomas (<1%); hepatoblastoma (1.6%); soft tissue and desmoid tumors; osteomas; polyps of gastric fundus, duodenum, colon	100%	2-3/100,000
BAP1	BRCA1 associated protein-1	004656	603089	Mesothelioma; lung adenocarcinoma; melanoma; meningioma; renal cell carcinoma	Unknown	Rare
MLH1	MutL homologue 1, colon cancer, nonpolyposis type 2	000249	120436	Lynch syndrome; colorectal (52-82%); endometrial (25-60%); ovarian (4-6%); gastric (6-13%); small intestine (3-6%); hepatobiliary tract; urinary tract; CNS glioblastomas (1-3%); sebaceous neoplasms (1-9%)	Incomplete	1 /440 for Lynch syndrome
MSH2	MutS homologue 2, colon cancer, nonpolyposis type 1	000251	609309	Lynch syndrome; colorectal (52-82%); endometrial (25-60%); ovarian (8-11%); gastric (6-13%); small intestine (3-6%); hepatobiliary tract; urinary tract; CNS glioblastomas (1-3%); sebaceous neoplasms (1-9%)	Incomplete	1/440 for Lynch syndrome
MSH6	MutS homologue 6	000179	600678	Lynch syndrome; colorectal (20-44%); endometrial (44%); ovarian (4-12%); gastric (6-13%); small intestine; hepatobiliary tract; urinary tract; CNS glioblastomas (1-3%); sebaceous neoplasms (1-9%)	Incomplete	1 /440 for Lynch syndrome
NF2	Neurofibromatosis 2 protein	000268	607379	Neurofibromatosis type 2; bilateral vestibular schwannomas; meningiomas; ependymomas; rarely astrocytomas	~100%	1/33,000
PHOX2B	Paired-like homeobox 2B	003924	603851	Congenital central hypoventilation syndrome; neural crest derivative tumors – neuroblastomas and gangliomas; Hirschsprung disease	Unknown	Rare
PTEN	Phosphatase and tensin homologue	000314	601728	Cowden syndrome; breast (85%); thyroid (35%); renal (35%); colorectal (9%); endometrial (28%); melanoma (>5%); occasionally brain tumors	99% by 30 yrs for Cowden	1/200,000
RB1	Retinoblastoma	000321	614041	Retinoblastoma; pinealoblastoma; sarcomas; melanoma	>90% for germline pathogenic variants	1/15,000-20,000

Gene Symbol	Gene Description	NM #	OMIM #	Associated Syndromes/Tumors (Cancer Risk)	Penetrance	Incidence of Disorder
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	003073	601607	Rhabdoid predisposition syndrome 1; renal; extrarenal; medullary thyroid cancer; CNS tumors, including choroid plexus carcinoma, medulloblastoma, and central primitive neuroectodermal; schwannomatosis; meningiomas	Unknown	Rare
STK11	Serine threonine kinase 11	000455	602216	Peutz-Jeghers syndrome (PJS); colorectal; gastric; pancreatic; breast; ovarian; sex cord; cervical; hamartomatous and adenomatous GI polyps	100%	1/25,000-280,000
SUFU	Suppressor of fused homologue	016169	607035	Medulloblastoma; desmoplastic melanoma; meningioma	Unknown	Rare
TP53	Tumor protein p53	000546	191170	Li-Fraumeni syndrome; sarcoma; osteosarcoma; leukemia; breast, brain (gliomas), hepatocellular, basal cell, pancreatic, nasopharyngeal, and adrenocortical carcinomas	50% by 30 yrs; 90% by 60 yrs	1/5,000-20,000
VHL	Von Hippel Lindau syndrome	000551	608537	von Hippel-Lindau syndrome (VHL); pheochromocytomas; CNS, retinal, adrenal, lung, and liver hemangioblastomas; renal, endolymphatic sac and pancreatic cancer	100% by 65 yrs	1/36,000