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

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Description</th>
<th>OMIM #</th>
<th>Associated Syndromes/Tumors (Cancer Risk)</th>
<th>Penetrance</th>
<th>Incidence of Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma receptor tyrosine kinase</td>
<td>004304</td>
<td>Neuroblastoma; ganglioneuroblastoma; ganglieneuroma (typically infancy to early childhood)</td>
<td>Unknown</td>
<td>Rare</td>
</tr>
<tr>
<td>APC</td>
<td>Adenomatous polyposis coli</td>
<td>Ex1b: 001127511 Ex1a-15: 001127510</td>
<td>Adenomatous polyposis coli: colon (100%); small bowel (4-12%); CNS medulloblastomas (&lt;1%); hepatoblastoma (1.6%); soft tissue and desmoid tumors; osteomas; polyps of gastric fundus, duodenum, colon</td>
<td>100%</td>
<td>2-3/100,000</td>
</tr>
<tr>
<td>BAP1</td>
<td>BRCA1 associated protein-1</td>
<td>004656</td>
<td>Mesothelioma; lung adenocarcinoma; melanoma; meningioma; renal cell carcinoma</td>
<td>Unknown</td>
<td>Rare</td>
</tr>
<tr>
<td>MLHI</td>
<td>Mutl. homologue 1, colon cancer, nonpolyposis type 2</td>
<td>000249</td>
<td>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%)</td>
<td>Incomplete</td>
<td>1 /440 for Lynch syndrome</td>
</tr>
<tr>
<td>MSH2</td>
<td>MutS homologue 2, colon cancer, nonpolyposis type 1</td>
<td>000251</td>
<td>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%)</td>
<td>Incomplete</td>
<td>1/440 for Lynch syndrome</td>
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<tr>
<td>MSH6</td>
<td>MutS homologue 6</td>
<td>000179</td>
<td>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%)</td>
<td>Incomplete</td>
<td>1/440 for Lynch syndrome</td>
</tr>
<tr>
<td>NF2</td>
<td>Neurofibromatosis 2 protein</td>
<td>000268</td>
<td>Neurofibromatosis type 2; bilateral vestibular schwannomas; meningiomas; ependymomas; rarely astrocytomas</td>
<td>~100%</td>
<td>1/33,000</td>
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<tr>
<td>PHOX2B</td>
<td>Paired-like homeobox 28</td>
<td>003924</td>
<td>Congenital central hypoventilation syndrome; neural crest derivative tumors – neuroblastosomas and gangliomas; Hirschsprung disease</td>
<td>Unknown</td>
<td>Rare</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homologue</td>
<td>000314</td>
<td>Cowden syndrome; breast (85%); thyroid (35%); renal (35%); colorectal (9%); endometrial (28%); melanoma (&gt;5%); occasionally brain tumors</td>
<td>99% by 30 yrs for Cowden</td>
<td>1/200,000</td>
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<tr>
<td>RB1</td>
<td>Retinoblastoma</td>
<td>000321</td>
<td>Retinoblastoma; pinealoblastoma; sarcomas; melanoma</td>
<td>&gt;90% for germline pathogenic variants</td>
<td>1/15,000-20,000</td>
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<td>Gene Symbol</td>
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<tr>
<td>SMARCB1</td>
<td>SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1</td>
<td>003073</td>
<td>601607</td>
<td>Rhabdoid predisposition syndrome 1; renal; extrarenal; medullary thyroid cancer; CNS tumors, including choroid plexus carcinoma, medulloblastoma, and central primitive neuroectodermal; schwannomatosis; meningiomas</td>
<td>Unknown</td>
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<tr>
<td>STK11</td>
<td>Serine threonine kinase 11</td>
<td>000455</td>
<td>602216</td>
<td>Peutz-Jeghers syndrome (PJS); colorectal; gastric; pancreatic; breast; ovarian; sex cord; cervical; hamartomatous and adenomatous GI polyps</td>
<td>100%</td>
</tr>
<tr>
<td>SUFU</td>
<td>Suppressor of fused homologue</td>
<td>016169</td>
<td>607035</td>
<td>Medulloblastoma; desmoplastic melanoma; meningioma</td>
<td>Unknown</td>
</tr>
<tr>
<td>TP53</td>
<td>Tumor protein p53</td>
<td>000546</td>
<td>191170</td>
<td>Li-Fraumeni syndrome; sarcoma; osteosarcoma; leukemia; breast, brain (gliomas), hepatocellular, basal cell, pancreatic, nasopharyngeal, and adrenocortical carcinomas</td>
<td>50% by 30 yrs; 90% by 60 yrs</td>
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<tr>
<td>VHL</td>
<td>Von Hippel Lindau syndrome</td>
<td>000551</td>
<td>608537</td>
<td>von Hippel-Lindau syndrome (VHL); pheochromocytomas; CNS, retinal, adrenal, lung, and liver hemangioblastomas; renal, endolymphatic sac and pancreatic cancer</td>
<td>100% by 65 yrs</td>
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