Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 47 Genes

Indications for Ordering

Individuals with
- A clinical diagnosis of a cancer at an earlier age than typical
- A rare form of cancer
- A cancer occurring in an individual of the sex not typically affected
- More than one primary cancer
- Bilateral or multifocal cancer
- A personal or family history suggestive of a hereditary cancer syndrome
  - Cancer diagnosed in numerous family members at an early age

Test Description

- Targeted capture followed by parallel sequencing of all exons and intron/exon boundaries of 45 genes (excludes EPCAM and PMS2)
  - See table for list of genes
- Sanger sequencing and multiplex ligation probe amplification (MLPA) of PMS2
- Targeted sequencing of the CHEK2 c.1100delC variant
- Custom comparative genomic hybridization (CGH) array to detect deletions and/or duplications of 46 genes (excludes PMS2)

Tests to Consider

Primary tests
Cancer Panel, Hereditary, Sequencing and Deletion/Duplication, 47 Genes 2012032
- Confirm diagnosis of a hereditary cancer syndrome with personal or family history consistent with features of more than one cancer syndrome
- Tests for specific genes or components of the hereditary cancer panel may be available individually at ARUP
  - For test availability and further information, see the test directory at www.aruplab.com/genetics

Related test
Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Specific cancer syndromes associated with variants in genes in this panel
- Breast/ovarian
- Central nervous system
- Endocrine
- Endometrial
- Gastrointestinal
- Melanoma
- Pancreatic
- Renal

Incidence
5-10% of cancers are hereditary

Symptoms
Highly variable and dependent on the specific gene variant and syndrome involved

Genetics

Genes – see table

Inheritance
- Primarily autosomal dominant
  - Affected individual inherits one variant in a tumor suppressor gene and acquires a second variant in the homologous gene during his/her lifetime
  - Affected individual inherits one variant in an oncogene
- Rarely autosomal recessive

Test Interpretation

Clinical sensitivity – unknown
Results

- **Positive**
  - One pathogenic variant detected in a gene with autosomal dominant inheritance
    - Confirms diagnosis of hereditary cancer syndrome
    - 50% chance of passing the variant on to offspring
  - Two pathogenic variants detected on opposite chromosomes in a gene with autosomal recessive inheritance
    - Confirms diagnosis of hereditary cancer syndrome
  - One pathogenic variant detected in a gene with autosomal recessive inheritance
    - Confirms carrier status for a hereditary cancer syndrome

- **Negative**
  - No pathogenic variants detected
    - Reduces the likelihood of, but does not exclude, a diagnosis of a hereditary cancer syndrome

- **Inconclusive**
  - Variants of unknown clinical significance may be identified

Limitations

- Not determined or evaluated
  - Deep intronic and regulatory variants
  - Breakpoints of large deletions/duplications
  - Sequence changes in EPCAM
  - Deletions/duplications in
    - ATM (exon 12)
    - BAP1 (exon 1)
    - BMPR1A (exon 9)
    - CDH1 (exon 1)
    - CHEK2 (exons 11-15), with the exception of the c.1100delC variant
    - FH (exons 1, 9)
    - FLCN (exon 8)
    - MSH2 (exon 1)
    - NF2 (exons 7, 13)
    - PTEN (exon 8)
    - RET (exon 1)
    - RAD51D (exon 1)
    - SMARCB1 (exon 5)
    - STK11 (exons 4, 6, 7)
    - TSC2 (exons 7, 17, 25, 29, 32, 41)

- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations
- Only genes in the following table will be tested

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>NM #</th>
<th>OMIM #</th>
<th>Inh.</th>
<th>Cancer/Tumor Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma receptor tyrosine kinase</td>
<td>004304</td>
<td>105590</td>
<td>AD</td>
<td>Neuroblastoma, ganglioneuroblastoma, ganglioneuroma</td>
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<td>APC</td>
<td>Adenomatous polyposis coli</td>
<td>ex1b:00112751</td>
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<td>Colon, small bowel, medulloblastoma, hepatoblastoma, soft tissue and desmoid tumors, osteomas</td>
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<td>ATM</td>
<td>Ataxia telangiectasia mutated (includes complementation groups A, C, and D)</td>
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<td>BAP1</td>
<td>BRCA1 associated protein-1</td>
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<td>AD</td>
<td>Mesothelioma, lung adenocarcinoma, meningiomas, cutaneous melanoma, uveal melanoma</td>
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<td>BARD1</td>
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<td>BMPR1A</td>
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<td>Cadherin 1, E-cadherin (epithelial)</td>
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<td>Cyclin-dependent kinase inhibitor 1B</td>
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<tr>
<td>Gene Symbol</td>
<td>Gene Name</td>
<td>NM #</td>
<td>OMIM #</td>
<td>Inh.</td>
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<td>EPCAM</td>
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<td>FH</td>
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<td>FLCN</td>
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<td>MYC associated factor X</td>
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<td>AD</td>
<td>Pheochromocytoma</td>
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<td>MUTYH</td>
<td>MutY homologue (E.coli)</td>
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<td>NF2</td>
<td>Neurofibromatosis 2 protein</td>
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<td>607379</td>
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<td>PALB2</td>
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<td>610335</td>
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<td>PHOX2B</td>
<td>Paired-like homeobox 2B</td>
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<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
<td>000314</td>
<td>601728</td>
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<td>RAD51C</td>
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<td>RB1</td>
<td>Retinoblastoma</td>
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<td>604041</td>
<td>AD</td>
<td>Retinoblastoma, pinealoblastoma, sarcomas, melanoma</td>
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<td>RET</td>
<td>Ret proto-oncogene</td>
<td>020975</td>
<td>164761</td>
<td>AD</td>
<td>Medullary thyroid carcinoma, pheochromocytoma, parathyroid adenoma</td>
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<td>SDHA F2</td>
<td>Succinate dehydrogenase complex assembly factor 2</td>
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<td>Paraganglioma, pheochromocytoma</td>
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<td>SDHB</td>
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<td>003000</td>
<td>185470</td>
<td>AD</td>
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<td>SDHC</td>
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<td>Paraganglioma, pheochromocytoma, GI stromal tumors</td>
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<td>602690</td>
<td>AD</td>
<td>Paraganglioma, pheochromocytoma</td>
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<td>SMAD4</td>
<td>SMAD, mothers against DPP homologue 4</td>
<td>005359</td>
<td>600993</td>
<td>AD</td>
<td>Colon, stomach, upper GI</td>
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<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>AD</td>
<td>Renal, extra renal, medullary thyroid, choroid plexus, medulloblastoma, central primitive neuroectodermal, schwannomatosis, meningiomas</td>
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<tr>
<td>STK11</td>
<td>Serine/threonine kinase 11 (LKB1)</td>
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<td>602216</td>
<td>AD</td>
<td>Colon, pancreatic, breast, ovarian</td>
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<td>SUFU</td>
<td>Suppressor of fused homologue</td>
<td>016169</td>
<td>607035</td>
<td>AD</td>
<td>Medulloblastoma, desmoplastic melanoma, meningioma</td>
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<td>TMEM127</td>
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<td>AD</td>
<td>Paraganglioma, pheochromocytoma</td>
</tr>
<tr>
<td>Gene Symbol</td>
<td>Gene Name</td>
<td>NM #</td>
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<td>TP53</td>
<td>Tumor protein 53</td>
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<td>AD</td>
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<td>605284</td>
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<td>AD</td>
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<td>VHL</td>
<td>von Hippel Lindau syndrome</td>
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<td>608537</td>
<td>AD</td>
<td>Renal cell carcinoma, hemangioblastoma, pheochromocytoma, neuroendocrine tumors</td>
</tr>
</tbody>
</table>

¹Inh. = inheritance; AD = autosomal dominant; AR = autosomal recessive
²Parent of origin