Melanoma Hereditary Cancer Panel

Indications for Ordering
Confirm suspected hereditary melanoma in individuals with personal or family history of melanoma

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 array

Tests to Consider
Primary test
Melanoma Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 6 Genes 2010209
  • Preferred test for individuals at high risk for hereditary melanoma  
  • Analysis of specific genes included in this panel may be available individually at ARUP  
  • For test availability and further information, please 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

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

Inheritance – autosomal dominant for all genes in panel

Mutations
• Large deletions/insertions/duplications account for  
  ○ ~6% of CDK4 gene mutations  
  ○ ~8% of PTEN gene mutations  
  ○ ~18% of RB1 gene mutations  
  ○ ~3% of TP53 gene mutations  
• These mutations are not identified by sequencing and require deletion/duplication analysis for detection

Test Interpretation
Results
• Positive – one pathogenic gene mutation detected  
  ○ Confirms diagnosis of hereditary melanoma in symptomatic individual  
  ○ Predicts increased risk for hereditary melanoma in asymptomatic individual  
• Negative – no pathogenic mutation detected  
  ○ Reduces, but does not exclude, the risk of a hereditary melanoma  
• 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 panel  
  ○ Deep intronic and regulatory region mutations  
  ○ Breakpoints for large deletions/duplications  
  ○ Large deletions/duplications in  
    ▪ Exon 1 of BAP1 gene  
    ▪ Exon 8 of PTEN gene  
• Lack of a detectable gene mutation does not exclude a diagnosis of hereditary melanoma  
  ○ Not all predisposing genes are 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 result

Disease Overview
Incidence – 77,000 new cases of melanoma diagnosed annually in the U.S.  
  • ~5-10% hereditary – clusters in families  
  ○ Potential increased risk for additional cancer types, depending on specific gene mutation  
  ○ Individuals with a pathogenic germline mutation have a 50% risk of passing the mutation on to their offspring  
  • Most melanomas are not caused by germline mutations

Diagnostic issues
• Genetic testing should be offered to individuals with  
  ○ 3 or more diagnoses of melanoma and/or pancreatic cancer in first- or second-degree relatives  
  ○ 3 or more synchronous or metachronous primary melanomas  
  ○ Synchronous or metachronous melanoma and pancreatic cancer
<table>
<thead>
<tr>
<th>Genes Symbol</th>
<th>Gene Name</th>
<th>NM #</th>
<th>OMIM #</th>
<th>GermLine Mutations Increase Risk for the Following Cancer Types (Lifetime Risk as %)</th>
<th>Percentage of Hereditary Melanoma Attributed to this Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAP1</td>
<td>BRCA1-associated protein-1</td>
<td>004656</td>
<td>603089</td>
<td>Mesothelioma; melanoma of the eye</td>
<td>Rare</td>
</tr>
<tr>
<td>CDK4</td>
<td>Cyclin-dependent kinase 4</td>
<td>000075</td>
<td>123829</td>
<td>Melanoma</td>
<td>2%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Cyclin-dependent kinase inhibitor 2A</td>
<td>000077</td>
<td>600160</td>
<td>Melanoma (75%); pancreatic (17%)</td>
<td>20-40%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homologue</td>
<td>000314</td>
<td>601728</td>
<td>Thyroid (35%); breast (85%); renal (35%); colorectal (9%); endometrial (28%); melanoma (&gt;5%)</td>
<td>Rare</td>
</tr>
<tr>
<td>RB1</td>
<td>Retinoblastoma</td>
<td>000321</td>
<td>614041</td>
<td>Retinoblastoma; pinealblastoma; sarcomas; melanoma</td>
<td>Rare</td>
</tr>
<tr>
<td>TP53</td>
<td>Tumor protein p53</td>
<td>000546</td>
<td>191170</td>
<td>Li-Fraumeni syndrome; sarcomas; leukemia; breast, brain, adrenocortical, and hepatocellular</td>
<td>Rare</td>
</tr>
</tbody>
</table>