melanoma is most frequently associated with familial atypical mole melanoma syndrome (FAMMM), which tends to occur in multiple members of the same family (also known as familial melanoma) [2, 3]. Mutations in a number of genes involved in cell proliferation and melanin biosynthesis increase the risk of melanoma development. Inheritance of these genes may manifest as multiple family members with melanoma, as multiple primary melanomas in a given individual; or as a primary melanoma with onset at an early age. In general, the overall risk of melanomas in individuals who have one or more first-degree relatives with melanoma is approximately 5–12%. Other hereditary cancer syndromes, such as hereditary breast and ovarian cancer syndrome (HBOC), Li–Fraumeni syndrome (LFS), etc., may also increase the risk of melanoma [1]. The majority of the gene mutations are transmitted in an autosomal dominant fashion. The identification of individuals at risk of developing hereditary melanoma is important in order to implement strategies for reducing the burden of early disease[3].

Our Hereditary Melanoma Gene Panel includes sequence of all 11 genes listed below. Our Hereditary Melanoma Deletion/Duplication Panel includes deletion/duplication analysis of 9 genes listed in bold below.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Life time risk of melanoma</th>
<th>Frequency of germline mutations in melanoma</th>
<th>Melanoma features</th>
<th>Cancer Syndrome</th>
<th>Non melanoma tumors</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN2A</td>
<td>By age 80, 28% in all population, 58% in Europe, 76% in the US, and 91% in Australia</td>
<td>20-40%</td>
<td>Multiple cases of melanoma in a family, early age at diagnosis, and family members with multiple primary melanomas or pancreatic cancer</td>
<td>FAMMM</td>
<td>Pancreatic cancer, neural system tumors, nonmelanoma skin cancers, uveal melanoma, and head and neck cancers, brain tumors.</td>
<td>[1, 4, 5]</td>
</tr>
<tr>
<td>CDK4</td>
<td>74.2% by age 50</td>
<td>rare</td>
<td>Similar to those with CDKN2A mutations.</td>
<td>FAMMM</td>
<td>Squamous cell carcinoma of head and neck.</td>
<td>[1, 3, 6, 7]</td>
</tr>
<tr>
<td>BAP1</td>
<td>32% of cutaneous and uveal melanoma</td>
<td>84% of uveal melanoma patients with metastases</td>
<td>Cutaneous and ocular melanoma, uveal melanoma, nevoid melanomas</td>
<td>NA*</td>
<td>Mesothelioma, renal cancer, paragangliomas, lung adenocarcinoma, and clear cell carcinoma of the kidney.</td>
<td>[8-12]</td>
</tr>
<tr>
<td>BRCA1</td>
<td>NA</td>
<td>rare</td>
<td>NA</td>
<td>HBOC</td>
<td>Skin cancer, breast and/or ovarian cancer, etc.</td>
<td>[13, 14]</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Relative risk: 2.6</td>
<td>4.8% of ocular melanoma</td>
<td>Cutaneous melanoma.</td>
<td>HBOC</td>
<td>Other skin cancer, breast and/or ovarian cancer, etc.</td>
<td>[1, 13, 14]</td>
</tr>
<tr>
<td>MC1R</td>
<td>Relative risk: 2</td>
<td>rare</td>
<td>3-4 fold more likely to have thick melanomas</td>
<td>NA</td>
<td>NA</td>
<td>[1, 15, 16]</td>
</tr>
<tr>
<td>TP53</td>
<td>NA</td>
<td>rare</td>
<td>NA</td>
<td>LFS</td>
<td>Sarcomas of bone and soft tissues, carcinomas of the breast and adrenal cortex, brain tumors, and acute leukemias, etc.</td>
<td>[14]</td>
</tr>
<tr>
<td>WRN (RECQL2)</td>
<td>NA</td>
<td>rare</td>
<td>Acral lentiginous melanomas on the palms, soles or in nail beds; mucosal melanomas in the nasal cavity or esophagus.</td>
<td>Werner syndrome</td>
<td>Thyroid neoplasms, meningioma, soft tissue sarcomas, leukemia, pre-leukemic conditions and osteosarcoma/bone neoplasms.</td>
<td>[1, 17]</td>
</tr>
<tr>
<td>ACD</td>
<td>NA</td>
<td>0.24% in CDKN2A negative cases</td>
<td>NA</td>
<td>Telomere biology disorders</td>
<td>Predisposition to hematological malignancies.</td>
<td>[18, 19]</td>
</tr>
<tr>
<td>POLE</td>
<td>NA</td>
<td>rare</td>
<td>Cutaneous melanoma</td>
<td>NA</td>
<td>Colorectal cancers and adenomas</td>
<td>[20]</td>
</tr>
</tbody>
</table>
Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Hereditary Melanoma Sequencing Panel (sequence analysis of 11 genes)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2000
CPT codes: 81445
Turn-around time: 6 weeks

Note: We cannot bill insurance for this test.

Hereditary Melanoma Deletion/Duplication Panel (deletion/duplication analysis of 9 genes)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1,545
CPT codes: 81407
Turn-around time: 6 weeks

Results:
Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. All abnormal results are reported by telephone or email.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:
