OncoGeneDx: Melanoma Panel

**Panel Gene List:** BAP1, BRCA2, CDK4, CDKN2A, MITF*, POT1, PTEN, RB1, TP53

*Testing includes sequencing and deletion/duplication analysis for all genes except *MITF*(only c.952G>A (p.Glu318Lys) will be analyzed and reported)

**Clinical Features:**

In the general population, approximately 1 in 50 individuals (2%) will develop melanoma in their lifetime.¹ Several individual factors and exposures, such as fair skin, light hair, freckling, multiple moles, a history of sunburn, excessive ultraviolet light exposure, and sun sensitivity, are important risk factors. While most cases of malignant melanoma (MM) develop sporadically with no family history, approximately 10% of individuals diagnosed with MM have at least one first- or second-degree relative with a history of the disease.² Of those individuals with familial MM, 10 to 40% are thought to be due to pathogenic germline variants in the *CDKN2A* gene, depending on inclusion criteria.²⁻⁷ The prevalence of pathogenic germline variants in the other genes included on this panel among familial MM cases is not well described.

The features suggestive of a hereditary MM predisposition may include, but are not limited to: early onset of disease, multiple primary melanomas and/or other cancers in a single individual, history of MM in one or more close relatives, and several relatives affected with MM spanning multiple generations.⁶⁻⁸

Hereditary MM can be divided into two categories: melanoma-predominant or melanoma-dominant syndromes and melanoma-including or melanoma-subordinate syndromes.⁷⁻⁹

Melanoma-predominant syndromes are caused by pathogenic variants in *BAP1*, *CDK4*, *CDKN2A*, *MITF*, and *POT1* and may confer up to a 90% lifetime risk to develop MM.⁹ Families with pathogenic variants in these genes generally display clustering of MM which will often be the most predominant cancer in these families. Individuals with germline pathogenic variants in *CDKN2A* and *CDK4* are often referred to as having Familial Atypical Multiple Mole Melanoma syndrome (FAMMM).

Melanoma-including syndromes are caused by pathogenic variants in *BRCA2*, *PTEN*, *RB1*, and *TP53*. These syndromes are not defined by their MM risk; however, MM can be part of the associated cancer spectrum. Individuals with a personal and/or family history of MM and other related cancers should be considered at risk for these conditions.

Begg et al. (2005) found that individuals who test negative for a previously identified familial *CDKN2A* pathogenic variant may still have an increased risk for MM likely due to multifactorial
effects, although their risk is lower compared to individuals with the familial germline pathogenic variant.

Inheritance Pattern:
All of the genes on this panel are associated with an autosomal dominant cancer risk. Some of the genes on this panel are also associated with extremely rare conditions when inherited in an autosomal recessive fashion. The specifics of this inheritance are outlined in the table below.

Test Methods:
Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. This DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. For MITF, only c.952G>A (p.Glu318Lys) is analyzed and reported. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data by next generation sequencing (NGS). Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the 9 genes included in the OncoGeneDx Melanoma Cancer Panel depends in part on the patient’s clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of a hereditary predisposition to cancer as outlined above. DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while NGS-CNV analysis, array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic
abnormalities may be undetectable by this test. The methods used cannot reliably detect deletions of 20bp to 250bp in size, or insertions of 10bp to 250 bp in size. Sequencing cannot detect low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect mosaicism and cannot identify balanced chromosome aberrations. Rarely, incidental findings of large chromosomal rearrangements outside the gene of interest may be identified. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results. False negatives may also occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In individuals with active or chronic hematologic neoplasms or conditions, there is a possibility that testing may detect an acquired somatic variant, resulting in a false positive result. As the ability to detect genetic variants and naming conventions can differ among laboratories, rare false negative results may occur when no positive control is provided for testing of a specific variant identified at another laboratory. The chance of a false positive or false negative result due to laboratory errors incurred during any phase of testing cannot be completely excluded.

Interpretations are made with the assumption that any clinical information provided, including family relationships, are accurate. Consultation with a genetics professional is recommended for interpretation of results.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
</tr>
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<tbody>
<tr>
<td>BAP1^10,11</td>
<td>UBIQUITIN CARBOXYL-TERMINAL HYDROLASE BAP1</td>
<td>AD</td>
<td>Uveal/cutaneous melanoma, mesothelioma, &amp; renal cancer</td>
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<tr>
<td>BRCA2^12–21</td>
<td>BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN</td>
<td>AD</td>
<td>Hereditary breast and ovarian cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate, melanoma, &amp; endometrial serous cancer</td>
</tr>
<tr>
<td>AR</td>
<td>Fanconi anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDK4^6,7,22</td>
<td>CYCLIN-DEPENDENT KINASE 4</td>
<td>AD</td>
<td>Melanoma, non-melanoma skin &amp; pancreatic cancer</td>
</tr>
<tr>
<td>CDKN2A^4,7,23–26</td>
<td>CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF</td>
<td>AD</td>
<td>Familial atypical multiple mole melanoma (FAMMM) syndrome: melanoma, pancreatic cancer &amp; astrocytoma</td>
</tr>
<tr>
<td>AR</td>
<td>Fanconi anemia</td>
<td></td>
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<tr>
<td>MITF^27–29</td>
<td>MICROPHTHALMIA-ASSOCIATED TRANSCRIPTION FACTOR</td>
<td>AD</td>
<td>Renal cancer &amp; melanoma</td>
</tr>
<tr>
<td>AR</td>
<td>Fanconi anemia</td>
<td></td>
<td></td>
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<tr>
<td>POT1^30–35</td>
<td>PROTECTION OF TELOMERES 1</td>
<td>AD</td>
<td>Melanoma &amp; brain glioblastoma</td>
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Test Information Sheet

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Mode of Inheritance</th>
<th>Features of Genetic Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTEN</strong>&lt;sup&gt;36–40&lt;/sup&gt;</td>
<td>Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN</td>
<td>AD</td>
<td>PTEN hamartoma tumor syndrome (PHTS): breast, thyroid, endometrial, colon, melanoma &amp; renal cancer, gastrointestinal polyps, Lhermitte-Duclos Disease</td>
</tr>
<tr>
<td><strong>RB1</strong>&lt;sup&gt;41–45&lt;/sup&gt;</td>
<td>Retinoblastoma-associated protein</td>
<td>AD</td>
<td>Hereditary retinoblastoma: retinoblastoma, sarcoma, leukemia, melanoma, &amp; pineoblastoma</td>
</tr>
<tr>
<td><strong>TP53</strong>&lt;sup&gt;36–51&lt;/sup&gt;</td>
<td>Cellular tumor antigen P53</td>
<td>AD</td>
<td>Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**</td>
</tr>
</tbody>
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Because of evolving and expanding phenotypes, this list of cancer/tumor types is not exhaustive. Gene-specific risk for some of the cancers and other features listed are not well-defined.

** High overall risk of cancer: 75% lifetime risk for males to develop cancer, nearly 100% risk for females.

**Abbreviations:**
- AD – Autosomal dominant
- AR – Autosomal recessive
- CGH – Comparative genomic hybridization
- MLPA – Multiplex ligation-dependent probe amplification

**References:**