Hereditary Melanoma Gene Panel

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 Sequencing 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.

CDKN2A	**CDK4**	**BAP1**	**BRCA1**	**BRCA2**	**MC1R**
TP53	**WRN (REC QL2)**	**POLE**	ACD	POT1	

Hereditary Melanoma Panel genes and associated cancers

Gene	Life time risk of melanoma	Frequency of germline mutations in melanoma	Melanoma features	Cancer Syndrome	Non melanoma tumors	References
CDKN2A	By age 80, 28% in all population, 58% in Europe, 76% in the US, and 91% in Australia	20-40%	Multiple cases of melanoma in a family, early age at diagnosis, and family members with multiple primary melanomas or pancreatic cancer	FAMMM	Pancreatic cancer, neural system tumors, nonmelanoma skin cancers, uveal melanoma, and head and neck cancers, brain tumors.	[1, 4, 5]
CDK4	74.2% by age 50	rare	Similar to those with CDKN2A mutations.	FAMMM	Squamous cell carcinoma of head and neck.	[1, 3, 6, 7]
BAP1	32% of cutaneous and uveal melanoma	84% of uveal melanoma patients with metastases	Cutaneous and ocular melanoma, uveal melanoma, nevoid melanomas	NA*	Mesothelioma, renal cancer, paragangliomas, lung adenocarcinoma, and clear cell carcinoma of the kidney.	[8-12]
BRCA1	NA	rare	NA	HBOC	Skin cancer, breast and/or ovarian cancer, etc.	[13, 14]
BRCA2	Relative risk: 2.6	4.8% of ocular melanoma	Cutaneous melanoma.	HBOC	Other skin cancer, breast and/or ovarian cancer, etc.	[1, 13, 14]
MC1R	Relative risk: 2	rare	3-4 fold more likely to have thick melanomas	NA	NA	[1, 15, 16]
TP53	NA	rare	NA	LFS	Sarcomas of bone and soft tissues, carcinomas of the breast and adrenal cortex, brain tumors, and acute leukemias, etc.	[14]
WRN (RECQL2)	NA	rare	Acral lentiginous melanomas on the palms, soles or in nail beds; mucosal melanomas in the nasal cavity or esophagus.	Werner syndrome	Thyroid neoplasms, meningioma, soft tissue sarcomas, leukemia, pre-leukemic conditions and osteosarcoma/bone neoplasms.	[1, 17]
ACD	NA	0.24% in CDKN2A negative cases	NA	Telomere biology disorders	Predisposition to hematological malignancies.	[18, 19]
POLE	NA	rare	Cutaneous melanoma	NA	Colorectal cancers and adenomas	[20]

POT1	NA	<1%	NA	Telomere biology disorders	Predisposition to hematological malignancies.	[18, 21]

*NA, Not available

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 to10 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 to10 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.

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