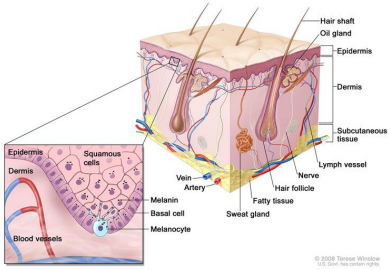
Melanoma of the Skin

Melanoma

The skin is the body's largest organ. It protects against heat, sunlight, injury, and infection; controls body temperature; and stores water, fat, and vitamin D. The skin has two main layers: the dermis (the inner or lower layer) and the epidermis (the outer or upper layer). The epidermis consists of three different kinds of cells: squamous cells, basal cells, and melanocytes. Squamous cells are thin, flat cells that form the top layer of the epidermis. Basal cells are round cells under the squamous cell layer. Throughout the lower part of the epidermis, melanocytes produce melanin, the protective skin-darkening pigment that gives skin its natural color. Melanoma is a type of skin cancer that develops in malignant melanocytes.



In the United States, there are an estimated 100,000 new cases of melanoma and approximately 6,800 deaths from melanoma. The median age at diagnosis is 65 years, and the median age of death is 71 years. The lifetime risk in the general population for developing melanoma is 2.3%. Melanoma is the rarest form of skin cancer. It is more likely to invade nearby tissues and spread to other parts of the body than other skin cancer types. When melanoma starts in the skin, it is called **cutaneous melanoma**. Cutaneous melanomas are categorized into four main types: superficial spreading melanoma (the most common), nodular, lentigo maligna, and acral lentiginous melanomas. Melanoma may also occur in mucous membranes, the thin, moist layers of tissue that cover surfaces such as the lips. The most common skin cancer types are non-melanoma skin cancers - basal cell carcinoma and squamous cell carcinoma. Non-melanoma skin cancers rarely spread to other parts of the body.

Hereditary Genetics

Malignant melanoma represents only 5% of new skin cancers but accounts for most skin cancer-related deaths. Hereditary melanomas account for 5% to 12% of all melanoma cases. Furthermore, individuals with hereditary melanoma may have an increased risk of other cancers, including pancreatic cancer or central nervous system tumors. **Table 1** summarizes genetic syndromes (all autosomal dominant disorders) associated with increased melanoma risk.

Table 1. Summary of genetic syndromes associated with increased melanoma risk.

Syndrome	Gene	Melanoma	Clinical Hallmarks	Other Cancers
Hereditary Melanoma	CDK4	Cutaneous	Greater mole count and many dysplastic nevi	Nervous System
	CDKN2A	Cutaneous	Greater mole count and many dysplastic nevi	Pancreatic and Nervous System
	POT1	Cutaneous	Greater mole count and many dysplastic nevi	Gliomas
BAP1 cancer syndrome	BAP1	Cutaneous and Uveal	Melanocytic, pink or tan, dome-shaped nevi	Renal and Mesothelioma
Susceptibility to melanoma and renal cell carcinoma	MITF	Cutaneous	Greater nevus count and non-blue eye color	Renal
Hereditary breast and ovarian cancer syndrome	BRCA2	Cutaneous and uveal	No unique hallmarks associated	Breast and Ovarian
Li–Fraumeni syndrome	TP53	Cutaneous and uveal	No unique hallmarks associated	Breast, Bone and Soft Tissue, CNS, and Leukemia
PTEN hamartoma tumor syndromes	PTEN	Cutaneous	Trichilemmomas and multiple hamartomas	Breast, Colorectal, Thyroid, Kidney, and Endometrial

Individuals with pathogenic variants in CDKN2A, CDK4, POT1 are reported to have the greatest lifetime melanoma risk of up to 90% compared to the average population (approximately 2%). Individuals with pathogenic variants of BAP1 often have multiple melanocytic BAP1-mutated atypical intradermal tumors (MBAITs) and an increased lifetime melanoma risk of about 12%. Individuals with BRCA2, PTEN, or TP53 pathogenic variants have an elevated risk of developing melanoma of up to 6%. Furthermore, families with BRCA1/2 mutations may have an increased risk for ocular melanoma in BRCA2 carriers. Although associated with increased lifetime risks of developing melanoma, the precise risk has not yet been determined for individuals with pathogenic variants of RB1 and MITF.

Germline Testing Recommendations:

- Personal history of melanoma (especially multiple melanomas) and/or a personal or family history of related cancers (such as melanoma, pancreatic, mesothelioma, or renal cancer)
- Multiple relatives diagnosed with the same or related cancers (including melanoma, pancreatic, mesothelioma, or renal cancer) on the same side of the family and spanning multiple generations

Management

According to the National Comprehensive Cancer Network (NNCN), patients with pathogenic variants of these genes should consider yearly skin and eye exams. Exams may include imaging such as MRI, CT, or ultrasound. Additionally, these patients may consider individualized risk management, including lifestyle changes such as sun protection strategies and self-skin examination. More information can be found at the website for the Skin Cancer Foundation (www.skincancer.org)

Furthermore, patients with known high-risk, pathogenic CDKN2A variants are candidates for annual pancreatic cancer screening via endoscopic ultrasonography or magnetic resonance cholangiopancreatography. Individuals with BAP1 pathogenic variants should be screened at least annually for uveal melanoma and mesothelioma.

Tumor Genetics

BRAF Codon 600 Somatic Mutation Analysis

BRAF is a gene that encodes the protein kinase, B-raf. B-raf is involved in controlling cell growth, and it is mutated in many cancers. The most common BRAF gene mutation found in human cancers is at codon 600, which results in increased kinase activity. Approximately 80% - 90% of BRAF codon 600 mutations are V600E (valine to glutamic acid). This mutation has been frequently found in an aggressive form of skin cancer called melanoma. It has also been identified in cancers of the colon and rectum, ovary, and thyroid gland. BRAF mutations are usually found in tumors wild type for NRAS, KIT, and other driver mutations. BRAF V600E mutations are associated with increased sensitivity to B-raf inhibitors (e.g., vemurafenib, dabrafenib, and encorafenib) and MEK inhibitors (e.g., binimetinib, cobimetinib, and trametinib). Other activating BRAF mutations at codon 600 include V600K, V600R, V600D, and V600M. Therefore, it is clinically important to determine BRAF codon 600 mutations, particularly in melanoma and colorectal cancer patients, to determine treatment.

KRAS Codons 12, 13, and 61 Somatic Mutation Analysis

KRAS is a gene that encodes the GTPase protein, K-Ras. K-Ras is involved in cell proliferation and differentiation. The KRAS gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. Common KRAS gene mutations found in human cancers are at codons 12, 13, and 61. The presence of KRAS mutations in codon 12, 13, or 61 is associated with a high likelihood of resistance to therapies targeting EGFR (e.g., Cetuximab and Panitumumab). It may also be possible that these KRAS mutations lead to sensitivity to therapies that inhibit MEK1/2 (e.g., binimetinib, cobimetinib, and trametinib). Therefore, it is clinically important to determine KRAS mutations to provide effective treatment.

References

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