Genetic Counseling and Testing for Hereditary Melanoma: An Updated Guide for Dermatologists

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Abstract

Melanoma is a multifactorial disease with environmental exposure, phenotype, and in rare cases, cancer predisposition genes each contributing to an individual’s risk. Approximately 10% of melanomas occur in familial clusters, and germline mutations in CDKN2A account for 20-40% of families at high risk for this cancer. Dermatologists play a key role in identifying patients who may have an inherited risk for melanoma and in offering them appropriate genetic counseling and testing services. Identifying high-risk families permits patients and their at-risk relatives to benefit from tailored screening recommendations and risk reducing strategies. Incorporating risk assessment and appropriate pre- and post-test counseling into routine clinical practice can be challenging; therefore, partnerships with genetic counseling resources are necessary. Genetic counselors are trained to assess cancer risk, provide personalized risk assessment and management recommendations, and counsel patients regarding the ethical and psychosocial implications of genetic testing. This review will provide an updated guide for dermatologists regarding factors to consider in melanoma risk assessment including environmental exposure, phenotype, and genetic status. We will also discuss the process and potential outcomes of genetic testing for hereditary melanoma in high-risk families.

Keywords: CDKN2A; P16; Melanoma; Familial melanoma; Hereditary melanoma; Genetic counseling; Genetic testing

Introduction

Melanoma is the second and third most commonly diagnosed cancer between the ages of 20 and 29 years in women and men, respectively [1]. Approximately 10% of cutaneous malignant melanomas have been found to occur in familial clusters [2]. This may be due to a combination of factors such as sharing a similar pattern and degree of ultraviolet radiation (UV) exposure and phenotype. However, rare families within this population have a greatly increased risk for melanoma due to mutations in a high-risk cancer predisposition gene. Dermatologists are typically on the forefront of identifying those patients who are at an increased risk for melanoma and who candidates are for further genetic evaluation. They are also in a unique position to encourage patients to adopt behavioral changes in order to reduce their melanoma risk and can refer them to specialists to further discuss strategies for risk reduction and cancer prevention. In this manuscript, we will provide an updated review of the environmental, phenotype characteristics, and genetic factors that contribute to melanoma risk. We will also review the benefits of communicating this information effectively to high-risk patients and their families within the context of their reported medical and family history and available genetic test results.

Melanoma Risk Assessment

Melanoma is a multifactorial disease in which factors such as ultraviolet radiation, family history, genes that determine phenotype, and high and moderate risk genes have been shown to contribute to its risk of development. All of these factors should be taken into account in the risk assessment process and the magnitudes of several of these risk factors are illustrated in Table 1.

Ultraviolet Radiation Exposure

Ultraviolet (UV) radiation exposure is a significant melanoma risk factor. While its impact is still being studied, in the Caucasian population, a history of blistering sunburns has been found to be associated with a 2.0 fold increased risk (95% CI 1.7-2.4) relative to individuals with no history of sunburn [3]. Other studies have shown that cumulative average sun exposure since age 20 years (measured per 5,000 minimal erythematic dosages) increases the risk of melanoma by 1.52 fold (95% CI 1.3-1.8). This risk increased 1.15 fold (95% CI 1.3-1.8) when the initial sun exposure occurred at relatively younger ages, specifically between the ages of 5 and 12 years [4].

Indoor tanning beds are an especially intense source of UV radiation and in many studies their use has been implicated as a major factor increasing the risk of early-onset melanoma. The more frequent use of tanning beds and a younger age at first use have been shown to increase an individual’s lifetime risk of melanoma, often with an earlier onset. Use of a tanning bed for more than 10 sessions with first use under the age of 25 years was associated with a 2.13 fold increased risk (95% CI 1.13-4.03) for melanoma when compared to no history of tanning bed use [5]. Studies continue to suggest that UV radiation is a major environmental risk factor for melanoma with both the frequency and intensity of exposure and the age at first exposure increasing the overall lifetime risk of melanoma.

Phenotype

Melanoma risk can be further modified by an individual’s physical characteristics including: skin type, number and type of nevi, and hair color. A strategy proposed by Thomas B Fitzpatrick in 1988 classified skin type based on individuals’ skin reaction to an initial sun exposure. These classifications have been and are still frequently used both clinically and often in research studies as a standard means to categorize an individual’s skin type from type I (always burn, never tan) to type IV (never burn, tan easily) [6]. Using this classification, studies have shown a 2.1 fold (95% CI 1.7-2.6) increased risk for melanoma associated with skin type I relative to individuals with skin type IV [7].

The number and type of nevi have also been shown to impact...
melanoma risk. The presence of more than 100 nevi counted on the whole body likely increases the risk of cutaneous malignant melanoma 6.89 fold (95% CI 4.63-10.25) when compared to the presence of fewer nevi, defined as less than 15 [8]. Of note, while the nevi counts in the studies analyzed in Gandini et al’s review were obtained through various means including self-report, the examiner counting the nevi on subjects’ arms, and total body skin examinations by a trained clinician, these were all considered statistically comparable. Finally, the anatomical location of typical nevi seems to play a role in melanoma risk as well. The risk of melanoma in individuals with approximately 11-15 typical nevi on their arms was shown to be 4.82 times greater (95% CI 3.05-7.62) when compared to individuals with no nevi on their arms [8].

While numerous nevi may be considered a significant melanoma risk factor, studies have also suggested that a smaller number of clinically atypical nevi may play an independent role in predicting melanoma risk. According to the International Agency for Research on Cancer (IARC), atypical nevi are defined as having at least three of the following: (1) poorly defined border, (2) equal to or greater than 5mm in size, (3) multiple colors, (4) uneven edges, and (5) presence of erythema. Individuals with just one atypical nevus were found to have almost a 2 fold increased melanoma risk (RR=1.60; 95% CI 1.38-1.85) while this increased to nearly tenfold (RR=10.49, 95% CI: 5.05, 21.76) when five atypical nevi were identified [8].

Finally, red hair is associated with greater than a 3-fold increased risk for melanoma compared to individuals with brown or black hair [7]. The red hair phenotype is related to variants in the melanosin receptor 1 (MCIR) gene, which is often also seen in association with a higher number of freckles, fair skin, and poor tanning ability [9]. One of the central functions of MCIR is to regulate the relative concentration of skin pigmentation and variants in MCIR have been shown to impact the function of this receptor. Not all variants in the MCIR gene that increase skin cancer risk are associated with red hair color phenotype, emphasizing that there are genetic changes that increase melanoma risk independent of the pigmentation effect. On the other hand, while genome-wide association studies (GWASs) performed in 2008 and 2009 helped to confirm previously reported candidate genes associated with melanoma predisposition, more recent melanoma GWASs with dense single-nucleotide polymorphism coverage have identified additional genes in other pathways associated with phenotype that may impact melanoma risk [10]. Therefore, while not all genetic changes that increase melanoma risk are associated with phenotype, the GWAS studies have shown the important role of pigment in assessing this risk.

**Family History**

While environment and phenotype are significant factors in determining melanoma risk, rare families are at a greatly increased risk for melanoma due to an inherited mutation in a cancer predisposition gene [4]. While having one first degree relative with melanoma has been found to be associated with between a 1.7- and 3.1-fold relative risk for melanoma, the risk in families with multiple cases of melanoma may be up to 30-70 times greater than individuals with no family history [7,11,12].

Melanoma risk is known to be increased, along with other cancer risks, in hereditary cancer syndromes caused by mutations in the *BR1* (hereditary retinoblastoma) and *BRCa2* (hereditary breast/ovarian cancer) [13,14]. However, these genes do not generally account for a significant portion of familial melanoma cases and the genetic basis of melanoma for many high-risk families remains unknown. The cyclin-dependent kinase inhibitor (*CDKN2A*) gene located on 9p21 is the most significant melanoma predisposition gene identified to date. Mutations in *CDKN2A* are identified in 20-40% of families with a hereditary pattern of melanoma and in less than 1% of all melanoma cases overall [15,16]. Due to an alternate reading frame in exon 1, *CDKN2A* encodes two proteins, p16 and p14ARF, and mutations affecting either or both of these proteins are thought to cause an increased melanoma risk. To a lesser extent, mutations in the oncogene, *CDK4*, and the gene encoding BRCa1 associated protein-1 (*BAP1*), have also been reported in high-risk families and clinical genetic testing is currently available for these genes. (Figure 1) Mutations in *BAP1* in particular have been found to segregate with cases of rare types of melanoma, such as uveal melanoma, and variants in this gene have also been associated with other cancers such as renal clear cell carcinoma and malignant mesothelioma. [17-19]. However, as *CDKN2A/p16* is still considered to be the most frequent genetic cause of melanoma risk in these high-risk families we will focus on discussing the role of genetic testing for *CDKN2A/p16* in this manuscript.

Mutations in the *CDKN2A/p16* gene are inherited in an autosomal dominant manner, meaning that a mutation in one copy of the *CDKN2A/p16* gene is enough to confer an increased risk for melanoma. An individual with a deleterious mutation likely inherited it from either his/her biological mother or father, as spontaneous mutations are rare.

**Relative risks for developing melanoma**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Approximate/Estimated Relative Risk</th>
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<tbody>
<tr>
<td>5 atypical nevi</td>
<td>10.5 (95% CI 5.1-21.8) Relative to those with no atypical nevi</td>
</tr>
<tr>
<td>Previous primary cutaneous melanoma</td>
<td>8.6 (95% CI 8.3-8.9) Relative to those without prior melanoma**</td>
</tr>
<tr>
<td>100 or more nevi</td>
<td>6.9 (5% CI 4.6-10.3) Relative to those with &lt; 15 nevi</td>
</tr>
<tr>
<td>Red Hair</td>
<td>3.6 (95% CI 2.6-5.4) Relative to those with dark hair†</td>
</tr>
<tr>
<td>Skin Type I (fair skin)</td>
<td>2.1 (95% CI 1.7-2.6) Relative to those with type IV or darker skin*</td>
</tr>
<tr>
<td>High density freckling</td>
<td>2.1 (95% CI 1.8-2.5) Relative to those with few freckles*</td>
</tr>
<tr>
<td>History of blistering sunburn</td>
<td>2.0 (95% CI 1.7-2.4) Relative to those with no history of sunburn**</td>
</tr>
<tr>
<td>Blue eyes</td>
<td>1.5 (95% CI 1.3-1.7) Relative to those with dark eyes*</td>
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</table>

**Table 1: Risk factors for melanoma [3,7,8,43,44].**
Each offspring of a parent with a CDKN2A/p16 mutation will have a 50% chance of inheriting the familial mutation.

**CDKN2A/p16 Cancer Risk**

In the US, the estimated lifetime melanoma risk associated with a CDKN2A/p16 mutation in families with multiple cases of melanoma is 76% [20]. However, population based studies have found a lower, but still significant, risk of 28% by age 80 [21]. The penetrance of CDKN2A/p16 mutations is related to the population incidence of melanoma and co-inheritance of phenotypic factors. CDKN2A/p16 penetrance estimates are lower in areas with a low melanoma incidence (i.e. 58% in England) and higher in high melanoma incidence areas (i.e. 91% in Australia) [20]. As previously discussed, MC1R has been found to be another modifier of melanoma risk. Box et al. suggest that when stratified by MC1R status, the risk for melanoma among individuals with only a CDKN2A/p16 mutation had a 50% risk for melanoma, while those who carried both a CDKN2A/p16 and MC1R mutation had an 84% risk [22]. Therefore, family history, geography, and phenotype should be taken into consideration when counseling a patient about the risk conferred by a CDKN2A/p16 mutation.

In addition to melanoma risk, CDKN2A/p16 mutations also confer an increased risk for pancreatic cancer. The Melanoma Genetics Consortium (GenoMEL) found that 28% of CDKN2A/p16 families included a relative with pancreatic cancer [15] though the likelihood of developing pancreatic cancer seems to vary by mutation. The association with pancreatic cancer has been studied most extensively in carriers of the p16-Leiden mutation which is a 19 base pair deletion and founder mutation in the Dutch population. Carriers of this specific mutation have been found to have between 17% to 25% risk for pancreatic cancer [23, 24]. Estimates from studies using population based identification of subjects have shown a 7.4 relative-risk (95% CI 2.3 to 18.7) for pancreatic cancers in families with other CDKN2A/p16 mutations [25].

**Genetic Counseling and Testing**

The first step in the process of evaluating a patient for hereditary melanoma is to obtain a family history. Ideally the family history would include three generations, all cancer diagnoses and their ages of onset, phenotypic features of relatives, and the family's ethnic background and region of residence. Family history is the most important tool for identifying high risk families; however, it is important to remember that reported family history alone may not be sufficient for risk assessment, as one study found that up to 40% of reported melanomas may be inaccurate. Confirmation with medical records should be obtained whenever possible [26].

The next step is determining whether the family history meets criteria for genetic counseling and potential testing. The threshold for when genetic testing should be considered varies based on the incidence of melanoma in the population. For example, in moderate to high melanoma incidence areas, such as the US, Northern Europe, or Australia, three or more cases of melanoma and/or pancreatic cancer should be present in the family for consideration of genetic testing. In geographical areas or populations with a lower incidence, only two cases of melanoma (or a combination of melanoma and pancreatic cancer) are required to suggest a hereditary pattern [27]. Table 2 lists more detailed criteria for consideration of genetic testing classified by low and moderate/high incidence area.

When CDKN2A/p16 genetic testing is being considered, pre- and post-test counseling is recommended. The goal of counseling is to ensure that patients can make an informed decision about whether to have genetic testing, that they will understand the implications of the results of genetic testing for them and their family members, and to facilitate psychological adjustment to learning their genetic status. Genetic testing should ideally be performed first in a family member who has had melanoma. This increases the likelihood of detecting a mutation if one is present in the family. Genetic testing is generally only informative for unaffected relatives once a mutation is present in the family. As part of the process of obtaining informed consent, patients should be informed of the purpose of the test (i.e. to plan their management, to determine risks for family members) and the possible outcomes of the testing [28].

There are three possible results that may come from genetic testing. First, the result may be positive, meaning a mutation associated with an increased cancer risk is identified in the CDKN2A/p16 gene. This result would confirm the cause of the elevated melanoma risk in the family and also alert the family to their increased risk for pancreatic cancer. At-risk relatives should be notified of the genetic test result and informed that they could be tested for this specific mutation in order to determine whether or not they are at increased risk. At-risk relatives would include all first-degree relatives including offspring and siblings of the proband or individual identified with the genetic mutation. Other relatives of the proband may also be at risk depending on which side of the family the mutation was inherited. This may be determined based on family history and can be confirmed by offering genetic testing to the parents of the proband. The second possible outcome from genetic testing is a negative result, which means that no mutation is identified. This result does not rule out an inherited risk for melanoma in the family. As was noted earlier, mutations in CDKN2A/p16 account for less than half of high-risk families. Other, as of yet, undiscovered high risk genes and/or clustering of other factors such as modifier genes, a melanoma-prone phenotype, and unprotected UV exposure may still be causing an increased risk in these families. Therefore, careful melanoma screening and minimization of UV exposure should still be recommended in these families. However, hereditary melanoma, in the absence of a CDKN2A/p16 mutation, has not been shown to be significantly associated with an increased risk for pancreatic cancer, and pancreatic cancer screening would not be recommended in these families. Of note, if no changes are identified in the CDKN2A/p16 gene in a proband with a family history highly suggestive of hereditary melanoma, sequencing of CDKN2A/p16 may

<table>
<thead>
<tr>
<th>Low Melanoma Incidence Area/Population</th>
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<tbody>
<tr>
<td>• An individual with two primary melanomas</td>
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<tr>
<td>• Two cases of melanoma among first or second degree relatives on the same side of the family</td>
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<tr>
<td>• One case of melanoma and one case of pancreatic cancer in first or second degree relatives on the same side of the family</td>
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<tr>
<th>Moderate/High Melanoma Incidence Area/Population</th>
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<tr>
<td>• An individual with three primary melanomas</td>
</tr>
<tr>
<td>• Three cases of melanoma among first or second degree relatives on the same side of the family</td>
</tr>
<tr>
<td>• One case of melanoma and two cases of melanoma and/or pancreatic cancer among first or second degree relatives on the same side of the family</td>
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</table>

Table 2: Criteria for considering CDKN2A/p16 gene testing [27].
still be warranted for other relatives who have a personal history of pancreatic cancer or early-onset/multiple diagnoses of melanoma. This is because of the possibility that the proband's diagnosis of melanoma was sporadic in an otherwise familial setting and thus making him/her a phenocopy. In this case, it may be helpful to offer genetic testing to additional family members with a personal history of melanoma or pancreatic cancer as they may still carry a mutation in the CDKN2A/p16 gene and thus have a greatly increased risk for developing cancer. The final possible outcome from genetic testing is a variant of uncertain significance. This refers to a variation in the genetic code that has been identified that has an unknown effect as of yet on gene function. Genetic variation is common and not all genetic alterations result in disease. When a variant of uncertain significance is identified, there may be research opportunities available for the patient and/or his/her family to pursue to try and determine the effect of the variant. However, in these rare cases, management recommendations should be made based on the available family history and testing of the variant should not be routinely offered or used to predict melanoma risk in unaffected relatives.

Once a mutation in the family has been identified, genetic testing for subsequent relatives, including those who are unaffected, is generally a much cheaper and more straightforward process. If there is a known CDKN2A/p16 mutation in the family, first degree relatives should be offered the option of site-specific testing. Genetic counseling should also be available to assist in discussing the benefits and limitations of testing and to further personalize the medical management recommendations made. For unaffected individuals in the family, genetic testing would be site-specific and would only look for the mutation previously identified in the family. The possible results would be positive or negative. If an unaffected family member tests positive for the familial CDKN2A/p16 mutation, their medical management recommendations would be comparable to those listed above and again reiterated in Table 4. However, if a CDKN2A/p16 gene mutation is identified as being associated with the melanoma and pancreatic cancers seen in the family, unaffected family member who test negative for the familial mutation would still be considered as having a moderately increased risk (2 to 3 fold) of developing melanoma compared to the general population [12,29]. This is based on their shared phenotypic characteristics and the common environmental, lifestyle, and behavior traits amongst family members. However, we would not expect them to be at increased risk for pancreatic cancer based on their negative genetic test results.

To date, utilization of genetic testing for hereditary melanoma has lagged behind other hereditary syndromes such as hereditary breast/ovarian cancer syndrome or Lynch syndrome. The reason for the limited use of genetic testing for hereditary melanoma is unknown, but concerns have centered on the supposition that since everyone could benefit from minimizing UV exposure regardless of their family history or genetic status, genetic testing to identify high risk individuals would not sufficiently change management recommendations. Another concern is that people who test negative for a genetic mutation previously identified in their family may be falsely reassured and abandon screening or protective practices. However, the currently available data do not support these concerns. A research study performed by Aspinwall, et al. in 2008 to assess the clinical utility of CDKN2A/p16 genetic testing showed how test result reporting led to significant positive changes in the intention and magnitude of intention to screen between baseline, immediately following results disclosure, and one month post-reporting amongst high risk patients. Furthermore, this research study concluded that test reporting did not decrease the level of adherence for those who tested negative for the CDKN2A/p16 mutation previously identified in their family. The participants in this study had a family history of melanoma, and these results suggest a positive impact of genetic test reporting and counseling on patient behavior beyond what was motivated based on family history and independent of the test result itself [30]. Additional analysis of this sample population also found that the degree of photoprotection increased among both those who tested positive and negative for a CDKN2A/p16 mutation. Overall, 33% of the participants in that study indicated using one or more new photoprotective behavior following disclosure of test results and counseling [31].

Parents with a CDKN2A/p16 mutation have reported a keen interest in genetic testing for their minor children because of a strong belief that knowledge of one's genetic status will allow children and their parents to make better decisions about screening and minimizing UV exposure early in life [32]. Finally, a study published by Kaspersian et al. in 2008 did not identify any clinically significant levels of generalized distress or anxiety among patients receiving CDKN2A/p16 test results; however, several individuals indicated a level of concern about the implications of their results for their family members [33].

Overall, research has indicated that genetic testing can play an important role in identifying high risk families and motivating adherence to screening and protective practices. However, these studies were done in settings in which participants were provided with thorough counseling and education. Providing comprehensive genetic counseling may be challenging in a busy clinical practice. Therefore, partnering with local genetic counseling resources may help ensure that this service is available for all at-risk patients. Resources for finding genetic counseling and testing services nationwide are available in Table 3.

### Management Recommendations

#### Melanoma risk management

The clinical management recommendations for individuals with a CDKN2A/p16 mutation continue to evolve due to developments in the medical field. The two major screening strategies currently used to

<table>
<thead>
<tr>
<th>Name of Resource</th>
<th>Description of Services</th>
<th>Web-site</th>
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<tbody>
<tr>
<td>American Board of Genetic Counseling (ABGC)</td>
<td>Locate genetic counselors nationwide that are certified by the ABGC, the credentialing organization for the genetic counseling profession.</td>
<td><a href="http://www.abgc.net">http://www.abgc.net</a></td>
</tr>
<tr>
<td>National Cancer Institute – Cancer Genetics Service Directory</td>
<td>Locate professionals who provide cancer genetics services, including cancer risk assessment, genetic counseling, genetic testing, etc.)</td>
<td><a href="http://www.cancer.gov/cancertopics/genetics/directory">http://www.cancer.gov/cancertopics/genetics/directory</a></td>
</tr>
<tr>
<td>GenoMEL</td>
<td>An international melanoma research consortium that provides information about melanoma genetic research and tutorials on genetic counseling and testing.</td>
<td><a href="http://www.genomel.org">http://www.genomel.org</a></td>
</tr>
</tbody>
</table>

Table 3: Genetic counseling and testing resources.
Annual total body skin examination with a dermatologist

This examination should include baseline and annual follow-up photographs of moles, if needed, and biopsy and/or removal of suspicious moles

Mutation carriers should be taught how to conduct these exams

Pancreatic cancer

No standard guidelines

Imaging of the pancreas with endoscopic ultrasound and/or MRI

Other recommendations

First-degree relatives should be referred for genetic counseling and testing.

The following are current screening recommendations for CDKN2A/p16 mutation carriers:

<table>
<thead>
<tr>
<th>Table 4: Management recommendations for CDKN2A/p16 mutation carriers.</th>
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<tbody>
<tr>
<td><strong>Melanoma</strong></td>
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<tr>
<td>Annual total body skin examination with a dermatologist</td>
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<tr>
<td>✓ This examination should include baseline and annual follow-up photographs of moles, if needed, and biopsy and/or removal of suspicious moles</td>
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<tr>
<td>Monthly self-skin examination</td>
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<tr>
<td>✓ Mutation carriers should be taught how to conduct these exams</td>
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<tr>
<td>✓ Pancreatic cancer</td>
</tr>
<tr>
<td>No standard guidelines</td>
</tr>
<tr>
<td>✓ Mutation carriers should consider screening beginning at age 50 or ten years prior to the youngest known diagnosis of pancreatic cancer in their family</td>
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<tr>
<td>✓ Current recommended screening protocol includes:</td>
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<tr>
<td>Imaging of the pancreas with endoscopic ultrasound and/or MRI</td>
</tr>
<tr>
<td>Other recommendations</td>
</tr>
<tr>
<td>✓ First-degree relatives should be referred for genetic counseling and testing.</td>
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</table>

Melanoma

- Annual total body skin examination with a dermatologist
- This examination should include baseline and annual follow-up photographs of moles, if needed, and biopsy and/or removal of suspicious moles
- Monthly self-skin examination
- Mutation carriers should be taught how to conduct these exams
- Pancreatic cancer
- No standard guidelines
- Mutation carriers should consider screening beginning at age 50 or ten years prior to the youngest known diagnosis of pancreatic cancer in their family
- Current recommended screening protocol includes:
  - Imaging of the pancreas with endoscopic ultrasound and/or MRI
  - Other recommendations
    - First-degree relatives should be referred for genetic counseling and testing.

The benefit of identifying a CDKN2A/p16 mutation in a family is that it allows genetic testing of other, unaffected, family members to determine their lifetime cancer risks. If an individual tests negative for the familial mutation, he/she still has a residual risk for melanoma that is 2-3 fold increased above the general population [12,28]. While moderately increased, it is important to note that this risk is not as high as if they tested positive or if genetic testing had not identified a mutation in their family. Determining appropriate screening recommendations for these individuals may be more difficult as it includes personal risk factors such as phenotype, use of tanning beds, and other behavior and lifestyle choices.

Pancreatic Cancer Risk Management

Consideration of pancreatic cancer screening has been suggested for those who test positive for a CDKN2A/p16 mutation due to the high risk for pancreatic cancer in this population [38]. However, data on the overall impact of pancreatic cancer screening in high risk individuals are still limited. Several recent studies of pancreatic cancer screening have included CDKN2A/p16 mutation carriers in their analyses to further understand this impact. Poley et al. [39] evaluated the findings from endoscopic ultrasound for 44 individuals with genetic mutations associated with pancreatic cancer risk, including 13 CDKN2A/p16 mutation carriers. Ten participants had findings in their baseline exam, three with masses and seven with side-branch intraductal papillary mucinous neoplasia (IPMN). The three patients with masses, two of whom had CDKN2A/p16 mutations, underwent resection and were found to have pancreatic adenocarcinoma. Two cases were N1 and one case was N0 suggesting that screening may have led to earlier detection than diagnosis based on symptoms alone [39]. A 2011 study by Vassen et al. [40] evaluated the efficacy of magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) based on screening 79 individuals with a common Dutch founder mutation in the CDKN2A/p16 gene. During four years of follow-up, 7 individuals were diagnosed with cancer. Three cases were diagnosed during their baseline exam and the others were diagnosed after prior negative scans. All patients had resectable lesions, but four had died within two years of their diagnosis. Additional lesions of uncertain clinical significance were identified in 9 other participants [40]. The International Cancer of the Pancreas Screening Consortium has recommended pancreatic cancer screening with endoscopic ultrasound and/or MRI/MRCP on an annual basis beginning at age 50 or 10 years prior to the earliest diagnosis of pancreatic cancer in the family [41]. However, since pancreatic cancer occurs in only a minority of CDKN2A/p16 families, they suggested that pancreatic cancer screening may be most appropriate for those families where a pancreatic cancer has occurred. A summary of the most updated medical management recommendations for CDKN2A/p16 mutation carriers, including recommendations for pancreatic cancer screening, can be seen in Table 4.

It is important to note that some lifestyle factors have been associated with an increased risk for developing pancreatic cancer. These include cigarette smoking, heavy consumption of alcohol, and increased body mass index [42]. Avoidance of the above lifestyle factors has not been proven to prevent pancreatic cancer. However, it is important to address these factors with patients who have a deleterious mutation in the CDKN2A/p16 gene as these factors may increase the risk of developing pancreatic cancer even further.

Conclusion

Dermatologists play a leading role in identifying those amongst
their patients who have a high-risk for melanoma based on their personal and family history, lifestyle, phenotype, and genotype. In this review we outlined the information currently available regarding high-risk and modifier genes associated with hereditary melanoma, how to identify an individual or family at high risk for melanoma, and those eligible for genetic counseling and testing. We have also described how to efficiently incorporate these medical management recommendations into clinical practice. Furthermore, extensive counseling and test reporting have been shown to be of greater benefit to the patient, especially with regards to increasing their intentions to adhere to the recommended behavioral and screening guidelines. Collaboration with a genetic counseling resource is an especially effective method for providing counseling, coordination of genetic testing, and consultations to discuss screening and prevention recommendations based on genetic test results and available family history. Genetic counselors can be especially helpful in obtaining family history, coordinating genetic testing for at-risk family members, and tailoring test results to each patient’s own history. The use of genetic counselors in this context represents an increasingly cost-beneficial strategy to extend physician influence and encourage prevention behaviors that have the potential to increase quality of life while reducing health care costs.

Information gained from genetic testing may have a greater impact on patients’ behavior than counseling based on family history alone. While test reporting and extensive counseling have been shown to increase the level of compliance to recommendations, continual reinforcement is needed, likely from dermatologists, to maintain healthy photoprotective behaviors over an extended period of time. It is also important to offer additional specialized support to patients who are identified as being at increased risk for hereditary melanoma. Genetic testing, informed consent, and appropriate results disclosure and follow-up counseling are critical due to the high probability of developing melanoma with a deleterious CDKN2A/p16 mutation, the poor prognosis of late stage disease, and the positive impact of these interventions on maintaining healthy photoprotective behaviors.

Conflict of Interest Statement

The authors declare the following: SAL participates on an MSAB for Myriad Genetics. MC and WK declare no conflicts of interest.

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