

Counseling and DNA Testing for Individuals Perceived to Be Genetically Predisposed to Melanoma: A Consensus Statement of the Melanoma Genetics Consortium

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THIS DOCUMENT represents the consensus view of the Melanoma Genetics Consortium on appropriate responses to requests for genetic counseling of persons perceived to be at high risk of cutaneous melanoma. The major determinant of interest in genetic testing is a positive family history of melanoma with multiple affected relatives, as members of melanoma-prone families are at substantially increased risk of melanoma.¹ This document is therefore concerned primarily with advice given to high-risk families and with recommended programs of surveillance and primary prevention for them. These same surveillance and prevention programs may, however, be justified in others deemed to be at high risk of developing melanoma for any of the other known risk factors listed in Table 1. The best currently available estimates of risk have been used.

MELANOMA SUSCEPTIBILITY GENES

The proportion of all cutaneous melanomas that is attributable to the inheritance of autosomal dominantly inherited mutations in melanoma susceptibility genes is unknown, but it is estimated by the Consortium to be less than 1% to 2%. This is the approximate proportion of melanoma cases involving multiple relatives also affected by melanoma. More frequently, a person newly diagnosed with melanoma will report one other relative with melanoma (Table 1). Such families may or may not have the same level of risk as families with many members with melanoma, and careful verification of their family history is a cornerstone of their risk assessment. Families in which these genes are inherited have members who may be distinguished by the presence of some, but not necessarily all, of the features listed in Table 2. Of particular interest is that in certain, but not all, of these families, there seems to be an association with the presence of multiple unusual or atypical moles.

Constitutional mutations in two genes, *CDKN2A* and *CDK4*, have so far been found to confer risk in melanoma families, although it is highly likely that there are others yet to be identified.

The *CDKN2A* locus on human chromosome 9p21 encodes two distinct proteins translated, in alternate reading frames (ARFs), from alternatively spliced transcripts. The alpha transcript, comprising exons 1 α , 2, and 3, encodes the p16INK4A cyclin-dependent kinase inhibitor, and the smaller beta transcript (exons 1 β , 2, and 3) specifies the alternative

product, p14ARF. These *CDKN2A* encoded proteins play a central role in maintaining cell-cycle control; p16INK4A regulates G1-phase exit by inhibiting the *CDK4*-mediated phosphorylation of the retinoblastoma protein. p14ARF acts via the p53 pathway to induce cell-cycle arrest or apoptosis in response to hyperproliferative oncogenic signals.^{10,11} Consequently, mice that lack p16INK4A/p19ARF (the mouse homolog of p14ARF) or p19ARF alone are highly susceptible to tumorigenesis,¹² and the *CDKN2A* locus is frequently deleted in human tumors and particularly in melanomas, gliomas, and mesotheliomas.

- Approximately 20% to 40% of families with three or more affected first-degree relatives show inheritance of mutations in the *CDKN2A* gene.¹³
- Two families in the United States and one in France have mutations in the *CDK4* gene on chromosome 12q which inhibit binding of its inhibitor, p16INK4A.^{14,15}
- The genetic basis for the remaining 60% to 80% of families, in which highly penetrant genes may be operating, is the subject of active research by the Melanoma Genetics Consortium. New families are keenly sought and may be reported to members of the Melanoma Genetics Consortium in the country of greatest convenience for referring clinicians. The Appendix gives a full list of current Consortium members.
- Mutations in the *CDKN2A* gene occur throughout the first two of the three exons,¹⁶ and a mutation in the 5'-untranslated region has also been described.¹⁷
- Because current information on each mutation is limited and confined to data from large, specifically ascertained families, the confidence limits on current

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Table 1. Risk Factors for the Development of Cutaneous Melanoma

Factor	Approximate Relative Risk	Reference
Member of melanoma-prone family*	Up to 35-70	2
Previous primary melanoma	8.5	3
Family history of melanoma†	2-3	4
Skin type I	1.4	5
Freckling	2-3	5, 6
Blue eyes	1.6	5, 6
Red hair	2.4-4	5, 6
History of blistering sunburn	2-3	5, 6
Multiple moles and atypical moles	2-12	7, 8, 9

*Multiple affected relatives on the same side of the family.

†One or more affected first-degree relatives.

estimates of penetrance of mutations in the *CDKN2A* gene are extremely wide. Assessment of penetrance is also the subject of intense interest for the Consortium.

- This penetrance seems to be strongly influenced by birth cohort,¹⁸ levels of sun exposure,^{19,20} and possibly by modifier genes, which, in certain families, may also be responsible for the presence of multiple moles.²⁰

WHO IS AT HIGH RISK BECAUSE OF GENETIC SUSCEPTIBILITY?

Characteristics of familial melanoma among high-risk families include frequent multiple primary melanomas, early age of onset of first melanoma, and frequently the presence of atypical or dysplastic nevi (moles) (Table 2). Neither these nor any other characteristics are good clinical predictors of the likelihood of carrying a mutation in a melanoma susceptibility gene. The best predictor at present is having

melanoma with a strong family history of melanoma. Even among these high-risk families, less than half will have *CDKN2A* mutations (Table 2).

Among patients with multiple primary melanomas without regard to family history, a small percentage may be found to have mutations in *CDKN2A* (Table 2). Genetic testing for mutations among individuals with multiple primary melanomas alone is still a research question; it is not recommended as part of routine care at this time. In a similar manner, early age of onset of melanoma is common in high-risk families, but in a clinical setting, genetic testing for *CDKN2A* mutations is currently a research tool only.

Atypical or dysplastic nevi are major risk factors for melanoma, both in high-risk families and in the general population.^{9,21} The relationship between these nevi and melanoma susceptibility genes is unclear at present. Although early on, dysplastic nevi and melanoma were proposed to be pleiotropic effects of a single gene,²² more recent data suggest that these nevi are independent risk factors for melanoma.²⁰

In addition to families in which the predominant cancer is melanoma, there are other rare families in which melanoma is part of the constellation of observed cancers. Cutaneous melanoma is among the most common second cancers in individuals with heritable retinoblastoma.²³ Cutaneous melanoma occasionally occurs in families with Li-Fraumeni syndrome, some of which have germline mutations in *TP53*.²⁴ Cutaneous melanoma is also increased in two autosomal recessive conditions, xeroderma pigmentosa^{25,26} and Werner's syndrome (adult progeria).^{27,28}

Table 2. Features Associated With Genetic Susceptibility to Melanoma

Feature	Comment
Multiple cases of cutaneous melanoma on the same side of the family	Mutations in the <i>CDKN2A</i> gene have been found in 20% to 40% of families with three or more affected members, but in less than 5% of two-member families. ¹³
Multiple primary cutaneous melanomas in the same individual(s)	Mutations in the <i>CDKN2A</i> gene have been found in 15% of patients with multiple primary melanoma lacking a family history ²⁹ and in 9% of patients for whom the family history is negative to the second degree (B. Bressac-de Paillerets, personal communication, November 1998)
Earlier age of onset of cutaneous melanoma	In hereditary melanoma kindreds showing an autosomal dominant pattern of inheritance, the median age of onset is considerably earlier than in a matching general population. ³⁰
Multiple nevi	The presence of melanocytic nevi is often distributed over both sun-exposed and non-exposed skin surfaces of melanoma patients. The nevi may be just unusually numerous (eg, > 100 nevi > 2 mm diameter), or they may be of unusual appearance (called atypical). Atypical nevi may be distinguished by their asymmetry, border (indistinct irregular margins), colour (presence of unevenness of pigmentation, red-brown color), and diameter \geq 5 mm. Multiple nevi of atypical appearance are called dysplastic nevi, the atypical mole syndrome, or familial atypical multiple mole-melanoma syndrome. Only one third of Australian hereditary melanoma families display this phenotype, ³¹ but the majority of northern hemisphere families do so.
Other cancers	There is no clear association with other cancers, although certain families with mutations in the <i>CDKN2A</i> gene show an association with pancreatic cancer, ^{1,32} and certain other families show an association with ocular melanoma.

WHO SHOULD BE OFFERED COUNSELING AND POSSIBLE GENETIC TESTING FOR SUSCEPTIBILITY TO CUTANEOUS MELANOMA?

There is a demand for gene testing from some families with an inherited pattern of melanoma and concern on the part of clinicians about the role of that testing. The demand for gene testing from families is frequently based on an unrealistic expectation of its definitiveness, sensitivity, and specificity. Given the current paucity of knowledge about the penetrance of *CDKN2A* mutations, the failure as yet to identify mutations in over 60% of hereditary melanoma kindreds, and the limited data on the efficacy of prevention and surveillance strategies,²¹ the most prudent clinical course is to enroll all members of high-risk kindreds in the same common-sense programs of surveillance and prevention, irrespective of their DNA status. The Melanoma Genetics Consortium recommends, therefore, that DNA testing for mutations in known melanoma susceptibility genes should only rarely be performed outside of defined research programs. With this general proviso, two distinct clinical situations need further consideration: families in which a *CDKN2A* mutation has been identified in a proband as part of a research study and families for which no prior testing of affected individuals has been conducted.

Families in Which a CDKN2A Mutation Has Been Identified in a Proband as Part of a Research Study

Individuals who participate in genetic research protocols frequently consent on the basis that relevant genetic information will be made available to them after appropriate education and genetic counseling, if they choose to receive the information. When a laboratory research program detects a potentially relevant mutation in such a family, participants in the study should be informed that a preliminary, but not definite, laboratory finding has been made that might have potential significance for family members. Participants should be offered the opportunity of genetic testing if they want it after appropriate education and counseling by qualified health care providers. Individuals who choose to undergo genetic testing should have a second independent diagnostic (as distinct from research) DNA test performed in an accredited genetic testing laboratory. This enforces a strict separation between research and diagnostic testing and ensures that there is no confusion between the widely different ethical, medicolegal, consent, counseling, and accreditation issues that pertain to each.

Some *CDKN2A* mutations have been identified in families around the world and have been shown to co-segregate with tumors in the family. Moreover, for a proportion, in vitro functional tests have shown evidence that the mutation is likely to be causal, as the mutant p16INK4A proteins were

impaired in their ability to inhibit the catalytic activity of the target cyclin D1/CDK4 and cyclin D1/CDK6 complexes.³³ It is reasonable to offer genetic counseling and education about melanoma prevention strategies to such families. Even for these families, there is little information about penetrance. In other families, novel putative mutations have been identified for which no functional data are available. Some of these mutations are likely to be population polymorphisms of no functional significance. The Consortium's view is that genetic counseling about these mutations is currently premature.

The pretest education and counseling should include information about the following:

- current uncertainties about the penetrance and genotype/phenotype correlations of *CDKN2A* mutation;
- the lack of proved efficacy of prevention and surveillance strategies based on DNA testing, even for mutation carriers;
- the fact that a negative test result at best returns risk to that of the general population, which in certain localities may be as high as one in 25 people. Prevention and surveillance strategies must, therefore, continue in this group. Within the families identified so far, in which a *CDKN2A* mutation has been identified, there is a lack of correlation between the presence of the atypical or dysplastic moles and gene carrier status,^{20,32,34} which has led to the suggestion that within these families, other genes may induce moles and may increase risk of melanoma. Recent data suggest that atypical or dysplastic moles confer a risk of melanoma in family members independent of *CDKN2A* mutation status²⁰;
- and the potential benefits and risks of positive and negative results of genetic testing (Table 3).

Table 3. Some Potential Benefits and Risks Associated With Positive or Negative Test Results for Mutations in Melanoma Susceptibility Genes

Test Result	Potential Benefits	Potential Risks
Positive (mutation found)	Particular focus on and motivation for prevention, surveillance Lowered threshold for biopsy of suspicious lesions Earlier detection of primary melanoma	Discrimination in insurance, employment Disruption of family relationships Over-biopsying
Negative (mutation ruled out in known mutation-carrying family)	Reduction in anxiety	Survivor guilt Disruption of family relationships "False security," abandonment of prevention and surveillance

When a mutation in *CDKN2A* has been found in affected members of a family, the sensitivity of genetic testing is not an issue, because results of a simple allele-specific oligonucleotide test, specific for the mutation already identified in the family, will be positive in all mutation carriers. However, the penetrance of such mutations remains so uncertain as to make accurate risk assessment extremely difficult for the genetic counselor. Not all mutations have been demonstrated to cause a functional deficit, and confusion with polymorphisms may potentially occur. Furthermore, melanomas have occurred in non-gene carriers in *CDKN2A* mutation-carrying kindreds,³² and some gene carriers living to older ages have not developed melanoma.³⁵ This further highlights the importance of recommending surveillance and prevention for all members of these families, irrespective of their DNA status, especially in countries such as Australia that have high population rates for the tumor.

An advantage of testing for certain individuals may be a subjective, psychologic one, poorly studied at present but anecdotally reported as a perception of freedom of parent guilt for those who test negative. These individuals report a sense of relief that they have not transmitted the disease-associated gene to their offspring. This potential “benefit” of testing must be weighed against the potential for survivor guilt, well described in those who test carrier-negative for other inherited diseases.³⁶

Families for Which No Prior Testing of Affected Individuals Has Been Conducted

When families present to a familial cancer clinic without an identified mutation-carrying proband, DNA testing should be performed only rarely, if ever, outside of defined research protocols. Individuals who seek such testing should be given information that adequately explains the following: (1) the small likelihood of finding a mutation in the *CDKN2A* gene. In these circumstances, a negative test result is meaningless and cannot be used as a basis for altering prevention and surveillance or as a basis for reassurance. The value of the test for the majority of families to date is, therefore, minimal; (2) current uncertainties about the penetrance of *CDKN2A* mutations, even if such a mutation is found; (3) the lack of proved efficacy of prevention and surveillance strategies, even for mutation carriers; and (4) the potential benefits and risks of positive and negative results of genetic testing (Table 3).

Table 4 gives an estimate of the frequency with which *CDKN2A* mutations will be found by genomic sequencing in individuals of different categories; these estimates may be useful in assisting this discussion. Because there are few

Table 4. Estimate of Yield of Positive Test Results for *CDKN2A* Mutations

Category	<i>CDKN2A</i> Mutations (%)	Reference
Two affected first-degree relatives	< 5	13, 37
Three or more affected first-degree relatives	20-40	37
Multiple primary melanoma	15	29

population-based data on which to base these estimates,¹⁶ they must be considered as guides only and almost undoubtedly as overestimates.

The potential benefits and risks associated with genetic testing for melanoma are similar to those for the testing of other cancer susceptibility genes and are summarized in Table 3.

MANAGEMENT OF INDIVIDUALS PERCEIVED TO HAVE HIGH GENETIC SUSCEPTIBILITY TO MELANOMA

Given current gaps in knowledge about the expression of melanoma susceptibility genes in the population, DNA testing cannot be used as a guide to the clinical practice of prevention and surveillance. All individuals deemed to be at high risk of melanoma, because of the presence of any of the risk factors outlined in Table 1, should be managed with the same attention to the following measures, as previously outlined by others for those at high-risk of melanoma.^{38,39} In the absence of randomized, controlled, clinical trial-based data, the evidence for each of these measures is level IV.

Education of all family members about the need for sun protection is essential. Parents in particular should be educated about sun protective measures for infants and children,^{38,40,41} including the use of sun-protective clothing, the use of hats and sunglasses, the use of broad-spectrum ultraviolet A and ultraviolet B protective sunscreens,^{42,43} avoidance of peak ultraviolet conditions, and absolute avoidance of sunburns.

Commencing at the age of 10 years, family members should have a baseline skin examination with characterization of moles. Overview photographs of the entire skin surface and close-up photographs of atypical nevi are useful. Individuals should be taught about routine self-examination in the hope that this will prompt earlier diagnosis and removal of melanomas. Patients may be given their own copy of photographs and shown how to use these in self-examination. The significance of change in shape and size of pigmented lesions should be understood, and the rules regarding asymmetry, border, color, and diameter (ie, the ABCD rules) are often helpful in this regard.⁴⁴ Color photographs of early melanomas and atypical moles may be given to the patient as an aid. It is recommended that an appropriately trained health care provider carry out skin examinations every 6 months until the nevi are stable and the

patient is judged competent in self-surveillance. Subsequently, the individual should be seen annually or have prompt access to that health care provider as necessary. During puberty or pregnancy, when the nevi may be unstable, more frequent health care provider examinations may be indicated. Examination should include adequate examination of the scalp and genitalia. Skin-surface microscopy (epiluminescence microscopy)^{45,46} may be helpful in a surveillance program.

The indication for surgical removal of a pigmented lesion is the same as in the general population, that is, suspicion of malignant change. There is no justification for prophylactic excision of moles, since the probability of a single nevus becoming melanoma is low and, with time, many nevi will mature and disappear. Furthermore, melanomas may occur on previously entirely normal skin,⁴⁷ so that “prophylactic” excision of all moles would not change guidelines on surveillance by the patient or the health care provider.

The Consortium recommends a monthly self-examination or examination by parent, partner, or family member. A careful initial extended family history is imperative, including the ages and verified histologic diagnoses of all family members with cancer. The pedigree should be revised annually.

Screening and surveillance guidelines for other cancers should be carried out as in the general population, with the following special considerations:

1. Melanoma in the context of the Li-Fraumeni syndrome. The hallmark for the Li-Fraumeni syndrome is the presence of sarcomas and other early-onset cancers, particularly breast cancer, in the pedigree. Rarely, individuals with this syndrome also develop melanoma. Screening should be conducted in accordance with guidelines for this condition.
2. Melanoma in the context of a presence of a family history (two or more family members) with pancreatic cancer. Certain hereditary melanoma families that carry *CDKN2A* mutations have an increased incidence of pancreatic adenocarcinoma.^{1,48} Even within this minority of families, the occurrence of pancreatic cancer is a rare event. At present, there is no reliable screening method for early operable pancreatic carcinoma, and survival is poor even with optimal treatment of early disease.⁴⁹ At-risk individuals in this subset of families could be a potentially informative group for evaluating the efficacy of endoscopic ultrasound⁵⁰ or positron emission tomography scanning⁵¹ as screening tools for detecting early-stage pancreatic cancer. This, however, is a research question and should not be considered as a standard of care.

3. Where cases of ocular melanoma have occurred in the family, annual funduscopy after adequate mydriasis is recommended, although it is of unproved efficacy in screening or early detection. The risk in any individual of developing this tumor is likely to be low.

The discovery of mutations in the melanoma susceptibility genes *CDKN2A* and *CDK4* in families showing an inherited pattern of cutaneous melanoma has raised expectations in health professionals and patients about the possible value of genetic testing for this disease.

The American Society for Clinical Oncology’s statement on genetic testing for cancer susceptibility recommends that this testing be performed only when “the test can be adequately interpreted; and the results will influence the medical management of the patient or family member.”⁵² The Melanoma Genetics Consortium, having reviewed current information about these mutations, concludes that neither of these criteria is met for the testing of known melanoma susceptibility genes. It is therefore premature to offer DNA testing outside of defined research protocols, except in rare circumstances and only after careful genetic counseling that adequately addresses the following issues: the low likelihood of finding mutations; current uncertainties about the penetrance of mutations, even if found; the lack of proved efficacy of prevention and surveillance strategies, even for mutation carriers; and the potential benefits and risks of positive and negative results of genetic testing.

The Consortium will review this advice regularly, in keeping with developments in the field, to maintain a current consensus opinion.

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APPENDIX

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