

Genetic testing for hereditary melanoma: controversial, standard of care, or somewhere between the two?

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Clinical genetic testing for hereditary melanoma has been available for several years. Germline mutations in the *CDKN2A* gene are responsible for hereditary melanoma in a sizeable minority of at-risk families. The availability of molecular testing for hereditary melanoma presents a unique challenge in the community oncology setting because clinical research has not yet demonstrated that increased surveillance and prevention strategies have an impact on morbidity and mortality. We present a case study and a brief review of hereditary melanoma, underscoring some of the challenges and uncertainties associated with clinical management and genetic testing of at-risk patients.

More than 1 million new cases of skin cancer are diagnosed in the US each year. Although malignant melanoma is less common than other forms of skin cancer, it accounts for approximately three fourths of all skin cancer deaths.¹ Most melanomas are caused by a combination of environmental and sporadic factors, but it is estimated that 10% of melanomas have hereditary bases.²

Multiple genes have been associated with an inherited predisposition to melanoma. Studies sug-

gest that mutations in the *CDKN2A* (cyclin-dependent kinase inhibitor 2A) gene on chromosome 9p21 account for melanoma in 1%–2% of all individuals with sporadic cutaneous melanoma.³ Additional candidate genes for melanoma susceptibility include the *CDK4* (cyclin-dependent kinase 4) gene located on chromosome 12q14, genes located at the 1p22 locus, and the *MC1R* (melanocortin 1 receptor) gene.^{4,5} Elevated risks for melanoma have also been reported in individuals with disease-causing mutations in the *BRCA2* gene, which primarily increases breast and ovarian cancer risks.⁶

The average lifetime risk for melanoma in the general population is approximately 1.5%.³ In the US, the lifetime risks of melanoma for individuals with germline *CDKN2A* mutations are up to 76%.² In addition, *CDKN2A* mutation carriers have been shown to have a 13- to 22-fold increased risk for the development of pancreatic cancer.⁷

Data on the particular benefits and risks associated with offering DNA testing for hereditary melanoma are currently lacking.⁸ However, early recognition of melanoma or its precursor lesions by skin screening for

KEY POINTS

Clinical genetic testing for hereditary melanoma has been available for several years.

Clinicians, patients with melanoma, and their families are requesting access to genetic testing for hereditary cancer risk.

Additional research is needed to evaluate the impact of genetic testing in the management of at-risk patients.

There is no clear consensus on the utility of predictive genetic testing in the setting of hereditary melanoma.

Genetic testing for hereditary melanoma should only be offered by centers with expertise in genetics risk assessment and with informed consent.

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those at risk is associated with a good clinical prognosis.^{8,9} Patients and clinicians in our community are requesting access to predictive genetic testing for hereditary melanoma.

Case report

A 26-year-old Caucasian female was referred to medical oncology by her dermatologist after being diagnosed with a melanoma of the scalp. At the time of the first excision, the lesion was 2.24 mm in depth and Clark level III, with malignant melanocytes extending laterally to both lateral surgical margins. Several satellite lesions were also removed, which were found to be benign compound nevi. Subsequent wide excision revealed residual melanoma in situ, 0.9 cm in thickness, in the epidermis adjacent to the healing excision site. All deep surgical margins were free of tumor, and the residual invasive disease was believed to be adjacent horizontal growth and not further deep disease. A sentinel lymph node was not detected, although radioactive and blue-dyed nodes submitted for pathology were negative for malignancy. Slides demonstrating various characteristics of the tumor are pictured in Figure 1.

Family history and molecular studies

The patient's family history, shown in Figure 2, was significant for multiple family members with melanoma and breast cancer.

A detailed analysis of the pedigree revealed melanoma in at least three, and possibly four, members of the proband's family. Four relatives were also diagnosed with breast cancer at or beyond age 50, and a paternal great uncle may have had pancreatic cancer. Mutations in *CDKN2A* and *BRCA2* were included as differential diagnoses regarding the potential hereditary cause of the cancer in this family. Based on the early age at which the proband was diagnosed with melanoma (26 years); the relative rarity of melanoma in the general population, compared with

the incidence of breast cancer; and the more advanced age of family members who were diagnosed with breast cancer, a *CDKN2A* molecular analysis was the first test offered to the proband.

Sequencing of the *CDKN2A* gene revealed a deleterious mutation in the proband. The specific mutation that was detected is called M53I and has been reported in other families with hereditary melanoma. The M53I *CDKN2A* mutation was not detected in the proband's sister.

Management

Additional research is necessary for the development of definitive management recommendations for people with *CDKN2A* mutations. Uncertainties exist in the tumor spectrum among patients with hereditary melanoma and the efficacy of screening and preventative modalities. These

uncertainties complicate the development of appropriate cancer surveillance and prevention regimens.

Under the management of her dermatologist, the proband has been receiving quarterly clinical skin examinations, performing monthly skin self-examinations, and implementing various sun-avoidance tactics. Regarding her risks for pancreatic cancer, we recommended an annual computed tomographic scan of the abdomen, rather than more invasive, yet unproven, screening measures. Based on the family history of breast cancer and the possible, albeit tenuous and unconfirmed, association between *CDKN2A* mutations and breast malignancies, we recommended monthly breast self-examinations and annual clinical breast examinations, beginning at age 30, and mammography every other year until

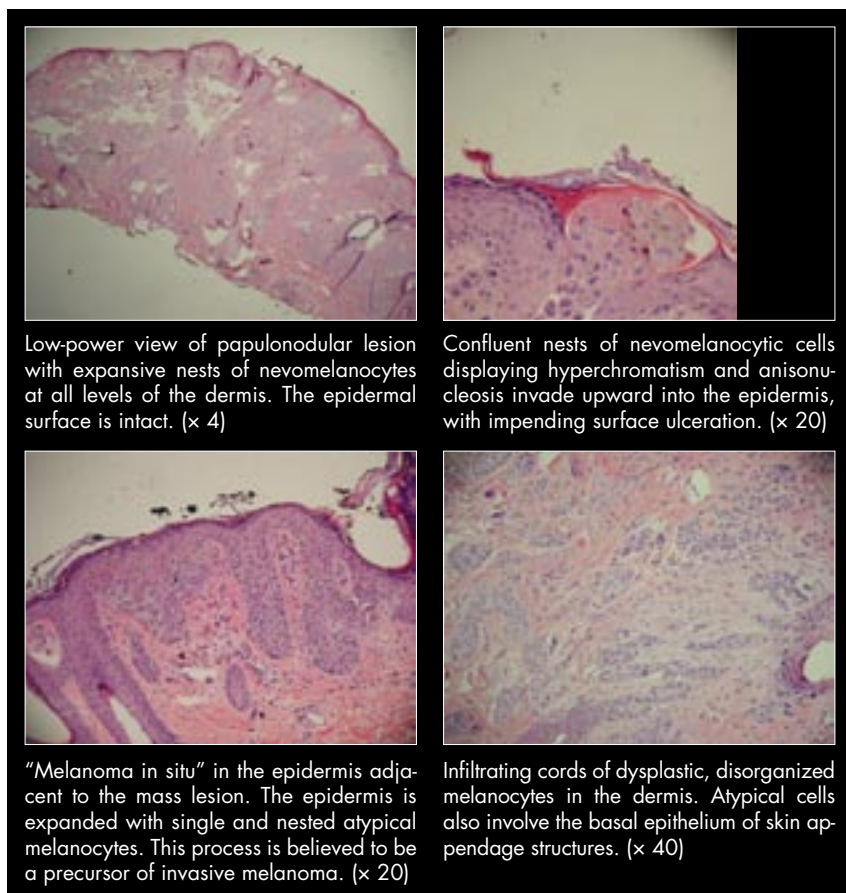


FIGURE 1 Pathological characteristics of the patient's tumor.

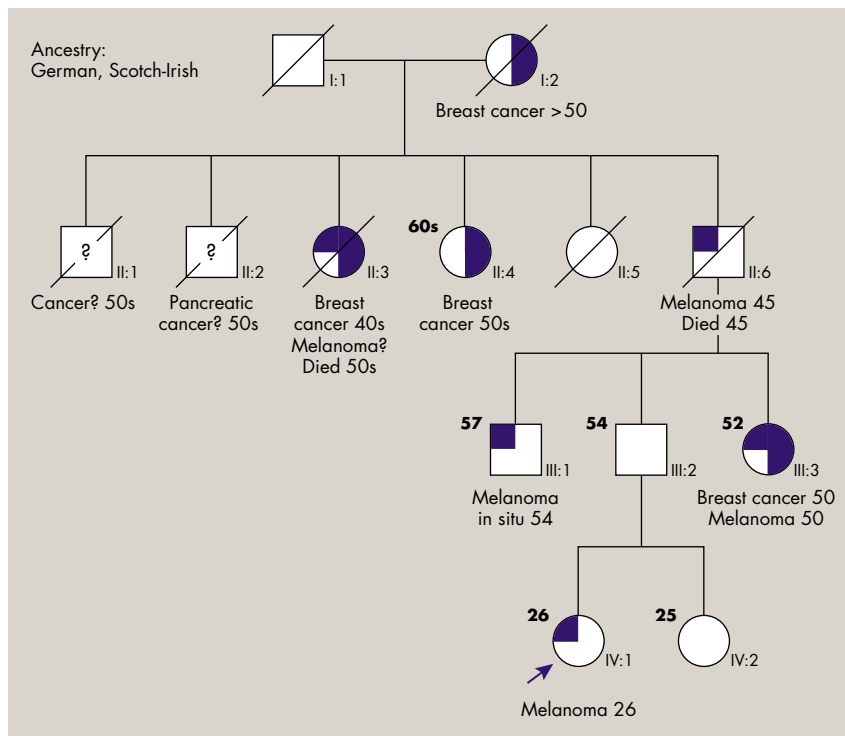


FIGURE 2 Pedigree of the proband described in the case report.

age 40, at which time annual imaging studies will be recommended.

Discussion

We hope that the prevention and early-detection strategies like those described in this report will decrease morbidity and mortality in families with a hereditary susceptibility to melanoma. Determining the impact that molecular analysis has on these variables requires ongoing research and the continued identification of at-risk families. In practice, taking a detailed family history, looking for recognizable patterns of cancers, and seeking the opinions of professionals trained with expertise in cancer genetics are the key approach.¹⁰

CDKN2A is a tumor-suppressor gene, and mutations are inherited in an autosomal-dominant manner. A family history of melanoma and other malignancies is essential to determining which patients are at risk of having germline mutations. The mutation likelihood based on clinical and fam-

ily history data can be estimated with appropriate family history information. Less than 5% of individuals with two affected first-degree relatives, 20%–40% of individuals with three or more affected relatives, and up to 10%–15% of individuals with multiple primary melanomas are estimated to carry mutations in *CDKN2A*.^{3,11}

In carriers of *CDKN2A* mutations, the calculated risk of developing melanoma before 80 years of age varies from about 58% to 91%. This variation reportedly depends on the geographical latitude and consequent exposure to sunlight, which has been hypothesized to influence penetrance.¹¹ Some families with *CDKN2A* mutations have been reported to have an elevated risk for developing both pancreatic cancer and breast cancer, although the absolute risks for these cancers in mutation carriers are still under investigation.¹¹

All family members known to carry mutations in *CDKN2A* should self-examine their moles monthly so that they can recognize any chang-

es in color, contour, or size. Patients should be educated about the natural history of moles and what changes would be considered worrisome. Photographs of atypical moles and melanomas may be used as teaching tools and references.¹⁰

The frequency of follow-up by a dermatologist depends upon the number and type of moles that are present. Some studies have suggested that more regular follow-up should be arranged during pregnancy, although there is little evidence that pregnancy has an effect on melanoma. Unless genetic testing clarifies the mutation status of an individual, all members of families with known *CDKN2A* mutations should consider themselves to be at risk for hereditary melanoma and must have prompt access to a dermatologist when suspicious lesions are discovered.¹⁰

The clinical genetic testing debate

Whether genetic testing for hereditary melanoma should be incorporated into clinical care or reserved for patients participating in research protocols is currently an open question. The Melanoma Genetics Consortium suggests that clinical *CDKN2A* genetic testing is premature because of the uncertainties in tumor penetrance and the efficacy of melanoma prevention and risk-reduction strategies.¹⁰ Other sources have supported the availability of clinical *CDKN2A* gene testing.²

There are several potential benefits of clinical *CDKN2A* testing. Patients with deleterious mutations may benefit from increased surveillance and earlier diagnosis of malignancies and in situ disease. Adoption of and adherence to sun-avoidance tactics may increase with the knowledge of hereditary susceptibility to melanoma. Physicians may increase the sampling of suspicious lesions in patients with mutations and develop more regimented methods of monitoring and tracking skin changes. Patients in

families with known germline mutations who test negative may be less anxious about developing melanoma.

Concerns regarding clinical *CDKN2A* testing have also been raised. The threshold may be too low for a biopsy of lesions in patients with *CDKN2A* mutations, resulting in unnecessary and excessive tissue sampling. Negative *CDKN2A* test results in families without known mutations would not disprove hereditary melanoma, because certain mutations may be undetectable with current molecular methodologies or because mutations might be present in other melanoma susceptibility genes. Patients with negative test results in families with documented mutations may believe that their non-carrier status precludes them from skin cancers, resulting in risky behaviors regarding sun and ultraviolet radiation exposure. Finally, some clinicians opine that all individuals in high-risk kindreds should adopt increased skin surveillance and sun-avoidance regimens, which makes the utility of molecular testing questionable.¹¹

Summary

In the standard community oncology setting, research protocols for hereditary

melanoma susceptibility testing are generally unavailable. We believe that pre- and post-test genetic counseling can address many of the concerns raised in this article, and that with appropriate education and informed consent, offering clinical *CDKN2A* testing to selected patients is reasonable. We offer clinical *CDKN2A* testing to patients with appropriate personal and family histories within a structured genetic counseling program.

The subject of this case report maintains that her test results have influenced her behavior, including limiting outside activities during the brightest or hottest daylight hours; wearing hats, long sleeves, and pants; increasing sunscreen use; and performing more vigilant and regular skin self-checks.

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