

10-1-2009

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## Recommended Citation

Grant-Kels, Jane M., "Selection Criteria for Genetic Assessment of Patients With Familial Melanoma" (2009). *Articles - Patient Care*. Paper 31.

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Published in final edited form as:

*J Am Acad Dermatol.* 2009 October ; 61(4): 677.e1–677.14. doi:10.1016/j.jaad.2009.03.016.

## Selection criteria for genetic assessment of patients with familial melanoma

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Conflicts of interest: None declared.

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## Abstract

Approximately 5% to 10% of melanoma may be hereditary in nature, and about 2% of melanoma can be specifically attributed to pathogenic germline mutations in cyclin-dependent kinase inhibitor 2A (*CDKN2A*). To appropriately identify the small proportion of patients who benefit most from referral to a genetics specialist for consideration of genetic testing for *CDKN2A*, we have reviewed available published studies of *CDKN2A* mutation analysis in cohorts with invasive, cutaneous melanoma and found variability in the rate of *CDKN2A* mutations based on geography, ethnicity, and the type of study and eligibility criteria used. Except in regions of high melanoma incidence, such as Australia, we found higher rates of *CDKN2A* positivity in individuals with 3 or more primary invasive melanomas and/or families with at least one invasive melanoma and two or more other diagnoses of invasive melanoma and/or pancreatic cancer among first- or second-degree relatives on the same side of the family. The work summarized in this review should help identify individuals who are appropriate candidates for referral for genetic consultation and possible testing.

## Keywords

*CDKN2A*; familial; genetic counseling; genetic testing; hereditary; melanoma; p16

## BACKGROUND

It is estimated that 5% to 10% of all malignant melanomas occur in familial clusters<sup>1</sup> and work continues to identify all the genetic factors that play a role in melanoma risk and optimal ways to use this information in treatment of the individual patient. There is increasing awareness among health care professionals and the public about the inherited basis of many cancers and the availability of genetic testing for relevant predisposing gene mutations.<sup>2</sup> Dermatologists and other health professionals should incorporate family history and risk assessment into clinical practice to identify patients who may be at increased risk for melanoma.

Germline mutations in cyclin-dependent kinase inhibitor 2A (*CDKN2A*) (*INK4a*) are reported to be present in up to 40% of hereditary cases of melanoma, making it the most significant high-risk melanoma susceptibility gene identified to date.<sup>3,4</sup> Mutations in *CDKN2A* are associated with increased risks for both melanoma and pancreatic cancer. By age 80 years, an individual ascertained from multiple-case families with a *CDKN2A* mutation has an increased risk of developing melanoma of 58% in Europe, 76% in the United States, and 91% in Australia.<sup>5</sup> Gene penetrance estimated by population-ascertained mutation carriers is considerably lower, although still substantial (28% by age 80 years).<sup>6</sup> The risk appears to vary between countries and families, and it is not yet clear whether this variation results from the type of mutation, coinheritance with other genetic variations, environmental exposures, or other not yet identified genetic variables. A correlation has been established between the presence of a *CDKN2A* mutation and pancreatic cancer risk in some families.<sup>7–19</sup> Within families that demonstrated a predisposition to pancreatic cancer, the relative risk for pancreatic cancer ranges from 9.4 (95% confidence interval 2.7–33.4)<sup>19</sup> to 47.8 (95% confidence interval 28.4–74.7),<sup>20</sup> or up to a 25% risk of developing pancreatic cancer by age 80 years in a study of *CDKN2A*-positive families in the Netherlands.

The classic family history features that raise the possibility of an inherited cancer syndrome are multiple affected family members (particularly with a vertical pattern of inheritance), occurrence of cancer types known to be associated with a specific hereditary syndrome, individuals given the diagnosis of multiple primary cancers, and early age of onset. Here we provide a review of the literature from 1994 to 2007 and an assessment of the predictive value of these features to identify families that are likely to harbor a mutation in the *CDKN2A* gene and would benefit from referral for genetic consultation and possibly testing. Data in this review were summarized into tables and specified by country or region where the study took place. Although we have attempted to synthesize these data into general guidelines that are internationally applicable, the variability in incidence and penetrance of *CDKN2A* mutations in different populations is such that clinicians must consider the patient's geographic region and genetic background when assessing individual patient risk.

There are no current relevant data on in situ melanomas and/or the lentigo maligna subtype of in situ melanoma, and these should not be counted as a melanoma for purposes of genetic risk assessment. Ocular melanomas are also not considered in this article.

### Family history of melanoma

The likelihood of *CDKN2A* mutation detection increases with the number of melanomas in the family (Table I; available online at [www.eblue.org](http://www.eblue.org)). Data from the two international melanoma consortium studies, one a combined analysis of familial studies and the other a cross-sectional survey of melanoma cases, indicate that the incidence of *CDKN2A* mutations in families with only one melanoma is approximately 1% whereas the likelihood of mutation detected in 2, 3, or 3 or more affected family members with melanoma are 4%, 8%, and 38%, respectively.<sup>4,6</sup> The combined GenoMEL analysis and data in Table I (available online at [www.eblue.org](http://www.eblue.org)) show that mutation detection rates are highly variable across regions. Families with similar histories have a greater likelihood of harboring a mutation in lower incidence countries. Importantly, mutation prevalence rates do not increase above 10% in high incidence regions such as Australia until there are at least five cases of melanoma in the family. In addition, mutations are more likely to be found in familial melanoma that has been identified by clinic-based ascertainment than in similar families identified by population-based ascertainment.

### Multiple primary melanomas

Approximately 3% to 5% of all patients with melanoma will develop additional primary melanomas in their lifetime.<sup>21</sup> As with family history, the prevalence of *CDKN2A* mutations increases with the number of primary melanoma diagnoses in the individual (Table II; available online at [www.eblue.org](http://www.eblue.org)). Data from the Genes Environment and Melanoma Study Group (GEM) indicate that the likelihood of a *CDKN2A* mutation in an individual with two or more primary melanomas is 2%, but increases to 7% if additional family history is present. The likelihood of mutation detection continues to increase with greater numbers of primary melanomas. Studies of patients having  $\geq 4$  melanomas indicate a 29% to 100% likelihood of mutation detection, at least in low incidence countries. Because of the impact of family history on the likelihood of mutation detection, the data from studies of multiple primary melanomas are subdivided in Table II (available online at [www.eblue.org](http://www.eblue.org)) by whether or not additional family history has been excluded.

### Melanoma and pancreatic cancer

GenoMEL data demonstrate that 28% of 178 families known to carry a *CDKN2A* mutation also had one or more pancreatic cancers in the family.<sup>4</sup> However, further analysis of these data by geographic location shows that the *CDKN2A* mutation-positive families from Australia do not have a significant association with pancreatic cancer, whereas there is an

association in Europe and North America.<sup>3</sup> Although it is not a feature of all *CDKN2A* families, the presence of pancreatic cancer in a family with melanoma greatly increases the likelihood of mutation detection (Table III; available online at [www.eblue.org](http://www.eblue.org)). A GenoMEL analysis of families with 3 or more melanomas found *CDKN2A* mutations in 38%.<sup>4</sup> However, if these families also had a pancreatic cancer diagnosis, the likelihood of a mutation went up to 72%<sup>4</sup> (Table III; available online at [www.eblue.org](http://www.eblue.org)). Data on individuals presenting with double primaries (one melanoma, one pancreatic cancer) are limited. Review of data from 5 separate studies looking at a combined total of 21 individuals with double primaries found that 3 (15.0%) were found to have a *CDKN2A* mutation. Despite the association of pancreatic cancer and *CDKN2A*, neither sporadic nor familial pancreatic cancer appears to be a predictor of harboring a mutation. Studies of unselected patients with pancreatic cancer who have no family history of melanoma or pancreatic cancer indicate a 2% likelihood of mutation detection.<sup>13,22</sup> These studies suggest that it is the combination of both pancreatic cancer and melanoma that increases the likelihood of a *CDKN2A* mutation, but that isolated pancreatic cancer and familial pancreatic cancer may not (Table III; available online at [www.eblue.org](http://www.eblue.org)).

### Age of melanoma diagnosis

A common feature of hereditary cancer syndromes is a younger age of diagnosis compared with the mean age of diagnosis for that particular cancer in the general population. Table IV (available online at [www.eblue.org](http://www.eblue.org)) compiles data on age of diagnosis of melanoma and pancreatic cancer in *CDKN2A* mutation carriers. The mean age of melanoma diagnosis in *CDKN2A* mutation carriers across the world is in the 30s to 40s, whereas the mean age in high-risk melanoma families without *CDKN2A* mutations is in the 40s to 50s. In the United States, the mean age of diagnosis of melanoma in known *CDKN2A* mutation carriers is 35 years (range 14–68 years)<sup>5</sup> compared with a median age of 59 years in the general population.<sup>23</sup> There is a wide range in age of diagnosis of sporadic melanoma, with very rare cases seen at younger than 10 years to older than 90 years.

Although younger onset is clearly a feature of *CDKN2A* mutations, in the absence of additional family history, young onset of melanoma alone does not predict a high likelihood of an identifiable mutation. Mutations are identified in less than 1% of individuals given the diagnosis of melanoma when they are younger than 40 years (Table V; available online at [www.eblue.org](http://www.eblue.org)).<sup>24–31</sup> Overall, selection of patients based on young age of melanoma diagnosis alone does not result in a sufficiently high likelihood of finding a mutation to merit referral.

### Clinically atypical nevi/dysplastic nevi

Some *CDKN2A* mutation-carrying families that exhibit numerous clinically atypical nevi (CAN) (defined based on atypical clinical features alone) and dysplastic nevi (DN) resulting in fulfillment of the formal criteria for familial atypical multiple mole melanoma syndrome<sup>32</sup> or atypical mole syndrome.<sup>33,34</sup> Within melanoma-prone families, whether *CDKN2A*-linked or not, the presence of CAN/DN is a strong risk factor for melanoma development; however, some individuals who develop melanoma in this setting do not have these markers.<sup>35</sup> Furthermore, the association of CAN/DN with mutation carrier status in known *CDKN2A* mutation families is complex, and many studies have indicated the nevus phenotype to be a very unreliable indicator of *CDKN2A* mutation carrier status.<sup>36–40</sup>

CAN/DN is also seen outside melanoma-prone families either sporadically or genetically. There have been limited studies to date examining germline *CDKN2A* mutation status in patients with CAN. Celebi et al<sup>41</sup> found no *CDKN2A* mutations in a study of 28 patients with CAN and Ung-Juurlink<sup>42</sup> found 8 mutations in 251 (3.2%) patients presenting with

melanoma, CAN, or both. In this study, the phenotype of the mutation carriers was not specified, but univariate analysis did not detect any relationship between CAN alone and *CDKN2A* status. Matsumura et al<sup>43</sup> found no mutations in 4 patients with nonfamilial CAN, and de Snoo et al<sup>44</sup> found 6 mutations in 167 (4%) patients with CAN, of whom 4 of the 6 turned out to have a positive family history for melanoma and one had 4 primary melanomas.

In summary, *CDKN2A* genetic testing in patients with CAN/DN without a positive family history of melanoma is not justified based on current data.

### **Other melanoma predisposition genes: Cyclin-dependent kinase 4, cyclin-dependent kinase inhibitor 2A/p14 alternate reading frame, melanocortin 1 receptor**

This article does not discuss the role of genetic testing for two other high-penetrance melanoma predisposition genes, cyclin-dependent kinase 4 *CDK4* or cyclin-dependent kinase inhibitor 2A/p14 alternate reading frame *CDKN2A/ARF*.<sup>4</sup> Risk estimates associated with mutations in these genes have wider confidence intervals than those estimated for *CDKN2A* mutations because so few have been reported. In patients who have a strong family history and are negative for *CDKN2A* mutation, these tests could be considered but are unlikely to be positive.

Melanocortin 1 receptor variants are associated with red hair and freckles. Melanocortin 1 receptor variants confer significant additional melanoma risk to *CDKN2A* mutation carriers and further refinement of this risk is ongoing in many research laboratories.<sup>45,46</sup> Melanocortin 1 receptor testing is currently available as a research investigation.

## **DISCUSSION**

### **Candidate patients for clinical melanoma genetic assessment**

Genetic testing is currently widely used for identifying individuals with hereditary colorectal cancer and hereditary breast/ovarian cancer, but genetic testing of *CDKN2A* in the context of melanoma is not part of routine practice. However, there are now at least 5 commercial laboratories in the United States offering clinical *CDKN2A* testing,<sup>47</sup> and there is growing awareness by the lay public about the genetic basis of cancer and the availability of testing. The objective of this article is to help clinicians identify individuals who are at significant risk for harboring a genetic mutation and who could be referred to a genetic counseling specialist.

We have summarized the predictive value of personal and family history of melanoma and pancreatic cancer for identifying individuals who have an increased probability of harboring a mutation in the *CDKN2A* gene. The likelihood of detecting a *CDKN2A* mutation depends greatly on the population being studied, which may be a result of differences in penetrance associated with variation in melanoma predisposing phenotype (eg, fair skin, red hair) and the local amount/intensity of ultraviolet radiation exposure. In geographic areas with higher background rates of melanoma, there is greater likelihood of having multiple family members with melanoma or multiple primary melanomas caused by reasons other than a *CDKN2A* mutation. However, melanoma penetrance in *CDKN2A* mutation carriers is also higher in areas with high background rates of melanoma, indicating a potential interaction between *CDKN2A* and the other predisposing factors for melanoma in these areas.

The variability in the background incidence of melanoma and penetrance of *CDKN2A* mutations between countries is such that there is no single guideline for genetic testing that would be appropriate to apply worldwide. We, therefore, provide a framework that clinicians can use to identify appropriate candidates for genetic evaluation with regard to the

specific populations they serve. For moderate to high melanoma incident areas, individuals with 3 or more primary melanomas and/or families with at least one invasive melanoma and two or more other diagnoses of melanoma and/or pancreatic cancer in aggregate among first- or second-degree relatives on the same side of the family are appropriate candidates for a genetics evaluation (Table VI; available online at [www.eblue.org](http://www.eblue.org)). For low melanoma incidence areas, two melanoma and/or pancreatic cancer events in a family may be sufficient to consider a genetics referral (Table VI; available online at [www.eblue.org](http://www.eblue.org)). There are insufficient data at this time to specifically determine the likelihood of mutation detection in individuals presenting with synchronous or metachronous diagnoses of melanoma and pancreatic cancer. However, this is another group that may warrant referral for genetics evaluation.

There are important considerations regarding the clinical use and potential implications of *CDKN2A* genetic testing. Before undergoing genetic testing, patients should be informed of the potential benefits and limitations of testing by a genetic counselor or other professional with expertise in melanoma genetics (Table VII; available online at [www.eblue.org](http://www.eblue.org)).<sup>48</sup> To date there are limited data regarding the implications of *CDKN2A* genetic testing. Aspinwall et al<sup>49</sup> found an increase in screening and precautionary behaviors among both mutation-positive and mutation-negative patients. After receiving test results, 55% reported adopting at least one screening behavior. Long-term follow-up data are needed to determine whether these behavioral changes are maintained, but data from testing of other hereditary cancer syndromes indicate that noncarriers in a mutation-positive family are likely to continue to undergo risk-appropriate screening.<sup>50,51</sup> Therefore, it is important that genetic testing be done in the context of counseling and education.

Regardless of whether or not genetic testing is part of the care for families with hereditary melanoma, there is likely benefit from identifying these highest risk families and targeting them for intensive screening and education.

## SUMMARY

The higher rates of *CDKN2A* mutation positivity in individuals with 3 or more primary melanomas and/or families with at least one melanoma and two or more other diagnoses of melanoma and/or pancreatic cancer in aggregate among first- or second-degree relatives on the same side of the family warrant referral for a genetics evaluation. Use of these guidelines would increase the proportion of individuals identified at high risk and referred appropriately to genetic services. Patients at high risk should be allowed to weigh the pros and cons of testing and will—irrespective of actually being testing—benefit from tailored education and screening.

## Acknowledgments

We would like to thank Sherri Bale at GeneDx Inc, Gaithersburg, MD, and Cindy Solomon and Jean Schaller at Myriad Genetic Laboratories, Salt Lake City, UT, for multiple discussions on genetic testing for melanoma.

Supported by numerous grants. The work of GenoMEL, including Drs Leachman, Bergman, Debniak, Newton-Bishop, Puig, Bianchi-Scarrà, Kefford, Mann, Tsao, and Elder, is supported by the National Institutes of Health (NIH) RO1 CA-83115 and GenoMEL 01872 Network of Excellence. The work of Dr Puig is partially supported by Fondo de Investigaciones Sanitarias, grant 0019/03 and 06/0265, National Cancer Institute (NCI). The work of Ms Kohlmann and Dr Leachman is supported by the Huntsman Cancer Foundation Genetic Counseling Shared Resource and core facilities supported by P30 CA042014 awarded to Huntsman Cancer Institute. The work of Dr Bressac-de Paillerets is supported by the Institut National du Cancer, Réseau Oncogénétique pour les Cancers Rares—Mélanome. The work of Dr Newton-Bishop is supported by Cancer Research-United Kingdom grant C588/A4994. The work of Drs Goldstein and Tucker are supported by the Intramural Research Program of the NIH, Division of Cancer Epidemiology and Genetics. The work of Dr Asgari is supported by the National Institute of

Arthritis Musculoskeletal and Skin Diseases (K23 AR 051037). The work of Dr Tsao is supported by P50 CA-93683 (NCI), RSG MGO-112970 (American Cancer Society), NIH R01 CA-83115.

## Abbreviations used

CAN	clinically atypical nevi
CDKN2A	cyclin-dependent kinase inhibitor 2A
DN	dysplastic nevi

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Table I

Percentage of cyclin-dependent kinase inhibitor 2A mutations increases with number of melanoma diagnoses in the family

No. of individuals with melanoma in family*	Study	Study location	Degree of relationship†	Families positive for CDKN2A mutation
1	Begg et al, <sup>6</sup> 2005 Population based	GEM: North America (British Columbia, Ontario, California, Michigan, New Jersey, and North Carolina)	n/a	24/1727 (1%)
	Begg et al, <sup>6</sup> 2005 Population based	GEM: Australia (New South Wales and Tasmania)	n/a	13/1109 (1%)
	Begg et al, <sup>6</sup> 2005 Population based	GEM: United States (California, Michigan, New Jersey, North Carolina), Australia (New South Wales, Tasmania), Canada (British Columbia, Ontario), Italy (Turin)	n/a	39/2996 (1%)
1 or 2	Vasen et al, <sup>8</sup> 2000‡	Netherlands	nd	4/8 (50%)
	Lamperska et al, <sup>52</sup> 2002	Poland	nd	0/16 (0%)
2	Fitzgerald et al, <sup>53</sup> 1996	United States (Massachusetts)	1, 2	3/24 (13%)
	MacKie et al, <sup>54</sup> 1998	United Kingdom (Scotland)	nd	4/14 (29%)
	Soufir et al, <sup>55</sup> 1998	France	nd	8/28 (29%)
	Holland et al, <sup>56</sup> 1999	Australia	nd	1/65 (2%)
	Newton-Bishop et al, <sup>57</sup> 1999/ Harland et al, <sup>58</sup> 1997	United Kingdom (England and Wales)	nd	1/22 (4%)
	Ruiz et al, <sup>59</sup> 1999	Spain	1, 2	2/18 (11%)
	Tsao et al, <sup>29</sup> 2000	United States (Massachusetts)	1, 2, 3	0/12 (0%)
	Yakobson et al, <sup>60</sup> 2000	Israel	1, 2, 3	2/24 (8%)
	Della Torre et al, <sup>61</sup> 2001‡	Italy	nd	2/8 (25%)
	Alao et al, <sup>62</sup> 2002	United Kingdom (London)	1	1/12 (8%)
	Mantelli et al, <sup>63</sup> 2002‡	Italy	1	11/47 (23%)
	Chaudru et al, <sup>64</sup> 2004	France	nd	7/34 (21%)
	Debniak et al, <sup>65</sup> 2004	Poland	nd	0/12 (0%)
	Landi et al, <sup>66</sup> 2004	Italy (South, Central, North, Sardinia, 1 family from Russia)	nd	3/42 (7%)
	Soufir et al, <sup>25</sup> 2004	France	1, 2	1/16 (6%)
	Begg et al, <sup>6</sup> 2005 Population based	GEM: North America (British Columbia, Ontario, California, Michigan, New Jersey, and North Carolina)	1	11/236 (5%)
Begg et al, <sup>6</sup> 2005 Population based	GEM: Australia (New South Wales and Tasmania)	1	7/221 (3%)	
Begg et al, <sup>6</sup> 2005 Population based	GEM: United States (California, Michigan, New Jersey, North Carolina), Australia (New South Wales, Tasmania), Canada (British Columbia, Ontario), Italy (Turin)	1	19/463 (4%)	
Lang et al, <sup>67</sup> 2005	United Kingdom (Scotland)	nd	4/28 (14%)	
Marian et al, <sup>68</sup> 2005	Israel	nd	0/7 (0%)	
Eliason et al, <sup>69</sup> 2006	United States (Utah)	1, 2	1/36 (3%)	

No. of individuals with melanoma in family *	Study	Study location	Degree of relationship †	Families positive for <i>CDKN2A</i> mutation
≥2	Hocevar et al, <sup>70</sup> 2006	Slovenia	1, 2	3/8 (38%)
	Huber and Ramos, <sup>71</sup> 2006	Brazil	1, 2	1/10 (10%)
	Niendorf et al, <sup>72</sup> 2006	United States (Massachusetts)	1	5/76 (7%)
	Kamb et al, <sup>73</sup> 1994	United States (7 Utah, 1 Texas), Netherlands	nd	2/13 (15%)
	Platz et al, <sup>74</sup> 1997	Sweden	1, 2, 3	5/100 (5%)
	Fargnoli et al, <sup>75</sup> 1998	Italy, Austria	1, 2	4/10 (40%)
	Liu et al, <sup>76</sup> 1999	Canada (Toronto)	nd	23/82 (28%)
	Borg et al, <sup>11</sup> 2000 <sup>‡</sup>	Sweden	1, 2	10/52 (19%)
	Mantelli et al, <sup>77</sup> 2004 <sup>‡</sup>	Italy	1	9/34 (26%)
	Marian et al, <sup>68</sup> 2005	Israel	nd	0/13 (0%)
3	Casula et al, <sup>78</sup> 2007	Italy (South Italy and Sardinia)	nd	5/29 (17%)
	Flores et al, <sup>79</sup> 1997	Australia	nd	1/19 (5%)
	MacKie et al, <sup>54</sup> 1998	United Kingdom (Scotland)	nd	1/1 (100%)
	Holland et al, <sup>56</sup> 1999	Australia	nd	4/38 (11%)
	Newton-Bishop et al, <sup>57</sup> 1999	United Kingdom (England and Wales)	nd	1/7 (14%)
	Yakobson et al, <sup>60</sup> 2000	Israel	1, 2, 3	0/5 (0%)
	Della Torre et al, <sup>61</sup> 2001 <sup>‡</sup>	Italy	nd	0/2 (0%)
	Alao et al, <sup>62</sup> 2002	United Kingdom (London)	1, 2	0/1 (0%)
	Mantelli et al, <sup>63</sup> 2002 <sup>‡</sup>	Italy	nd	6/11 (55%)
	Debniak et al, <sup>65</sup> 2004	Poland	nd	0/3 (0%)
	Landi et al, <sup>66</sup> 2004	Italy (South, Central, North, Sardinia, 1 family from Russia)	nd	0/11 (0%)
	Soufir et al, <sup>25</sup> 2004	France	1, 2	1/5 (20%)
	<b>Begg et al,<sup>6</sup> 2005 Population based</b>	<b>GEM: North America (British Columbia, Ontario, California, Michigan, New Jersey, and North Carolina)</b>	<b>1</b>	<b>4/38 (11%)</b>
	<b>Begg et al,<sup>6</sup> 2005 Population based</b>	<b>GEM: Australia (New South Wales and Tasmania)</b>	<b>1</b>	<b>2/35 (6%)</b>
	<b>Begg et al,<sup>6</sup> 2005 Population based</b>	<b>GEM: United States (California, Michigan, New Jersey, North Carolina), Australia (New South Wales, Tasmania), Canada (British Columbia, Ontario), Italy (Turin)</b>	<b>1</b>	<b>6/73 (8.2%)</b>
≥3	Lang et al, <sup>67</sup> 2005	United Kingdom (Scotland)	nd	2/3 (67%)
	Eliason et al, <sup>69</sup> 2006	United States (Utah)	1, 2	1/18 (7%)
	Hocevar et al, <sup>70</sup> 2006	Slovenia	1, 2	2/3 (67%)
	Huber and Ramos, <sup>71</sup> 2006	Brazil	1, 2	1/2 (50%)
	Niendorf et al, <sup>72</sup> 2006	United States (Massachusetts)	nd	2/23 (9%)
	Fitzgerald et al, <sup>53</sup> 1996	United States (Massachusetts)	1, 2	2/4 (50%)
	Soufir et al, <sup>55</sup> 1998	France	nd	13/20 (65%)
	Ruiz et al, <sup>59</sup> 1999	Spain	1, 2	3/9 (33%)

No. of individuals with melanoma in family <sup>*</sup>	Study	Study location	Degree of relationship <sup>†</sup>	Families positive for <i>CDKN2A</i> mutation
≥4	Tsao et al, <sup>29</sup> 2000	United States (Massachusetts)	1, 2, 3	1/2 (50%)
	Vasen et al, <sup>8</sup> 2000 <sup>‡</sup>	Netherlands	nd	15/19 (79%)
	Chaudru et al, <sup>64</sup> 2004	France	nd	13/19 (68%)
	<b>Goldstein et al,<sup>4</sup> 2006</b>	<b>GenoMEL</b>	<b>nd</b>	<b>178/466 (38%)</b>
	Flores et al, <sup>79</sup> 1997	Australia	nd	9/29 (31%)
	MacKie et al, <sup>54</sup> 1998	United Kingdom (Scotland)	nd	1/1 (100%)
	Holland et al, <sup>56</sup> 1999	Australia	nd	6/28 (21%)
	Newton-Bishop et al, <sup>57</sup> 1999	United Kingdom (England and Wales)	nd	7/13 (54%)
	Yakobson et al, <sup>60</sup> 2000	Israel	1, 2, 3	0/1 (0%)
	Della Torre et al, <sup>61</sup> 2001 <sup>‡</sup>	Italy	nd	3/4 (75%)
	Mantelli et al, <sup>63</sup> 2002 <sup>‡</sup>	Italy	nd	4/4 (100%)
	Debniak et al, <sup>65</sup> 2004	Poland	nd	0/1 (0%)
	Landi et al, <sup>66</sup> 2004	Italy (South, Central, North, Sardinia, 1 family from Russia)	nd	1/2 (50%)
	Soufir et al, <sup>25</sup> 2004	France	1, 2	1/2 (50%)
	<b>Begg et al,<sup>6</sup> 2005 Population based</b>	<b>GEM: North America (British Columbia, Ontario, California, Michigan, New Jersey, and North Carolina)</b>	<b>1</b>	<b>1/6 (17%)</b>
	<b>Begg et al,<sup>6</sup> 2005 Population based</b>	<b>GEM: Australia (New South Wales and Tasmania)</b>	<b>1</b>	<b>0/12 (0%)</b>
	<b>Begg et al,<sup>6</sup> 2005 Population based</b>	<b>GEM: United States (California, Michigan, New Jersey, North Carolina), Australia (New South Wales, Tasmania), Canada (British Columbia, Ontario), Italy (Turin)</b>	<b>1</b>	<b>1/18 (6%)</b>
	Lang et al, <sup>67</sup> 2005	United Kingdom (Scotland)	nd	1/1 (100%)
	Eliason et al, <sup>69</sup> 2006	United States (Utah)	1, 2	3/6 (50%)
	Huber and Ramos, <sup>71</sup> 2006	Brazil	1, 2	0/1 (0%)
Niendorf et al, <sup>72</sup> 2006	United States (Massachusetts)	nd	6/18 (33%)	
Unknown	Aitken et al, <sup>80</sup> 1999	Australia (Queensland)	nd	9/87 (10%)

*CDKN2A*, Cyclin-dependent kinase inhibitor 2A; *n/a*, not applicable; *nd*, not discussed.

Bolded studies reflect large consortium-based data sets.

\* Families may have included individuals with multiple primary melanoma (MPM). Specific information on MPM can be found in Table II.

<sup>†</sup> 1 = First degree, 2 = second degree, 3 = third degree.

<sup>‡</sup> Population in which common mutation accounts for majority of *CDKN2A* mutations identified.



Table II

Percentage of cyclin-dependent kinase inhibitor 2A mutations increases with number of primary melanomas

No. of primaries	Study	Study location	Family history*	Cases positive for CDKN2A mutation
2	MacKie et al, <sup>54</sup> 1998 <sup>†</sup>	United Kingdom (Scotland)		1/14 (7%)
	Monzon et al, <sup>81</sup> 1998	Canada (Toronto) and United States (Maryland)	✓	3/25 (8%)
	Hashemi et al, <sup>82</sup> 2000 <sup>†</sup>	Sweden	✓	3/61 (5%)
	Auroy et al, <sup>83</sup> 2001 <sup>†</sup>	France		6/85 (7%)
	Blackwood et al, <sup>84</sup> 2002	United States (Pennsylvania)	✓	5/72 (7%)
	Peris et al, <sup>85</sup> 2004	Europe (Germany, Italy, and Austria)		1/8 (13%)
	Soufir et al, <sup>25</sup> 2004	France		0/14 (0%)
	Puig et al, <sup>86</sup> 2005	Spain	✓	8/81 (10%)
	Eliason et al, <sup>69</sup> 2006	United States (Utah)	✓✓	1/6 (17%)
≥2	Harland et al, <sup>58</sup> 1997	United Kingdom		0/3 (0%)
	MacKie et al, <sup>54</sup> 1998 <sup>†</sup>	United Kingdom (Scotland)		2/17 (12%)
			✓✓	5/5 (100%)
	Soufir et al, <sup>55</sup> 1998	France (1 family living in Italy)	✓✓	16/20 (80%)
	Holland et al, <sup>56</sup> 1999	Australia	✓✓	6/28 (21%)
	Liu et al, <sup>76</sup> 1999	Canada (Toronto) and United States (Maryland)	✓	5/33 (15%)
	Newton-Bishop et al, <sup>57</sup> 1999	United Kingdom (England and Wales)	✓✓	6/20 (30%)
	Ruiz et al, <sup>59</sup> 1999	Spain		1/8 (13%)
	Hashemi et al, <sup>82</sup> 2000 <sup>†</sup>	Sweden		2/65 (3%)
			✓	7/15 (47%)
	Yakobson et al, <sup>60</sup> 2000	Israel		0/2 (0%)
			✓	1/1 (100%)
	Auroy et al, <sup>83</sup> 2001 <sup>†</sup>	France		9/100 (9%)
	Alao et al, <sup>62</sup> 2002	United Kingdom		0/4 (0%)
			✓	1/1 (100%)
	Blackwood et al, <sup>84</sup> 2002	United States (Pennsylvania)	✓	5/44 (11%)
	Mantelli et al, <sup>63</sup> 2002 <sup>†</sup>	Italy (Liguria)	✓✓	11/23 (48%)
	Landi et al, <sup>66</sup> 2004	Italy (South, Central, North, Sardinia, 1 family from Russia)	✓✓	2/15 (13%)
	Mantelli et al, <sup>77</sup> 2004 <sup>†</sup>	Italy (Liguria)		4/14 (21%)
	Nielsen et al, <sup>87</sup> 2004 <sup>†</sup>	Sweden (South)	nd	3/15 (20%)
Peris et al, <sup>85</sup> 2004	Europe (Germany, Italy, Austria)		3/14 (21%)	
Rutter et al, <sup>88</sup> 2004	United States (Pennsylvania and California)	✓	1/22 (5%)	
<b>Begg et al,<sup>6</sup> 2005 Population based</b>	<b>GEM: United States (California, Michigan, New Jersey, North Carolina), Australia (New South Wales, Tasmania), Canada (British Columbia, Ontario), Italy (Turin)</b>	✓	<b>17/946 (2%) 19/263 (7%)</b>	
Lang et al, <sup>67</sup> 2005	United Kingdom (Scotland)	✓✓	3/5 (60%)	

No. of primaries	Study	Study location	Family history*	Cases positive for <i>CDKN2A</i> mutation
	Marian et al, <sup>68</sup> 2005	Israel	nd	0/5 (0%)
	Nagore et al, <sup>27</sup> 2005	Spain	✓	1/3 (33%)
	Puig et al, <sup>86</sup> 2005	Spain		6/73 (8%)
			✓	11/31 (36%)
	Casula et al, <sup>78</sup> 2007	Italy (South Italy and Sardinia)	✓	5/34 (15%)
	<b>Goldstein et al,<sup>4</sup> 2006</b>	<b>GenoMEL: North America and Europe</b>	✓✓	<b>97/129 (75%)</b>
	Hocevar et al, <sup>70</sup> 2006	Slovenia	✓✓	5/6 (83%)
	Stratigos et al, <sup>30</sup> 2006	Greece (Athens)		2/2 (100%)
3	MacKie et al, <sup>54</sup> 1998 <sup>†</sup>	United Kingdom (Scotland)		0/2 (0%)
	Monzon et al, <sup>81</sup> 1998	Canada (Toronto) and United States (Maryland)		1/5 (20%)
	Hashemi et al, <sup>82</sup> 2000 <sup>†</sup>	Sweden	✓	4/12 (33%)
	Auoy et al, <sup>83</sup> 2001 <sup>†</sup>	France		0/9 (0%)
	Blackwood et al, <sup>84</sup> 2002	United States (Pennsylvania)	✓	1/14 (7%)
	Peris et al, <sup>85</sup> 2004	Europe (Germany, Italy, Austria)		0/2 (0%)
	Soufir et al, <sup>25</sup> 2004	France		0/3 (0%)
	Puig et al, <sup>86</sup> 2005	Spain	✓	4/14 (29%)
≥3	Eliason et al, <sup>69</sup> 2006	United States (Utah)	✓✓	3/3 (100%)
	Niendorf et al, <sup>72</sup> 2006	United States (Massachusetts)		0/6 (0%)
≥4	MacKie et al, <sup>54</sup> 1998 <sup>†</sup>	United Kingdom (Scotland)		1/1 (100%)
	Monzon et al, <sup>81</sup> 1998	Canada (Toronto) and United States (Maryland)		1/3 (33%)
	Hashemi et al, <sup>82</sup> 2000 <sup>†</sup>	Sweden	✓	2/7 (29%)
	Auoy et al, <sup>83</sup> 2001 <sup>†</sup>	France		3/6 (50%)
	Blackwood et al, <sup>84</sup> 2002	United States (Pennsylvania)	✓	3/9 (33%)
	Peris et al, <sup>85</sup> 2004	Europe (Germany, Italy, and Austria)		2/4 (50%)
	Puig et al, <sup>86</sup> 2005	Spain	✓	5/9 (56%)

*CDKN2A*, Cyclin-dependent kinase inhibitor 2A; *nd*, not discussed.

Bolded studies reflect large consortium-based data sets.

\* Blank = no family history of melanoma;

✓ ascertained multiple primary cases regardless of family history;

✓✓ ascertained by family history consistent with a melanoma-prone family.

<sup>†</sup> Population in which common mutation accounts for majority of *CDKN2A* mutations identified.

Table III

Percentage of cyclin-dependent kinase inhibitor 2A mutations in families with pancreatic cancer increases when 3 or more cancer events are present

No. of cancer events (pancreatic cancer with/without melanoma) in individual or family	Description	Study	Study location	Families positive for <i>CDKN2A</i> mutation	
1	Pa ca in individual	Ghiorzo et al, <sup>13</sup> 2004	Italy (Liguria)	1/47* (2%)	
		Ghiorzo et al, <sup>22</sup> 2007	Italy (Liguria)	1/63* (2%)	
	Pa ca in individual aged ≤ 50 y	Lal et al, <sup>15</sup> 2000	Canada (Toronto)	0/10 (0%)	
	Pa ca and nonmelanoma cancer in individual	Gerdes et al, <sup>89</sup> 2000	Germany (Marburg)	1 <sup>7</sup> /14 (7%)	
2	Pa ca and melanoma in individual	Lal et al, <sup>16</sup> 2000	Canada (Toronto)	2/14 (14%)	
		Lal et al, <sup>15</sup> 2000	Canada (Toronto)	0/1 (0%)	
		Austin et al, <sup>90</sup> 2003	United States (various)	0/2 (0%)	
		Ghiorzo et al, <sup>13</sup> 2004	Italy (Liguria)	0/2 (0%)	
		Soufir et al, <sup>25</sup> 2004	France	1/1 (100%)	
		Ghiorzo et al, <sup>22</sup> 2007	Italy (Liguria)	1/1 (100%)	
		1 Pa ca and 1 melanoma in family	Lal et al, <sup>15</sup> 2000	Canada (Toronto)	0/2 (0%)
		Bartsch et al, <sup>12</sup> 2002	Germany	2/4 (50%)	
		Prowse et al, <sup>91</sup> 2003	United States (Philadelphia)	0/2 (0%)	
		Ghiorzo et al, <sup>13</sup> 2004	Italy (Liguria)	1/1 (100%)	
		2 Pa ca in family	Lal et al, <sup>15</sup> 2000	Canada (Toronto)	0/12 (0%)
			Bartsch et al, <sup>12</sup> 2002	Germany	0/13 (0%)
			Ghiorzo et al, <sup>22</sup> 2007	Italy (Liguria)	1/7 (14%)
≥ 2	1 Pa ca and ≥ 1 melanoma in family	Austin et al, <sup>90</sup> 2003	United States (various)	0/4 (0%)	
	≥ 2 Pa ca in family	Moskaluk et al, <sup>92</sup> 1998	United States (various)	0/20 (0%)	
		Austin et al, <sup>90</sup> 2003	United States (various)	0/6 (0%)	
≥ 3	1 Pa ca and ≥ 2 melanoma in family	Lal et al, <sup>15</sup> 2000	Canada (Toronto)	1/1 (100%)	
		Landi et al, <sup>66</sup> 2004	Italy	2/3 (67%)	
	1 Pa ca and ≥ 3 melanoma in family	Bartsch et al, <sup>12</sup> 2002	Germany	0/1 (0%)	
		Prowse et al, <sup>91</sup> 2003	United States (Philadelphia)	1/1 (100%)	
		<b>Goldstein et al,<sup>4</sup> 2006</b>	<b>GenoMEL</b>	<b>31/43 (72%)</b>	
	≥ 1 Pa ca and ≥ 2 melanoma in family	Soufir et al, <sup>55</sup> 1998	France (1 in Italy)	4/9 (44%)	
		Mantelli et al, <sup>63</sup> 2002	Italy (northern, central)	6/9 (67%)	
		Lang et al, <sup>67</sup> 2005	United Kingdom (Scotland)	0/2 (0%)	
	2 Pa ca and 1 melanoma in family	Moskaluk et al, <sup>92</sup> 1998	United States (various)	1/1 (100%)	
		Ghiorzo et al, <sup>22</sup> 2007	Italy (Liguria)	1/1 (100%)	
		≥ 2 Pa ca and ≥ 3 melanoma	<b>Goldstein et al,<sup>4</sup> 2006</b>	<b>GenoMEL</b>	<b>13/16 (81%)</b>

No. of cancer events (pancreatic cancer with/without melanoma) in individual or family	Description	Study	Study location	Families positive for <i>CDKN2A</i> mutation
	Member of pa ca registry with FAMMM cutaneous phenotype	Lynch et al, <sup>18</sup> 2002	United States (Creighton)	8/8 (100%)
	≥ 3 Pa ca in family	Lal et al, <sup>15</sup> 2000	Canada (Toronto)	0/4 (0%)
		Bartsch et al, <sup>12</sup> 2002	Germany	0/5 (0%)

*CDKN2A*, Cyclin-dependent kinase inhibitor 2A; *FAMMM*, familial atypical multiple mole melanoma; *Pa ca*, pancreatic cancer.

Bolded studies reflect large consortium-based data sets.

\* Complete family history not provided on all cases.

† Mutation carrier had cancer of pancreas, thyroid, vocal cord, and basal cell. No family history of cancer was present.

Table IV

Age of diagnosis of melanoma and pancreatic cancer in individuals with cyclin-dependent kinase inhibitor 2A mutations

Study	Study location	High-risk <i>CDKN2A</i> negative family (range), y <sup>*</sup>	<i>CDKN2A</i> positive family (range), y
Melanoma			
Burden et al, <sup>93</sup> 1999 <sup>†</sup>	United Kingdom (Scotland)	51 mean	37 mean
Ghiorzo et al, <sup>94</sup> 1999	Italy (Liguria)	47 median	48 median <sup>‡</sup>
Goldstein et al, <sup>95</sup> 2000	United States (various)	nd	34.2 median <sup>§</sup>
Hashemi et al, <sup>82</sup> 2000 <sup>‡</sup>	Sweden	54 median	42 median
Vasen et al, <sup>8</sup> 2000 <sup>†</sup>	Netherlands	44 (12–71) mean	39 (15–72) mean
Auroy et al, <sup>83</sup> 2001	France	44.1 (17–75) mean	43.9 (28–60) mean
<b>Bishop et al,<sup>5</sup> 2002</b>	<b>GenoMEL</b>	<b>nd</b>	<b>37.5 (12–86) mean</b>
Blackwood et al, <sup>84</sup> 2002	United States (Pennsylvania)	50 mean	39.7 mean
Mantelli et al, <sup>63</sup> 2002 <sup>†</sup>	Italy (northern and central)	48 median	42 median
Rulyak et al, <sup>10</sup> 2003	United States (various)	nd	51 median
Ghiorzo et al, <sup>13</sup> 2004 <sup>†</sup>	Italy (Liguria)	49.4 mean	46.5 mean
Mantelli et al, <sup>77</sup> 2004 <sup>†</sup>	Italy (Liguria)	47 median	41 median
Lang et al, <sup>67</sup> 2005	United Kingdom (Scotland)	46 mean	35 mean
Puig et al, <sup>86</sup> 2005	Spain	45.8 (± 16.1) mean	32.9 (± 12.6) mean
<b>Goldstein et al,<sup>4</sup> 2006</b>	<b>GenoMEL</b>	<b>45 median</b>	<b>36 median</b>
Niendorf et al, <sup>72</sup> 2006	United States (Massachusetts)	44.4 (95% CI 42.0–46.9) mean	33.2 (95% CI 25.9–40.5) mean
Pancreas			
Vasen et al, <sup>8</sup> 2000 <sup>†</sup>	Netherlands	nd	58 (38–77) mean
de Vos tot Nederveen Cappel et al, <sup>96</sup> 2003 <sup>†</sup>	Netherlands	nd	58 (43–74) mean
Rulyak et al, <sup>10</sup> 2003	United States (various)	nd	59 median

*CDKN2A*, Cyclin-dependent kinase inhibitor 2A; *CI*, confidence interval; *nd*, not discussed.

Bolded studies reflect large consortium-based data sets.

<sup>\*</sup> *CDKN2A* negative families fulfilled the same eligibility criteria as *CDKN2A* positive families; study dependent.

<sup>†</sup> Population in which common mutation accounts for majority of *CDKN2A* mutations identified.

<sup>‡</sup> Median age of diagnosis in general population was 60 y.

<sup>§</sup> Median age of diagnosis in general population was 54 y.

**Table V**  
 Young age of melanoma diagnosis in nonfamilial setting does not warrant cyclin-dependent kinase inhibitor 2A testing

Study	Study location	Age criteria, y	MPM	Family history of melanoma	CDKN2A-positive
Whiteman et al. <sup>31</sup> 1997	Australia (Queensland)	<15	nd	✓	1/10 (10%)
Tsao et al. <sup>29</sup> 2000	United States (Massachusetts)	<40	✓(4%)	✓	0/21 (0%) 1/14 (7%)
Youl et al. <sup>26</sup> 2002	Australia (Queensland)	15–19	nd	nd*	0/35 (0%) 2/147 (1%)
Berg et al. <sup>28</sup> 2004	Sweden	<20	nd	✓	1/6 (17%) 0/45 (0%)
Soufir et al. <sup>25</sup> 2004	France (Paris)	<25	nd	nd	0/21 (0%)
Nagore et al. <sup>27</sup> 2005	Spain (Valencia)	<31	✓(7.5%)	✓	2/6 (33%) 0/34 (0%)
Stratigos et al. <sup>30</sup> 2006	Greece (Athens)	≤ 40			1/18 (6%)
Debniak et al. <sup>24</sup> 2008	Poland	≤ 40	nd	nd	0/72 (0%)

CDKN2A, Cyclin-dependent kinase inhibitor 2A; MPM, multiple primary melanoma; nd, not determined.

\*Two CDKN2A carriers did not have family history of melanoma among first-degree relatives.

**Table VI**

## Candidacy for consideration of genetic testing

Low melanoma incidence area/population	Moderate to high melanoma incidence area/population
<ul style="list-style-type: none"> <li>• Two (synchronous or metachronous) primary melanomas in an individual and/or</li> <li>• Families with at least one invasive melanoma and one or more other diagnoses of melanoma and/or pancreatic cancers among first- or second-degree relatives on the same side of the family</li> </ul>	<ul style="list-style-type: none"> <li>• Three (synchronous or metachronous) primary melanomas in an individual and/or</li> <li>• Families with at least one invasive melanoma and two or more other diagnoses of invasive melanoma and/or pancreatic cancer among first- or second-degree relatives on the same side of the family</li> </ul>

This table refers to pathologically confirmed invasive melanoma.

**Table VII**

## Resources for finding genetic services and research opportunities

National Society of Genetic Counselors	<a href="http://www.nsgc.org">http://www.nsgc.org</a>	Find local cancer genetics resources
National Cancer Institute Cancer Genetics Service Directory	<a href="http://www.cancer.gov/search/geneticsservices/">http://www.cancer.gov/search/geneticsservices/</a>	Find local cancer genetics resources
GenoMEL: international melanoma genetics research consortium	<a href="http://www.genomel.org/">http://www.genomel.org/</a>	Information about familial melanoma and research opportunities
GeneTests	<a href="http://www.genetests.org">http://www.genetests.org</a>	Find laboratories offering clinical genetic testing services