Hereditary melanoma: Update on syndromes and management

Genetics of familial atypical multiple mole melanoma syndrome

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Learning objectives
After completing this learning activity, participants should be able to describe algorithms used to assess patients with possible familial atypical mole melanoma syndrome (FAMM); explain the genetic basis of FAMM predisposition, in light of novel susceptibility genes identified recently in genomic studies; discuss the current role of genetic counseling in patients with FAMM and their relatives; and determine when patient referral to other specialists for FAMM is appropriate.

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Malignant melanoma is considered the most lethal skin cancer if it is not detected and treated during its early stages. About 10% of melanoma patients report a family history of melanoma; however, individuals with features of true hereditary melanoma (ie, unilateral lineage, multigenerational, multiple primary lesions, and early onset of disease) are in fact quite rare. Although many new loci have been implicated in hereditary melanoma, *CDKN2A* mutations remain the most common. Familial melanoma in the presence of multiple atypical nevi should raise suspicion for a germline *CDKN2A* mutation. These patients have a high risk of developing multiple primary melanomas and internal organ malignancies, especially pancreatic cancer; therefore, a multidisciplinary approach is necessary in many cases. The value of dermoscopic examination and total body photography performed at regular intervals has been suggested by a number of studies, and should therefore be considered for these patients and their first-degree relatives. In addition, genetic counseling with the possibility of testing can be a valuable adjunct for familial melanoma patients. This must be performed with care, however, and only by qualified individuals trained in cancer risk analysis. (J Am Acad Dermatol 2016;74:395-407.)

Key words: *CDK4*; *CDKN2A*; familial melanoma syndromes; FAMMM; melanoma genetics; mixed cancer syndromes.

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GENERAL CONSIDERATIONS FOR HEREDITARY MELANOMA

Key point

- **Hereditary melanomas can appear as part of a familial melanoma syndrome or a mixed cancer syndrome**

Cutaneous malignant melanoma (CMM) can be highly lethal if it is not detected and treated during its early stages. The incidence of melanoma has increased in the past several decades. In developed countries, CMM is the sixth most common cancer, accounting for >47,000 deaths worldwide annually (45% occurring in Europe). The rise in incidence affects both young and older populations, while the global projected incidence of melanoma for the year 2025 is estimated to be 317,000 new cases compared to the 200,000 cases reported in 2008.[1]

About 7% to 15% of melanoma cases occur in patients with a family history of melanoma; however, this does not necessarily indicate that a single genetic mutation is being transmitted in those kindreds.[2] Most cases of familial melanoma are caused by shared sun exposure experiences among family members with susceptible skin types.[2] In aggregate, about 45% of familial melanomas are actually associated with germline mutations in *CDKN2A* or *CDK4*. There does not appear to be another major locus beyond *CDKN2A*, because the prevalence of the new melanoma predisposition genes are quite rare (see part II of this continuing medical education article). Although great strides have been made in identifying other novel cosegregating variants within melanoma kindreds, it is likely that many rare disease—causing mutations remain undiscovered.[3] The term mixed cancer syndrome (MCS) can be applied to familial conditions for which there is a high incidence of various cancers in general, including melanoma. In the past few years, melanomas have also been found to arise in families that are generally prone to specific patterns of malignancies. The term melanoma tumor syndrome might be more appropriate to discriminate it from hereditary melanoma, where the dominant cancer phenotype is that of CMM.

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (OMIM 155601) AND FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA—PANCREATIC CANCER (OMIM 606719) SYNDROMES

Key point

- **A positive association between melanoma, multiple nevi, pancreatic cancer, and *CDKN2A* mutations is now well established**

The first documented case of familial melanoma was reported by Norris[4] in 1820; his patient was a 59-year-old man with melanoma, a high total body nevus count, and a family history of melanoma. More than a century after Norris made his observations, Lynch and Krush[5] described familial atypical multiple mole melanoma (FAMMM) syndrome, which comprised an association between pancreatic cancer (PC), multiple nevi, and melanoma. Contemporaneously, Clark described a similar phenotype, B-K mole syndrome, consisting of familial melanoma in the setting of numerous atypical nevi.[6] In the early 1990s, several groups reported germline mutations in the cell cycle gene *p16* (now *CDKN2A*) among a subset of FAMMM kindreds.[7,8]

CLINICAL FEATURES OF FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

Key points

- **Patients suspected to have FAMMM present with multiple atypical nevi (>50) and have a positive personal or family history of melanoma**
- **Patients with FAMMM present with melanomas at a younger age and are at a higher risk to develop a second primary melanoma compared to the general population**
- **Patients with FAMMM may also develop cutaneous melanomas on normal skin in spite of the large number of atypical nevi at presentation**

FAMMM is a clinical phenotype comprised of numerous nevi (Fig 1, *A*), some atypical, and a family history of melanoma; some diagnostic elements of the FAMMM phenotype are outlined in Table I. Documenting a thorough family history of cancer, particularly melanoma, is of utmost importance because it is a critical element of FAMMM syndrome. Particular attention should be paid to the age at which CMM and other cancers (Table II) have been diagnosed in family members—as well as family skin phototype (ie, red hair and fair skin)—because these traits may be associated with higher disease risk.[9] In patients suspected of having FAMMM, careful examination of all nevi should be performed not only on the patient of interest but also their first- and second-degree relatives.

Nevi in patients with FAMMM are phenotypically diverse (Fig 1, *A*). It is not unusual to observe multiple nevi with marked atypia, some bearing a striking resemblance to melanoma, interspersed between numerous benign-looking nevi. Atypical nevi

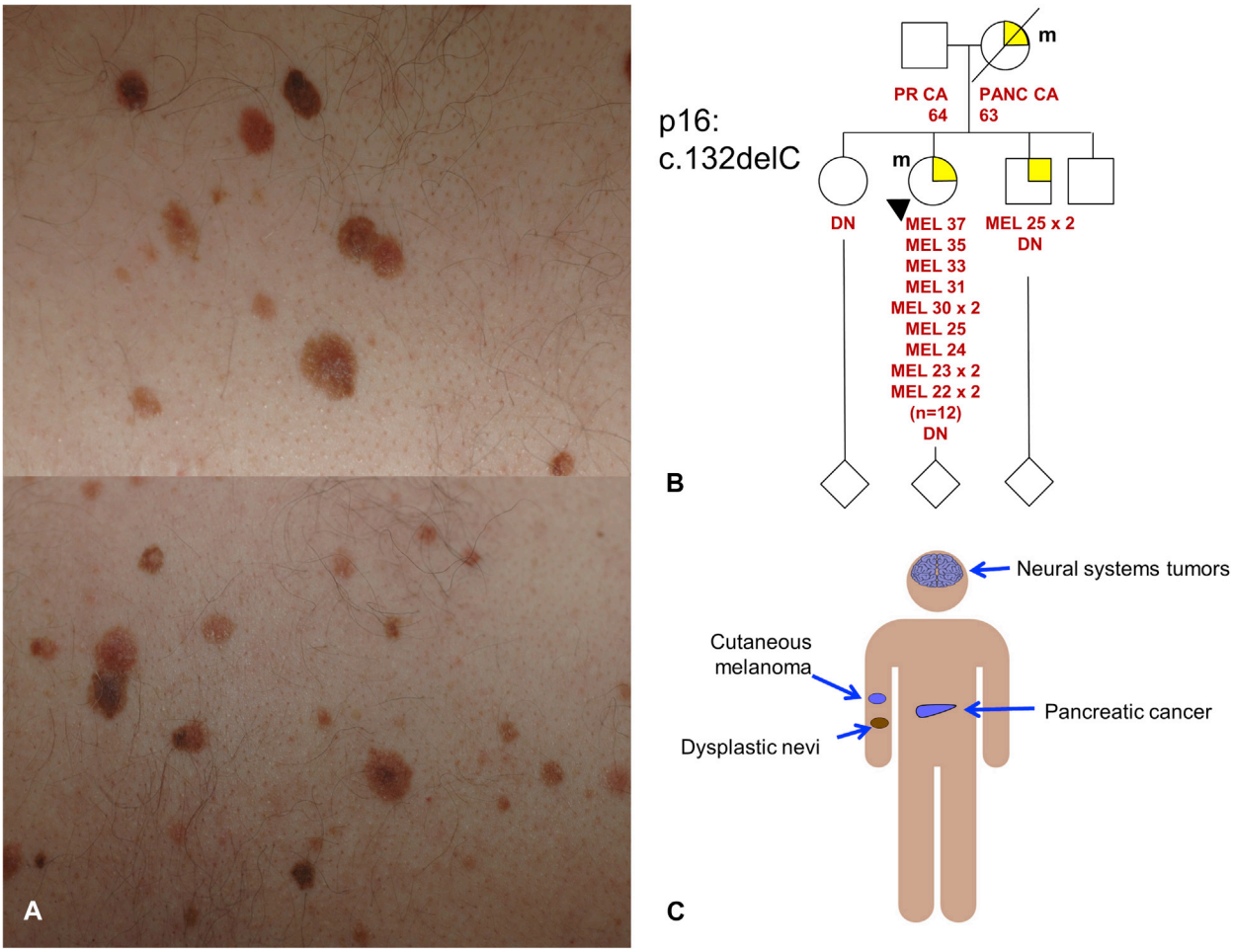

Fig 1. The familial atypical multiple mole melanoma (FAMMM) phenotype. **A**, Clinically atypical moles frequently associated with FAMMM syndrome. **B**, Pedigree of a FAMMM kindred showing multiple early onset cutaneous melanomas (proband and brother) and pancreatic cancer (PANC CA; mother). The patient and mother are carriers of a p16 mutation (m). **C**, Patients with FAMMM syndrome (in particular those with germline *CDKN2A* mutations) are at risk for cutaneous melanoma, pancreatic cancer, and neural systems tumors (melanoma-astrocytoma syndrome). *DN*, Dysplastic nevi; *MEL*, cutaneous melanoma; *PANC CA*, pancreatic cancer; *PR CA*, prostate cancer.

are more likely to undergo malignant transformation when compared to banal nevi; melanomas in patients with FAMMM, however, often develop on normal skin.[10,11]

While it is clear that patients with FAMMM syndrome have a dramatically increased risk of melanoma, it is less clear whether there are inherent differences between FAMMM-associated and sporadic melanomas. Patients with FAMMM seem to be more prone to developing superficial spreading and nodular melanomas,[12] which is interesting in light of other findings suggesting that *CDKN2A*-mutant CMMs are significantly less invasive (ie, with lower Clark levels) than *CDKN2A*—wild type CMMs.[13] No statistically significant differences in location and Breslow thickness have been reported between sporadic melanoma controls and patients with FAMMM. Sargen et al[14] have recently reported that *CDKN2A* mutation—positive CMMs tend to have histologic features that are compatible with superficial spreading melanomas, including higher pigmentation (P for trend = .02), increased pagetoid scatter (P for trend = .07), and a non—spindle cell morphology in the vertical growth phase. However, more information is required to establish specific histopathologic features indicative of a CMM from a *CDKN2A* mutation—positive patient. Gillgren et al[15] found that familial melanomas have a tendency to occur on the trunk more so than on the head and neck. Recent studies have shown similar rates of somatic *BRAF* and *NRAS* mutations in patients with or without germline

Table I. Criteria for the diagnosis of familial atypical multiple mole melanoma*

1. Cutaneous melanoma in ≥1 first- or second-degree relatives
2. High total body nevi count (>50) and multiple atypical nevi
3. Specific histologic features present in nevi, including: asymmetry, subepidermal fibroplasia, lentiginous melanocytic hyperplasia with spindle or epithelioid melanocytes, variable dermal lymphocyte infiltration, and the presence of "shouldering" phenomenon

*All criteria must be present to make a diagnosis.[58]

CDKN2A mutations. Zebary et al[16] reported that *BRAF* and *NRAS* mutations occurred in 43% and 11% of CMMs, respectively, in *CDKN2A* mutation carriers, compared to 39% and 14% of CMMs in non–*CDKN2A* mutation controls; similar findings were echoed by others.[17] The pattern of metastasis between patients with familial and sporadic melanoma does not appear to differ, so a distinct postmelanoma follow-up program is probably not necessary for patients with FAMMM.[18] However, as will be discussed below, the risk of PC among some patients with FAMMM does warrant special consideration.

An example of a typical FAMMM pedigree is shown in Fig 1, *B*. The proband presented with multiple atypical nevi (>200) and has had >10 histologically confirmed CMMs. Her mother developed PC at 63 years of age and died. Genetic testing revealed a single base pair deletion (c.132delC) that was shared by both the proband and the mother. The key elements of FAMMM are embodied in this pedigree: early age of onset (22 years of age), multiplicity of CMMs (n = 12), a family history of melanoma, dysplastic nevi, PC, and a documented deleterious cosegregating mutation on one side of the family.

THE GENETICS OF FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

Key points

- **The *CDKN2A* locus is the major recurrent source of germline mutagenesis in hereditary melanoma**
- **The prevalence of germline *CDKN2A* mutations in families with melanoma and *CDKN2A* mutation penetrance vary with geographic location**
- **Patients that harbor the mutation have a higher risk of developing melanoma; however, some evidence suggests that these CMMs may be less invasive than *CDKN2A*–wild type CMMs**

Table II. Malignancies (besides melanoma) reported with *CDKN2A* and *CDK4* mutations[3,20,21,38,59-61,69-71]

CDKN2A mutations	*CDK4* mutations
Uveal melanoma	—
Breast cancer	Breast cancer (Phyllodes tumor)
Ovarian tumors	Ovarian tumors
Cervical cancer	Cervical cancer
Endometrial cancer	—
Pancreatic cancer	Pancreatic cancer
Stomach cancer	Stomach cancer
Esophageal cancer	—
Colon cancer	Colon cancer
Lung cancer	Lung cancer
Leukemia	—
Lymphoma (Hodgkin)	Lymphoma
Brain/central nervous system tumors	—
Renal cell carcinoma	—
Urinary bladder carcinoma	—
Prostate cancer	Prostate cancer
Hepatic cancer	—
Sarcomas	—
Parotic gland tumors	—
Tonsillar tumors	—
Nasopharyngeal/laryngeal tumors	—
Tongue cancer	—

The dominant molecular pathway involved in FAMMM is shown in Fig 2. *CDKN2A* is located on chromosome 9p21.3, and its alterations are most commonly associated with FAMMM syndrome. Typically, germline mutations of *CDKN2A* seen in CMM and PC-prone kindreds are missense or nonsense mutations that impair the inhibitory functions of p16 and/or p14ARF. *CDKN2A* is comprised of 4 exons (1α, 1β, 2, and 3) that are used to encode for 2 proteins: p16 (1α, 2, and 3) and p14ARF (exons 1β, 2, and 3). p16 inhibits cyclin-dependent kinase 4 (CDK4) and CDK6, thereby preventing the phosphorylation of retinoblastoma protein (RB1). A hypophosphorylated RB1 molecule sequesters and prevents the transcription factor E2F1 from inducing S phase genes and triggering G_1 to S transition. On the other hand, p14ARF antagonizes HDM2, which ubiquitinates the tumor suppressor p53, thereby condemning p53 for proteasomal degradation.[19] Accelerated destruction of p53 abolishes the normal DNA damage and G2 checkpoint responses.[19] Therefore, inactivation of the *CDKN2A* locus enhances proliferation and reduces apoptosis. The prevalence of germline *CDKN2A* mutations has been found to vary with

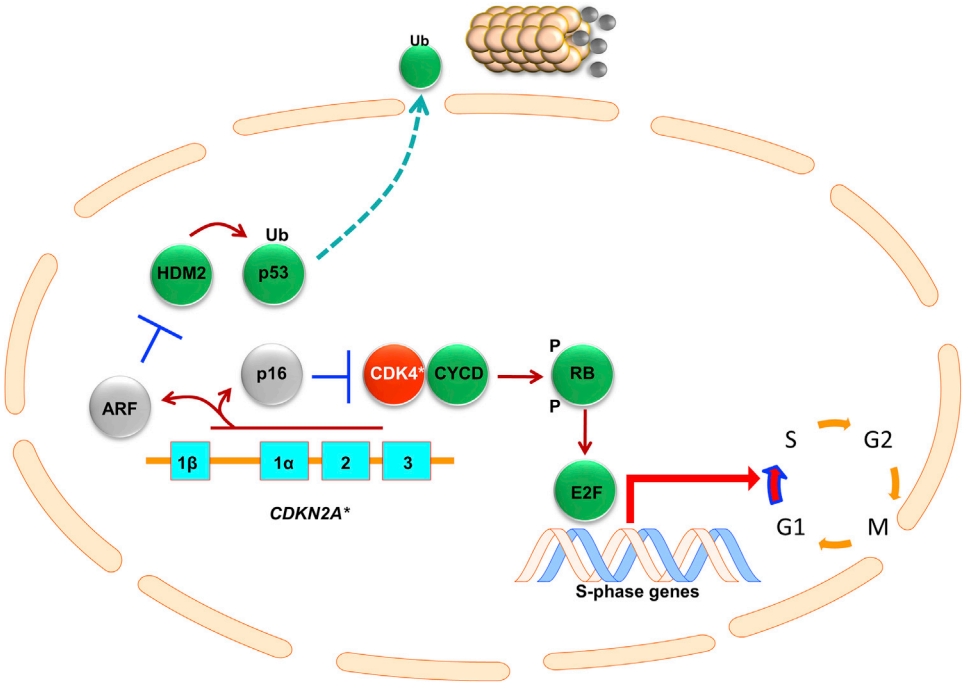

Fig 2. Pathways linked to familial atypical multiple mole melanoma (FAMMM) predisposition. *CDKN2A* is comprised of 4 exons (ie, 1α, 1β, 2, and 3). Exons 1α, 2, and 3 encode for p16; exons 1β, 2, and 3 encode for p14ARF (ARF). p16 inhibits CDK4, which, without p16, binds cyclin D (CYCD) and phosphorylates (P) the retinoblastoma protein (RB). This in turn releases E2F transcription factors, which induces G_1 phase genes and triggers G_1 to S cell cycle transition. p14ARF inhibits HDM2, which normally ubiquitinates (Ub) p53, condemning it to destruction by the proteasome. Mutations in *CDKN2A* (*CDKN2A**) leads to the loss of p14ARF and p16 function (*gray*) while mutations in *CDK4* (*CDK4**) renders CDK4 resistant to p16 inhibition, thereby activating CDK4 activity (*red*); nonmutated genes are shown in *green*.

geography and the family context.[3,20,21] In a metaanalysis by Goldstein et al,[22] 39% of families (with ≥3 affected family members) had germline *CDKN2A* mutations, ranging from 20% (32/162) in Australia to 45% (29/65) in North America to 57% (89/157) in Europe. Similarly, in a study of Greek families, Nikolaou et al[23] reported that 22% of familial melanoma cases and 57% of individuals with multiple primary melanomas carried a *CDKN2A* mutation. When melanoma cases were ascertained independent of family history, there was a much lower rate of mutation. The frequency of *CDKN2A* mutations in patients with a single primary melanoma or multiple primary melanomas were 1.2% and 2.9%, respectively.[24] The likely explanation is that other coinherited modifiers (eg, additional risks conferring variant mutations) exist in a pedigree or that select members of some families share extremely high levels of sun exposure histories.

CDKN2A mutation penetrance (or the likelihood of developing melanoma over time) also varies by geography. The estimated penetrance rates are 30% to 91%, 50% to 76%, and 13% to 58% among patients 50 to 80 years of age in Australia, the United States, and Europe, respectively. These broad risk differences could also be attributed to different sun exposure patterns and the presence of other genetic risk factors in the families.[25,26] For instance, coinheritance of melanocortin 1 receptor (MC1R) variants and specific interleukin-9 and glutathione S-transferase theta 1 variants have been described as risk modifiers for *CDKN2A* mutation penetrance.[9,27,28] In a population-based study, Begg et al[29] found that the estimated risks of CMM among *CDKN2A* mutation carriers were 14%, 24%, and 28% by 50, 70, and 80 years of age, respectively; the lower risk estimates may reflect the lack of other melanoma risk variants in these sporadic cases.

Various studies have also shown a much lower median age of onset of CMM in patients from germline *CDKN2A* mutation families (33-45 years of age) compared to patients without a *CDKN2A* mutation (53-61 years of age); this trend remains largely consistent regardless of geographic region.[3,30,31] There are reports of *CDKN2A* kindreds where CMM

has occurred in the early teens and twenties.[20] As would be expected, the increased risk of CMM in these patients does not diminish with their first diagnosis because they also have a much higher 5-year cumulative incidence of a second melanoma compared to mutation-negative controls (23.4% and 2.3%, respectively).[32]

Germline *CDK4* mutations have also been described in patients with FAMMM syndrome, albeit rarely.[33-35] As alluded to above, CDK4, which is the target for p16 inhibition, plays an important role in normal cell cycle progression (Fig 2). The oncogenic *CDK4* mutations described in affected families translates into a substitution of arginine-24, which disrupts p16 binding.[35] Puntervoll et al[36] have reported an increased CMM risk in 17 families from 8 different countries that harbor *CDK4* mutations. Of 103 patients with 1 CMM, 41.7% developed a second primary CMM and 21.1% developed CMM before 30 years of age (median, 39 years of age). In addition, 70% to 75% of patients had multiple atypical nevi, which was considered to be a modifier for CMM risk given that these patients developed CMMs at a younger age.[36] This study investigated the clinical phenotype of these *CDK4*-mutant melanoma families and determined that it is indistinguishable from the more well characterized *CDKN2A*-mutant melanoma phenotype (ie, a high burden of atypical nevi, early age of disease onset, and a predilection for multiple primary melanoma).[36] Because p16 directly interacts with CDK4, it is not surprising that the 2 phenotypes overlap significantly; in essence, the same biochemical event (increased RB1 phosphorylation) occurs with either mutation (Fig 2).

MELANOMA ASTROCYTOMA SYNDROME (OMIM 155755)

Melanoma astrocytoma syndrome (MAS) is a variant of FAMMM that may be more linked to the loss of $p14^{ARF}$ function.[37] Larger scale chromosome 9p21 alterations (including deletions involving the *CDKN2A/CDKN2B/CDKN2BAS* gene cluster up to the *MLLT3* gene) have been described in some isolated cases.[38-41] Kaufman et al[42] described this syndrome in 1993 when they reported concurrent CMMs and multiple types of nervous system tumors (NSTs) in 8 members of a family over 3 generations. Later, Azizi et al[43] reported that 17 individuals with CMM, among 15 families, had ≥1 additional relatives with tumors of the nervous system. Conflicting data exist on this rare syndrome. Patients are generally young (<30 years of age) and can develop CMM either before or after NSTs.[38-40,44] A positive association between radiotherapy for the NSTs and the incidence of CMM in these patients has been proposed but remains unsubstantiated.[41]

MANAGEMENT OF PATIENTS WITH FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME, INCLUDING *CDKN2A* CARRIERS

Key points

- **Patients with FAMMM syndrome should undergo total body skin examination and dermoscopic examination of clinically atypical nevi with possible total body photography every 3 to 6 months**
- **Children from families with FAMMM may begin screening in late adolescence**
- **Because of the reported association between *CDKN2A* mutations and internal organ malignancies (specifically pancreatic cancer), all patients suspected to harbor the mutation should be referred to a specialist for appropriate screening**

The significant risk of melanoma inherent to FAMMM syndrome means that these patients need heightened dermatologic surveillance. Some general management considerations for patients with hereditary syndromes are presented in Table III. Given the rarity of melanoma syndromes, most data regarding follow-up recommendations are based on small studies or expert opinion. Given the plethora of clinically atypical moles, dermoscopy is an important tool in approaching patients with FAMMM. It is also prudent for children from families with FAMMM syndrome to undergo routine skin examinations beginning in late adolescence (level of evidence, IV). This recommendation is supported by observational studies showing that patients with FAMMM tend to develop melanomas at much younger ages. Surveillance of patients with FAMMM should entail an extensive baseline total body skin examination (TBSE), including the scalp, oral mucosa, genital area, and nails. Most authors suggest that screening performed at 6-month intervals is adequate,[10,20,45,46] although formal prospective trials of outcome do not exist (level of evidence, IV). Haenssle et al[47] have reported that patients with FAMMM may develop up to 1 new melanoma for every 3 years of follow-up and suggest that 3-month interval examinations may be more appropriate. There are no current data supporting the idea that 3-month interval examinations are superior to 6-month interval examinations regarding patient outcomes (level of evidence, IV). Nevi should be checked for any changes in morphology (eg, color or symmetry) and size. Because these patients may

Table III. Recommendations for patients with suspected hereditary melanoma[3,70,71]

Obtain a thorough medical history from the patient, including:
Sun exposure patterns
Personal history of MM or other type of skin cancer (age at diagnosis should be noted)
History of internal organ malignancies
Age at diagnosis should be noted
Should be updated annually
Special interest: pancreatic, renal, breast, or other rare types of cancer
Family medical history should include:
Relatives with multiple and/or atypical nevi
Sun exposure patterns
Fitzpatrick skin type/clinical phenotype (eg, red hair, etc)
Family history of MM (first- and second-degree relatives)
No. of primary MMs and age at diagnosis should be noted
Family history of internal organ malignancies (3-generation pedigree)
Age at diagnosis should be noted
Should be updated annually
Special interest: pancreatic, ocular melanoma, mesothelioma, renal, breast, or other rare types of cancer
In cases of positive personal or family history of MM or other cancer, relevant medical information should be obtained (eg, histology reports, medical reports, etc)
Physical examination
Fitzpatrick skin type/clinical phenotype (ie, red hair, etc)
No. of banal and atypical nevi (<50 or >50)
Signs of solar elastosis (eg, lentigines, actinic keratoses, etc.)
Presence of multiple "Spitzoid" nevi or lesions resembling dermal nevi
Special attention should be given to examining for atypical features in clinical appearance (eg, the presence of trichilemmomas, various types of minor malformations, etc)
Dermoscopy should be applied to all nevi
Clinical recommendations
In general, patients and families should be educated in the importance of skin cancer prevention measures (eg, sunscreen, sun avoidance, abstaining from tanning beds, etc)
If patient exhibits multiple banal nevi and has negative personal or family history for MM and/or other cancers:
Dermoscopic examination should be repeated at least annually
Total body photography can be considered
If patient exhibits multiple and/or atypical nevi or has positive personal or family history for MM and/or other cancers or if patient exhibits lesions resembling MBAITs:
Dermoscopic examination should be repeated every 3 to 6 months depending on the clinical phenotype
Total body photography can be considered at 6-month intervals
Recommend dermatologic evaluation all first- and second-degree relatives
If suspicious lesions present (dysplastic nevi or MBAITs), selection and removal should be made for histopathologic examination
If rapidly changing nevi or new lesions appear, surgical removal and histopathologic examination should be recommended to all patients
If melanoma cancer syndrome suspected, patient should be referred for genetic counseling and possible work-up of internal malignancies

MBAIT, Melanocytic BAP1-mutated atypical intradermal tumor; *MM*, malignant melanoma.

have many atypical nevi, lesions that stand out, exhibiting the so called "ugly duckling sign," may warrant special attention. Beyond a thorough TBSE, the use of more advanced techniques, such as total body photography (TBP) and sequential digital dermoscopy imaging (SDDI) for patients at extreme risk for melanoma has also been suggested[48]—although the adoption of these procedures may be limited by practice logistics. Moloney et al[49] reported that in 311 high-risk patients evaluated at 6-month intervals, 38% of postbaseline melanomas were detected using TBP and 39% with SDDI. Importantly, these tools allowed for earlier detection and treatment, both of which are known to impact melanoma outcome.[49] In the study by Moloney et al,[49] most of the excised melanomas were categorized as in situ tumors, and the ratio of benign to malignant excised lesions was reported to be

1.6:1. In addition, Rademaker and Oakley[50] have reported that the melanomas diagnosed in patients after TBP and SDDI examination were thinner compared to those diagnosed with clinical inspection (69% with a Breslow thickness <0.75 mm compared to 52%; $P = .0216$). Previous studies have also advocated the benefit of TBP in earlier diagnosis of melanoma.[51,52] An interesting point, though, is that these studies do not report patient outcomes, and their impact on patient survival is therefore unknown. In addition, the recommendations supported by those studies depend on the notion that earlier recognition of melanomas may lead to overall better patient outcome. A small number of studies have reported evidence to support this.[53] However, the exact frequency of follow up (eg, at 3-month, 6-month, or 1-year intervals) is not clear. When planning follow-up visits for high risk patients, 2 factors must be weighed: (1) the psychological burden of having to be examined at specific intervals and (2) the cost effectiveness of this process. Risser et al[54] reported that the number of biopsy specimens obtained from patients undergoing TBP and clinical inspection was the same. Therefore, the cost effectiveness of TBP use is questionable.[54] It must be mentioned, however, that patients selected for TBP belong to high-risk groups. In addition, the decision to obtain a biopsy specimen of a suspicious lesion after TBSE, is primarily related to nevus morphology at the time of examination, while TBP relates to morphologic changes over time (ie, morphology changing from a previous examination).[55] Therefore, in theory, melanomas could be diagnosed earlier if TBP were used. In a recent study by Watts et al,[56] a cost analysis of the surveillance of high-risk melanoma patients was performed. Watts et al[56] reached the conclusion that although these patients are indeed more costly with regard to follow-up, it is overall cheaper to screen than having to later treat a stage IV melanoma. It is important, however, to find an ideal position where cost and patient benefit are perfectly balanced.[56] Patients must be encouraged and taught to perform self-examinations at regular intervals either alone or with the assistance of a spouse or relative. Routine sun protective behaviors must be reinforced at every visit. Screening of all family members of FAMMM kindreds should be encouraged. Preemptive removal of observable stable or benign-appearing nevi is not recommended because the practice has not been shown to reduce melanoma risk meaningfully and is associated with increased morbidity and costs (level of evidence, IV). Isolated lesions that are visually inaccessible to the patient, such as those on the mid-lower back or scalp, may be removed prophylactically.

The association between PC and FAMMM syndrome is well documented, with an estimated risk 13 to 22 times higher than that of the average population; this risk increases to 38-fold in *CDKN2A*-mutant FAMMM patients.[20,57,58] PC seems to be the second most commonly observed malignancy in patients with FAMMM who harbor a *CDKN2A* mutation.[3,59] In a study by Goldstein et al,[3] PC was observed in 28% of *CDKN2A*-mutant families compared to only 6% of *CDKN2A*−wild type families. Conversely, 74% of families with PC harbored a *CDKN2A* mutation compared to 33% of "melanoma only" families.[3] Another study estimated that 17% of *CDKN2A*-mutant patients would develop PC by 75 years of age.[60] In general, the mean age of onset for PC ranges from 65 to 71 years of age.[20,45,61] It is unclear whether the age of onset for PC is lower for patients with FAMMM compared to sporadic cases. Various studies on this topic have reported mixed data, with only 1 study by James et al[62] showing a statistically significant difference in age of PC diagnosis between the 2 groups. Of note, smoking was a strong confounding factor in this study.[61,62] Evidence regarding the association of FAMMM and other cancers is more equivocal. Associations with digestive tract, breast, and respiratory tract cancer, among others, have been described; however, *CDKN2A* mutation status does not seem to influence the age of onset in these cancers.[20,59,60,63]

The role of genetic testing for hereditary melanoma has been somewhat controversial because dermatologic management of individuals with familial melanoma (ie, surveillance and sun protection education) rarely requires knowledge of the patient's *CDKN2A* status. However, as alluded to above, the melanoma phenotype may be a window to a latent PC risk. Therefore, a basic understanding of genetic risk assessment and counseling is worthwhile, but referral to a genetic counselor for more formal evaluation is preferred, given the time constraints of a busy dermatologic practice. The following are just a sampling of some fundamental discussion points (also outlined in Fig 3).

Does my patient have hereditary melanoma? The individual seeking counseling is known as the proband. Currently, there are no firm criteria that would allow easy diagnosis of a proband with hereditary melanoma. Some have adopted the rule of 3s[64]—ie, 1 individual with invasive CMM along with 2 additional members with either CMM or PC on 1

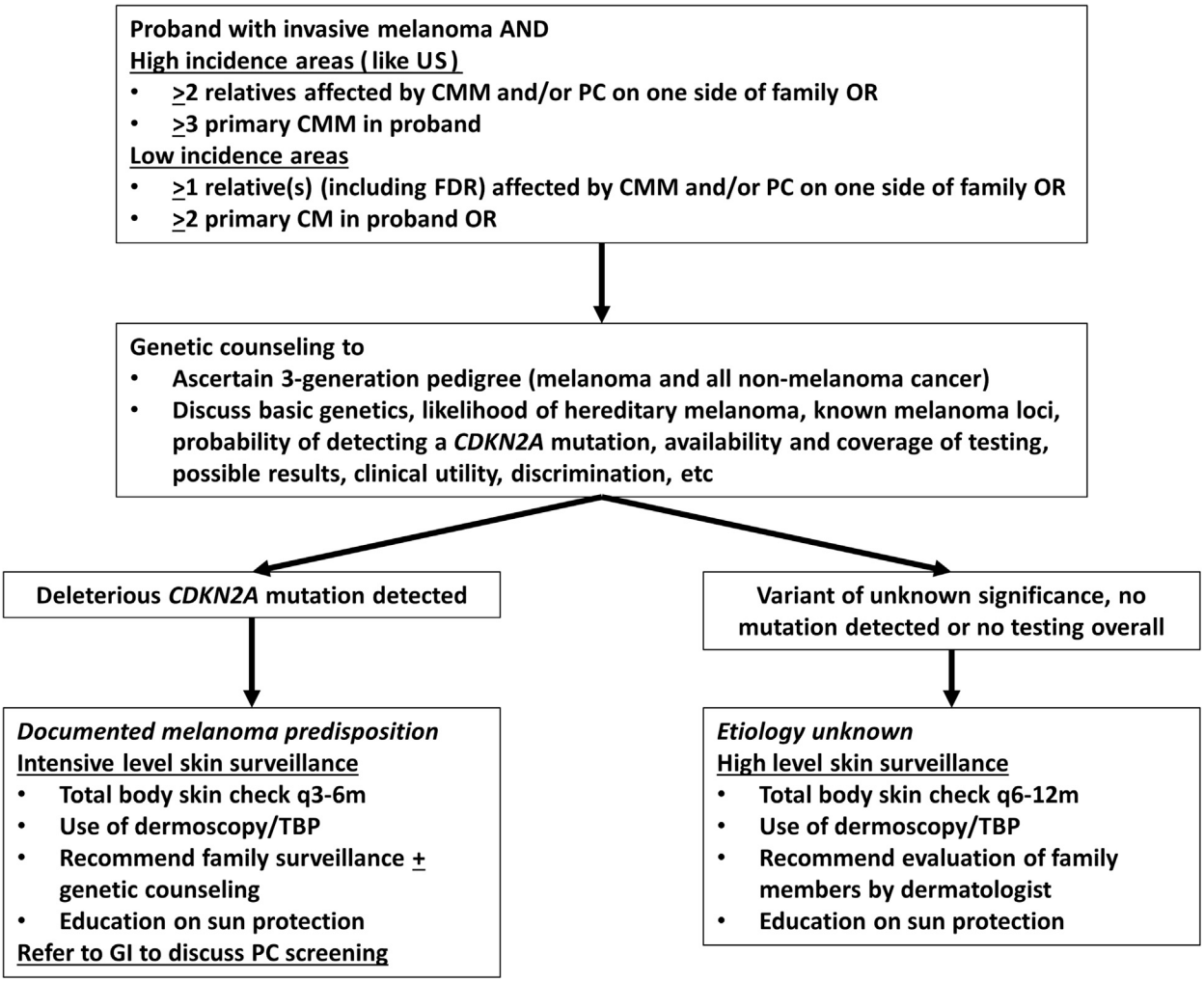

Fig 3. Genetic counseling algorithm for patients with familial atypical multiple mole melanoma (FAMMM). Patients with a personal history of melanoma may be considered for genetic counseling if certain criteria from high and low incidence areas are met. The United States and Australia are high incidence areas; England and Greece are low incidence areas. A genetic counselor would ascertain a 3-generation pedigree and discuss the likelihood of hereditary melanoma, the molecular genetics related to familial melanoma risk, testing options, costs, risks of discrimination, and possible test results. If the patient undergoes *CDKN2A* testing and a deleterious mutation is detected, intensive skin surveillance is recommended, along with a referral to a gastrointestinal specialist for discussion of pancreatic cancer screening. If testing is not pursued or if a normal or variant of unknown significance result is returned, the etiology of the familial pattern remains unknown. Given the family history, the patient is considered high risk and should undergo high level skin surveillance. *CMM*, Cutaneous malignant melanoma; *FDR*, first degree relative; *PC*, pancreatic cancer; *TBP*, total body photography.

side of the family *or* 1 individual with 3 primary CMMs. One caveat is that severely photodamaged patients may develop 3 melanomas, especially later in life as sun damage accumulates. One perhaps slightly more stringent practical criterion would be a 3 by 40 modification—that is, individuals with 3 CMMs diagnosed before 40 years of age may be more likely to be under genetic influences.

The benefit of formal genetic counseling is the analysis of an in-depth ≥3-generation pedigree. Although dermatologic charts may document a family history of melanoma, other critical information may not be ascertained. For instance, 3 melanoma cases in a small pedigree is different than 3 melanoma cases in a large extensive pedigree. The age of onset, current age, and other concurrent nonmelanoma

cancers all contribute to the final interpretation of hereditary melanoma or mixed cancer syndrome (MCS). The presence of PC in a kindred is also important in assessing genetic risk. Formal training is typically required for accurate pedigree acquisition, and a full family history is essential for accurate risk assessment.

What are the possible genes to be tested? To understand genetic testing, fundamental principles of genetics must first be reviewed. Hereditary melanoma, like nearly all cancer syndromes—with the exception of xeroderma pigmentosum—is autosomal dominant.[19] Therefore, there is a 50% chance of sharing a mutation among first-degree relatives. The major locus to be considered in a patient with FAMMM syndrome is *CDKN2A*, although a small percentage (<1%) of patients with FAMMM harbor *CDK4* mutations. In addition, there are likely many other unknown predisposing loci. Therefore, the first important message is that *CDKN2A* will be normal in a majority of individuals suspected of having FAMMM, especially in areas of high melanoma incidence, such as the United States. This is because there are environmental factors and other genetic factors (whether they be dominant genes or polygenetic factors) that have not been discovered.

Who is likely to be a carrier? Phenotypically, the presence of multiple atypical nevi is not enough for the diagnosis of FAMMM, although it has been published that their presence in family members correlates with a 3-fold higher likelihood of carrying a genetic mutation.[33] It is important to note, however, that the presence of atypical nevi is not a carrier signature, because noncarriers, even in *CDKN2A*-mutated families, can have multiple atypical moles. Therefore, there is a complex relationship between melanomas and atypical, or dysplastic, nevi. Two statistical models have been developed in order to assist in identifying *CDKN2A* mutation–bearing individuals or families. MELPREDICT is based on logistic regression, while MelaPRO (which can be obtained as part of CancerGene [https://www4.utsouthwestern.edu/breasthealth/cagene/]) incorporates 3 different penetrance models (ie, the Bayes–Mendel algorithm).[31,32] These models provide a probability of mutation carriage for any given proband (MELPREDICT) or family member (MelaPRO) based on the family cancer pattern. Cancer risk counselors usually have access to MelaPRO as other similar algorithms, such as BRCAPRO for determining BRCA1/2 carrier risk, have been part of the counseling practice.

What are the possible results? The identification of a deleterious *CDKN2A* mutation (a "positive result") establishes a disease-causing mutation in the kindred. First-degree relatives (ie, parents, siblings, and children) will have a 50% chance of harboring the same mutation and risk. Penetrance is never 100%, and therefore there will be carriers in the family who may not develop melanoma although the risk will be substantially higher than population rates. If unaffected relatives undergo subsequent testing and are found to have a normal *CDKN2A*, their risks may still elevated because of other risk factors, such as an MC1R variant or excessive sun exposure. However, a noncarrier will have a substantially lower risk of malignancy than a carrier—although it may not return to general population risk levels.

In an affected patient with FAMMM who returns a normal *CDKN2A* result (a "negative result") or a variant of unknown significance, little advice can be offered. The patient may harbor a high-risk mutation in an undiscovered gene, and therefore the risk is incalculable. These patients should continue to undergo the same dermatologic surveillance. For a nonaffected member of a FAMMM kindred, there is no role for genetic testing without concomitant evaluation of at least 1 if not 2 other affected relatives from the same family. In short, the designation of carrier vs. noncarrier can only be made if the familial mutation can be identified.

How can I use the results? *CDKN2A* mutation carriers should be referred to a health care provider familiar with PC screening[65] (level of evidence, IV) in addition to ongoing intensive dermatologic surveillance at 3- to 6-month intervals with the possible use of TBP. Relatives of *CDKN2A* mutation carriers, regardless of genetic test results, should continue to be under careful dermatologic surveillance and strict sun protection.

No low-cost, criterion standard screening approach exists for PC, although studies in high-risk cohorts have shown that early, preinvasive pancreatic lesions can be detected with screening programs and then treated preemptively.[66] Although PC screening lies outside the purview of dermatologists, familiarity with the available screening modalities is useful. Currently, these include endoscopic retrograde cholangiopancreatography (ERCP), which is able to detect small tumors but has associated complications because of its invasive nature; computed tomography and magnetic resonance imaging, which are less sensitive but also less invasive; and endoscopic ultrasound (EUS), which is the most sensitive and safe option at this time[67] (level of evidence, IV). Some authors suggest that screening should start at 50 years of age or 10 years earlier than the PC age of

onset in the family, but no specific consensus exists for a specific protocol in cancer screening of *CDKN2A* mutation carriers.[13] Patients with FAMMM who forego testing, test negative for *CDKN2A*, or who have a variant of unknown significance should remain under careful dermatologic surveillance, but PC screening is probably not necessary.

How will the patient use the results? Families in general share exposure risks (eg, sunny vacations together), risk-conferring traits (eg, sun-sensitive skin or blue eyes), and disease-causing variants (eg, *CDKN2A* mutation). The lack of a high-risk mutation in *CDKN2A* should not empower patients to abandon sun protective practices. Parents should also recognize that their children will continue to need strict sun protection even in the face of a normal *CDKN2A*. "True negatives," however, would not need to undergo PC screening. There are various psychological benefits from undergoing genetic testing in *CDKN2A* families, including decreased anxiety.[68]

Will my patient experience genetic discrimination? In 2008, the US Government passed the Genetic Information Nondiscrimination Act (GINA; http://www.ginahelp.org) which protects all individuals from health and employment discrimination based on genetic information. The GINA went into effect in 2009 and provides comprehensive protection against genetic discrimination for all Americans. Under GINA, it is against the law for most health insurers to use genetic test results or family history information as a preexisting condition. In addition, under the GINA law, most health insurers cannot use genetic information to make decisions regarding eligibility, premiums, underwriting, or coverage. It is also against the law for employers with ≥15 employees to use genetic information in hiring, firing, promotion, or other employment decisions. GINA does not protect against discrimination from life insurance, disability insurance, or long-term care insurance companies. GINA's protections do not apply to the US military or employees of the federal government who get care through the Federal Employees Health Benefits Plans; however, these groups have their own policies in place that may protect their members from insurance discrimination. For more information about the protections offered by GINA, visit www.ginahelp.org.

In conclusion, malignant melanoma pathogenesis is multifactorial and complicated. However, hereditary cancer syndromes, such as FAMMM, provide excellent genetic models for studies that may increase early detection rates and improve existing prevention and management protocols. Patients with a high nevus count and multiple atypical nevi should always be asked about personal or family history of melanoma or other internal organ cancer. Considering that ≤10% of melanomas may be familial, increased physician awareness can lead to faster diagnosis of melanomas and, through patient education, to improved preventive behaviors.

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