The Role of Genetics in Malignant Melanoma

A Comprehensive Review

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KEYWORDS

• Cutaneous malignancy • Malignant melanoma • Familial melanoma syndrome
• Melanoma genetics • Germline mutation • Somatic mutation
• Genetic screening guidelines • Polygenic risk scoring

KEY POINTS

- Most patients, greater than 80%, diagnosed with cutaneous malignant melanoma result from somatic genetic mutations within BRAF, KRAS, or c-KIT.
- Familial melanoma syndrome represents less than 15% of patients with cutaneous melanoma and within this subset of patients, only 45% have an identifiable associated germline mutation.
- Several inheritable gene mutations are implicated in the development of melanoma dominant syndromes including cyclin-dependent kinase inhibitor 2A, cyclin-dependent kinase 4, BRCA1-associated protein-1, telomerase reverse transcriptase, protection of telomeres 1, adrenocortical dysplasia protein/TERF2IP, and ataxia-telangiectasia mutated.
- Genetic screening guidelines are currently dictated by the *rule of twos, threes, fours* based on the disease prevalence of sporadic melanoma within the region.

INTRODUCTION

Cutaneous malignancies represent one of the most frequently diagnosed cancers in the Western world.[1] Among these, malignant melanoma (MM) is the most lethal form despite being less common than basal or squamous cell carcinoma.[1] The global distribution of melanoma correlates strongly with ultraviolet (UV) radiation intensity, reinforcing UV exposure as a major etiologic driver of cutaneous malignancy in combination with acquired genetic factors.[2] The disproportionate mortality associated with melanoma has led to its prominence in contemporary oncologic and genomic research to promote early recognition, diagnosis, and treatment.

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Abbreviations	
ACD	adrenocortical dysplasia protein
BAP1	BRCA1-associated protein-1
c-KIT	cellular KIT
CDK4	cyclin-dependent kinase 4
CDKN2A	cyclin-dependent kinase inhibitor 2A
FANCI	Fanconi anemia complementation group I
FMS	familial melanoma syndrome
MAPK	mitogen-activated protein kinase
MM	malignant melanoma
NRAS	neuroblastoma RAS
RB	retinoblastoma
SNP	single nucleotide polymorphism
TERF2IP	telomeric repeat-binding factor 2 interacting protein
TERT	telomerase reverse transcriptase
UV	ultraviolet

Most melanoma cases arise sporadically. Approximately 7% to 15% of patients exhibit a hereditary predisposition, constituting the familial melanoma subset.[3,4] Familial melanoma syndrome (FMS) is defined as 2 first-degree relatives or 3 or more first- and second-degree relatives on the same side of a family who all develop melanoma.[5] The concept of *melanoma-dominant* and *melanoma-subordinate* syndromes provides further granularity in characterizing FMS hereditary predisposition.[6] Individuals with melanoma-dominant syndromes fulfill formal criteria for FMS and present with multiple primary melanomas with other malignancies driven by the same germline mutation being less prevalent. Conversely, melanoma-subordinate syndromes describe patients whose germline mutation predisposes to melanoma among other cancers, but in whom nonmelanoma malignancies predominate clinically.

Within the population of FMS patients, there is an even smaller subpopulation of individuals who harbor a specific, identified gene mutation (45%) as noted in **Table 1**.[3,4] The remaining 55% of individuals who exhibit FMS do not have an identified germline genetic mutation on current algorithms. This review aims to collate information on high- and medium-penetrance germline mutations involved in the development of FMS while also exploring the genetic evolution of melanoma lesions, the role that inconsistencies in global screening thresholds and the emergence of polygenetic risk stratification (PRS) will play in future genetic screening recommendations.

Major Somatic Genetic Mutations

Melanoma often arises from a clinically identifiable precursor lesion that evolved from normal melanocytes through a staged morphologic and molecular progression.[7] This transformation occurs through accumulation of somatic mutations in a well-defined fashion, analogous to the stepwise progression observed in other malignancies. Although most pre-existing melanocytic lesions (30%–50%) will remain stable or regress, a small subset undergo malignant transformation following an initial oncogenic insult.[8] UV radiation is the principle environmental driver typically inducing a driver gain of function point mutation within v-Raf murine sarcoma viral oncogene homolog B1(BRAF) to initiate oncogenic transformation.[7,9] Subsequent genetic alterations often involve additional components of the mitogen-activated protein kinase (MAPK) signaling cascade pathway including mutations affecting neuroblastoma RAS (NRAS) viral oncogene homolog.[7,8] The MAPK signaling cascade is critical for regulating cellular proliferation, differentiation, and survival.[8] As these alterations

Table 1
Germline genetic mutation overview

Gene	Function/Pathway	Penetrance/Frequency	Histopathology/Notes	Other Associated Malignancies
CDKN2A	Tumor suppressor; regulates cellular senescence	20%–40% of FMS cases, ~65-fold increase risk melanoma	Similar to sporadic melanoma	Pancreas, mesothelioma, renal cell carcinoma, astrocytoma
CDK4	Promotes G1 → S phase via RB protein phosphorylation	Rare, ~74% lifetime risk of melanoma	Similar to sporadic melanoma	Breast, pancreas, ovarian, cervical, stomach
BAP1	Deubiquitinating enzyme; regulates DNA repair, apoptosis, cell cycle	~1% of cutaneous melanoma; 3% of uveal melanoma	No histopathologic predilection noted	Uveal melanoma, basal cell carcinoma malignant mesothelioma, renal cell carcinoma
TERT	Telomerase catalytic subunit; telomere length regulation	High penetrance, ~1% of FMS cases	Associated with superficial spreading and nodular melanoma	Bladder, colon, prostate, testicular, breast, kidney, CNS tumors
POT1	Shelterin complex; telomere protection	0.6%–3.8% depending on population	Spitzoid morphology	Angiosarcoma, glioma, chronic lymphocytic leukemia, thyroid, colorectal
ACD/TERF2IP	Shelterin complex; telomere protection	High penetrance	Superficial spreading or lentigo meligna at a young age, occasional spitzoid morphology	B cell lymphomas, esophagus, breast, lung, kidney, cervical, bladder, colon, prostate
ATM	DNA damage response kinase; double-strand break repair	Low-to-moderate penetrance, 2–3 × lifetime risk of melanoma	No histopathologic predilection noted	Breast, pancreas, prostate, stomach, ovarian, colorectal
FANCI	Fanconi anemia pathway; DNA repair	Novel likely pathogenic variants identified in small cohorts	Uncertain; more studies needed	Ovarian

accumulate, melanocytic lesions progress along a continuum from benign nevi to melanoma in situ and ultimately invasive lesions.[8]

BRAF

In Western melanoma populations, BRAF mutations account for approximately 50% to 60% of all somatic genetic alterations, with more than 90% occurring at codon 600 within exon 15 as a substitution of glutamic acid for valine (V600 E).[9,10] The prevalence of this mutation demonstrates an inverse relationship with patient age, occurring more frequently in younger patient and rapidly declining in those of advance age.[9] *BRAF* encodes a serine–threonine kinase that functions as a key regulator within the MAPK signaling pathway. Mutations in *BRAF* result in constitutive MAPK pathway activation, promoting uncontrolled cellular proliferation independent of upstream RAS-mediated signaling.[9,11] Given its central role in melanoma pathogenesis, substantial effort has been directed toward developing reliable diagnostic assays, predictive biomarkers, and targeted therapies aimed at exploiting BRAF-driven oncogenesis.

Neuroblastoma RAS

Mutations in NRAS represent the second most common somatic driver genetic mutation in cutaneous melanoma, occurring in approximately 15% to 25% of cases.[12,13] NRAS encodes a small GTPase that functions upstream of the MAPK and PI3K signaling pathways, acting as a molecular switch to cellular proliferation, differentiation, and survival. Activating mutations within NRAS commonly affect codon 61 at exon 2 or 3 leading to constitutive activation of MAPK independent of extracellular growth signals, thereby promoting melanocyte proliferation and oncogenic progression.[12] Substitutions at codons 12 and 13 have also been described but are rare.[12]

NRAS mutations also promote tumor-mediated evasion from immune cell surveillance, increasing tumor pathogenicity.[13] NRAS mutations are commonly associated with nodular melanoma subtype, advanced age and chronically sun-damaged skin.[7,12,13] These tumors display an aggressive biological behavior and are difficult to target with existing pharmacologic agents.

Cellular KIT

Cellular KIT (c-*KIT)* proto-oncogene encodes a receptor tyrosine kinase which plays a central role in melanocyte development, migration, and survival through downstream pathway stimulation.[14] Mutations in c-KIT occur in approximately 3% to 8% of cutaneous melanomas. Unlike *BRAF* and *NRAS* mutations, c-KIT mutations are also commonly observed in acral lentiginous and mucosal melanoma (up to 50% of patients).[15,16] The frequency of c-KIT mutations is directly influenced by the primary tumor location.[16] The identification of c-*KIT* mutant melanoma has important therapeutic implications. Certain tumors demonstrate a strong sensitivity to tyrosine kinase inhibitors such as imatinib. However, its efficacy varies significantly depending on the mutation location within the protein. For example, tumors harboring mutations in exons 11 and 13 exhibit favorable treatment response to therapeutic agents, whereas mutations in other locations show a much more variable treatment response.[15,16]

MAJOR GERMLINE MUTATIONS

Cyclin-Dependent Kinase Inhibitor 2A

The cyclin-dependent kinase inhibitor 2A (CDKN2A) gene remains the most extensively studied and clinically relevant germline mutation in FMS.[5,17,18] Mutations in CDKN2A account for approximately 20% to 40% of FMS cases.[5] The pathogenicity of this gene lies in its regulation of cellular senescence. Under normal conditions,

UV-induced DNA damage triggers melanocytes to enter irreversible cell cycle arrest, a process mediated by tumor suppressor pathways such as TP53/P21 and $P16^{INK4a}$/retinoblastoma (RB). Mutations in CDKN2A lead to impaired $P16^{INK4a}$ expression and ultimately preventing transition into a senescent state.[5] Without senescence, melanocytes with critical DNA damage are allowed to proliferate and expand resulting in melanoma development.

Individuals harboring CDKN2A mutations exhibit melanoma-dominant phenotypes and have up to a 65-fold increased personal risk of developing melanoma.[1] Patients who progress to develop MM have a poor overall survival in stage III/IV melanoma patients.[17,19] Harboring this mutation confers an increased risk of first-degree relatives also carrying the mutation (standardized incident ratio [SIR], 7.47; 95% confidence interval [CI], 3.97–12.77) as well as the risk for other cancer types such as pancreatic cancer, mesothelioma, renal cell carcinoma, and other neurologic tumors such as astrocytoma resulting in melanoma-astrocytoma syndrome.[6,18,20–22] Histopathologically CDKN2A-associated melanomas are largely indistinguishable from sporadic forms, and there is no consistent anatomic predilection for lesion development.[18,23]

Cyclin-Dependent Kinase 4

Cyclin-dependent kinase 4 (CDK4) is a downstream product of CDKN2A. CDK4 with CDK6 facilitates cell cycle progression from G1 to S phase via phosphorylation of the RB protein.[1] Germline mutations that result in MM always occur as a substitution for arginine within the codon critical for p16 protein binding.[1,18] Without p16 binding, constitutive kinase activation and uncontrolled cellular proliferation occurs. Although rare, CDK4 mutations confer a lifetime melanoma risk of approximately 74%.[1] Similar to CDKN2A-mutant tumors, CDK4-associated melanomas exhibit no distinct histologic or anatomic features.[23]

BRCA1-Associated Protein-1

Germline mutation in BRCA1-associated protein-1 (BAP1) represents a high penetrance mutation responsible for 1% of all MM.[1] Functionally, BAP1 is a deubiquitinating enzyme that regulates DNA repair, cell cycle progression, and apoptosis.[1] On UV-induced DNA damage, BAP1 activation promotes cell cycle arrest through serine/threonine kinase-mediated pathways.[18] Loss-of-function mutation within the BAP1 gene disrupt this checkpoint control predisposing cells to malignant transformation as there is no enzyme to trigger cell cycle arrest. Its impact in uveal melanoma is higher, cited at 3%, and when there is a concurrent uveal and cutaneous melanoma patients, one study cited 29% of families had germline mutations.[18] Mutations in BAP1 are also linked with the development of other cancers such as basal cell carcinoma, malignant mesothelioma and renal cell carcinoma.[24,25]

Telomerase Reverse Transcriptase

Germline mutations in telomerase reverse transcriptase (TERT) are uncommon but of high penetrance contributing to approximately 1% of FMS cases.[1,18] This gene encodes a protein involved in the shelterin protein complex, a complex of 8 proteins involved in telomere length regulation.[1,18,26] Shorting of cellular telomeres is a trigger for the cell to enter a senescent state, preventing further replication. Mutations in this protein allow for telomere lengthening and thus unchecked cellular growth. TERT mutations typically occur in the promoter region and other proteins involved include in this complex and result in high penetrance germline mutations including adrenocortical dysplasia protein (ACD), TERF21P, and protection of telomeres 1 (POT1).[18] This

mutation is directly associated with superficial spreading and nodular subtypes of melanoma.[1]

Protection of Telomeres 1

The POT1 gene is another critical component of the shelterin complex, functioning in telomere length regulation and genomic stability.[18,27,28] POT1 variants have been associated with a significantly increased risk of melanoma, though reported frequencies vary among populations. In a US familial cohort, individuals with pathogenic POT1 variants demonstrated a markedly elevated melanoma risk (Odds Ratio [OR]] 7.03; 95% CI, 4.7–10.5; $P<.001$) and a higher incidence of multiple primary tumors.[29] Conversely, the MelaNostrum database reported variant frequencies of 3.8%, a separate study of CDKN2A/CDK4 wild-type Spanish families revealed and incidence of 1.75% and finally a Swedish cohort of 168 FMS cases identified POT1 pathogenic variants in only 0.6% of families, underscoring population variability.[27,28,30] Consistent with these findings, UK clinical practice guidelines recognize POT1 as a rare but relevant high-risk germline mutation.[31] These guidelines encourage POT1 germline genetic testing in individuals; however, if discovered, no additional clinical monitoring is required beyond yearly skin exams.[31] Histologically, POT1-associated melanomas frequently exhibit Spitzoid morphology.[23,27]

Adrenocortical Dysplasia Protein/Telomeric Repeat-Binding Factor 2 Interacting Protein

ACD and telomeric repeat-binding factor 2 interacting protein (TERF2IP) both play a role in comprising the shelterin complex in addition to POT1.[21,32,33] Their main role is in telomere maintenance, and they represent high-penetrance germline mutations.[21,32,34] Melanoma resultants due to these mutations typically present at a young age with superficial spreading or lentigo meligna subtypes.[32] Spitzoid morphology may also be seen.[35]

Ataxia-Telangiectasia Mutated

The ataxia-telangiectasia mutated (ATM) gene encodes a serine/threonine kinase that mediates DNA double-strand break repair and cellular response to oxidative and ionizing radiation or UV radiation. Biallelic ATM mutations cause the autosomal recessive disorder ataxia-telangiectasia or Louis-Barr syndrome, while heterozygous loss-of-function variants confer susceptibility to several cancers, including breast carcinoma and melanoma.[36–38] A large case–control evaluation performed between 2 centers demonstrate a higher frequency of deleterious or uncertain ATM variants among FMS cases compared with sporadic cases ($P=.027$).[36] Additional evidence indicates a low-to-moderate melanoma risk associated with ATM mutations (OR 1.46; 95% CI, 1.18–1.81).[27,28] Although rare, carriers exhibit a 2- to 3-fold increased lifetime melanoma risk compared to the general population.[39]

Fanconi Anemia Complementation Group I

Emerging data have implicated Fanconi anemia complementation group I (FANCI) variants in melanoma predisposition. In a small Hungarian cohort (n = 17) with FMS, novel FANCI variants were identified, one of which was classified as likely pathogenic.[40] However, most reported variants represent low- to moderate-penetrance alleles without confirmed clinical relevance. Further large-scale studies are required to clarify the role of FANCI and related Fanconi pathway genes in melanoma susceptibility.[40,41]

Melanoma Subordinate Syndromes

Melanoma subordinate syndromes arise in the context of other well-established inherited gene mutations such as those associated with breast cancer or ovarian cancer. Although melanoma may be seen in these instances, it does not predominate likely secondary to variable gene expressivity and incomplete penetrance.[6] Examples of melanoma subordinate syndromes include Cowden Syndrome, xeroderma pigmentosum, and Li Fraumeni syndrome.[6] Each of these well-studied syndromes are governed by their own genetic screening recommendations, surveillance guidelines, and gene panels. Recognition of melanoma's role within these syndromes remains clinically important and requires appropriate patient counsel.

Genetic Screening Recommendations

With respect to somatic genetic mutations, current National Comprehensive Cancer Network (NCCN) guidelines recommend germline testing primarily in stage III/IV disease, high-risk stage II disease based on pathologic features, or stage I or II melanoma only when results may inform clinical trial participation.[42] The goal of genetic testing is to identify mutations for which targeted medical therapy can be administered.

Germline genetic screening in familial melanoma facilitates early detection and intervention, improving melanoma-specific survival to near that of the general population.[43,44] Advances in genetic testing for both germline and somatic mutations have increased affordability, accessibility, and accuracy, prompting updates to clinical screening strategies. Early screening guidelines, established in 2009, focused only on CDKN2A testing.[6] Currently, these guidelines have evolved and are now indicated in patients who meet the "rule of twos or threes".[42]

The *rule of twos and threes* aids in estimating the pretest probability of detecting clinically actionable germline mutations and to guide the decision to pursue genetic testing.[6] The *rule of threes* is used in higher-prevalence melanoma regions such as the United States and is defined as 3 or more primary melanomas in the patient or first-/second-degree relatives. Inclusion of certain nonmelanoma cancers known to be caused by similar germline mutations is permitted. Cancers considered for inclusion include breast, colon, pancreatic, and prostate cancers.[4,6,45,46] Similarly, the *rule of twos* is used in lower-prevalence regions, requiring 2 primary melanomas or one primary melanoma plus a first-/second-degree relative with a relevant malignancy. Regions that constitute lower prevalence include European countries like Italy, Spain and France.[6] In lower- to medium-prevalence regions, some studies are emerging to suggest that the *rule of threes* may be an acceptable guideline for genetic testing; however, strict abidance by the *rule of twos* should be used if the individual diagnosed with melanoma is younger than age 40.[45] The *rule of fours* is used in Australia given the high prevalence of sporadic disease.[6,19] Although the concept is similar, global consensus on whether including melanoma in situ lesions as a *hit* remains lacking.

In addition to using the guidelines stated above, providers must also account for their clinical acumen for ultimate decision making. This is guided by a thorough history including detailed oncologic family history followed by physical exam. The decision to pursue genetic testing requires shared decision-making with patients and families. Overscreening can increase health care costs, laboratory utilization, procedural risks, and patient burden, without improving outcomes. A survey of clinicians recently performed believe that over screening for melanoma has become a public health concern.[47] However, underscreening can confer elevated risks for additional malignancies within the patient as well as their first- and second-degree relatives, such

as pancreatic cancer, which carry significant prognostic implications. Therefore, when pursing genetic testing of family members, it is recommended to begin by screening the youngest affected individual within a family.[6] By screening an affected individual at a young age, the hope is to maximize identifying an actionable mutation while minimizing the risks of over screening additional family members as noted above.

Polygenic Risk Scoring

The genetic interplay within melanoma cells is complex. PRS has a role in stratifying patients who could be at genetically high risk for melanoma development but without a clearly identified germline mutation, representing ~55% of the FMS population.[48–50] PRS scoring combines many single nucleotide polymorphisms (SNPs) that have previously been previously identified and validated as holding melanoma risk in genome-wide association studies and combines them into an assessment tool.[48,51] Based on a genetic assessment, a score is then generated, and patients are placed into low- intermediate- or high-quartiles.

PRS helps to supplement current melanoma risk assessments as it provides a more comprehensive picture of an individual's genetic interplay.[52] PRS scoring allows clinicians to better identify and stratify patients into a high-risk category who may have otherwise been overlooked.[50,52] Consideration of a patient's genetic ancestry is important when consider SNPs to analyze when calculating PRS as it may influence the type and frequency of melanoma subtype a patient develops.[52] Validation studies of the multiple PRS risk prediction models are ongoing but have shown promising results.[53,54]

DISCUSSION

In summary, most melanotic lesions arise in a staged morphologic progression as accumulation of driver genetic mutations are acquired. There are 3 major identified somatic mutations: BRAF, NRAS, and c-KIT. The first major genetic mutation most often occurs in BRAF and results in autologous activation of the MAPK pathway. As the precursor lesion progresses, it next acquires activating mutations within NRAS. NRAS mutations promote independent cell cycle proliferation in addition to tumor-mediated immune cell evasion increased its pathogenicity. The third most encountered somatic mutation is c-KIT; however, these mutations have a predilection for mucosal melanoma as opposed to cutaneous. All melanoma tissue in unresected stage III and IV disease or stage II-III disease under consideration for adjuvant therapy undergoes BRAF testing to facilitate targeted medical therapy.[42] However, NCCN guidelines caution providers that current gene expression profiling (GEP) data are not robust enough to provide clinically actionable prognostic information.[42] Validation studies are ongoing.

There are 7 well-established germline mutations identified as principal drivers of MM development; however, these account for only approximately 45% of FMS cases, leaving more than half of hereditary susceptibility unexplained. Efforts to identify additional high-penetrance loci have been hindered by the rarity, heterogeneity, and inconsistent presence of variants even within affected first degree relatives.[40] Many large-scale genomic analyses documented in the literature have revealed numerous rare mutations of uncertain pathogenicity, underscoring the complexity of the genetic landscape underlying melanoma predisposition. PRS offers a promising avenue for quantifying cumulative genetic risk by integrating the additive effects of multiple SNP variants that are not currently tested for on widely established genetic tests. Implementation of PRS may enhance clinicians' ability to identify individuals at elevated

risk for developing multiple primary melanomas or those who might harbor undetected susceptibility within the 55% of familial cases unexplained by current genetic testing. Ultimately, the integration of polygenic models with established screening frameworks represents a critical next step toward a comprehensive, precision-based approach to melanoma risk assessment and prevention.

When looking at genetic testing from a patient-centered approach, studies examining patient attitudes toward genetic testing before conception indicate that motivations are predominantly centered on control over personal and familial oncologic risk management.[55] Concerns exist regarding potential additional living costs (eg, mortgage and insurance), as well as availability of life insurance coverage.[55] Ultimately, family planning appeared to be unaffected because patients have a relatively poor understanding of germline genomic inheritance and wish to continue meeting their family planning goals.[55] Examination of psychological distress among high-risk MM patients do not significantly differ from the general population.[56] As expected, patients who are at known increased risk for MM desire the additional appropriate screening.[56]

Despite all ongoing work in the genetics space, NCCN guidelines currently state that GEP does not provide clinically actionable prognostic information and it is unclear whether they are a reliable tool for clinically actionable decisions.[42] This evidence is supported by recent meta-analysis. However, FMS patients were excluded from analysis in this study.[57] To date, there are no meta-analysis that have been performed investigating GEP effectiveness in FMS patients. Lastly, armed with evidence that screening in FMS facilitates early detection, intervention, and improves melanoma-specific survival to near that of the general population, further work should continue in this space.[43,44]

LIMITATIONS AND FUTURE DIRECTIONS

Several limitations affect the interpretation and application of genetic testing within the cutaneous melanoma population. Currently, gene expression profile panels for somatic genetic mutations are not adequately validated within literature, limiting their ability to be used for clinical prognostication.[42] In addition, there are multiple gene expression panels available ranging in evaluation from anywhere between 11 to 31 genes and there is no standardization among their utilization. Most studies in the current literature evaluating the efficacy of these profiles are retrospective in nature and more robust evaluations are ongoing in the form of large meta-analyses and prospective randomized trials.[58–60]

In terms of germline genetics, only 45% of FMS patients have a detectable high-penetrance mutation leaving over half the population without a clear germline mutation association.[6] This is likely as a result from low- or medium-penetrance genes in combination with epigenetic, environmental and geographic factors. Identifying true driver, high-penetrance mutations remains challenging. In review of the literature, there are many studies published regarding rare or new variants with uncertain clinical relevance, and larger studies are required to validate their pathogenicity.[61]

In addition to the extreme difficulty identifying high penetrance gene mutations among a sea of many unique, but nongeneralizable mutations, the FMS population is small. Within the FMS population, patients with the same genetic mutations are even smaller. Most studies focus on highly selected, high-risk populations, limiting power analysis. Data on specific gene mutations at population-level cohorts remain sparse. The development of consortium and gene databanks is growing; ongoing work is required to help identify genes that are likely to be driver mutations for further development is required. Large-scale genomic databases and collaborative networks

are essential for identifying novel driver mutations and clarifying the penetrance of rare variants.

Lastly, global variability in genetic screening criteria for melanoma exists. Differences in melanoma classification for screening thresholds complicate cross-study comparisons. For example, some countries include melanoma in situ as a qualifying lesion, whereas others do not.[6] Future directions could include standardizing these definitions.

Emerging strategies in melanoma genomics aim to enhance risk stratification and personalize oncologic surveillance. Many gene expression profile panels are currently undergoing validation with hopes that soon they can be used to provide clinically actionable prognostic information. Incorporating the use of polygenic risk scores (PRS) to assist in risk, stratifying patients into low or high-risk categories for further assist in advancing precision medicine within the melanoma population.[62] Using PRS, patients and their first-degree relatives with pathogenic or likely pathogenic variants in high-risk genes (eg, CDKN2A) who currently fall outside the *rule of twos and threes* could benefit from more inclusive testing strategies.[46]

CLINICS CARE POINTS

- 45% of FMS patients have a detectable high-penetrance mutation leaving over half the population without a clear germline mutation association.
- NCCN guidelines recommend germline testing primarily in stage III/IV disease, high-risk stage II disease based on pathologic features, or stage I or II melanoma only when results may inform clinical trial participation.
- Current screening guidelines have evolved and are now indicated in patients who meet the "rule of twos or threes".
- Gene expression profile panels for somatic genetic mutations are not adequately validated within literature, limiting their ability to be used for clinical prognostication.

DISCLOSURE

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