New Insights into Melanoma Tumor Syndromes

Sarem Rashid1,2, Sameer Gupta3, Shelley R. McCormick4 and Hensin Tsao1,5

Melanoma tumor syndromes (MTS) represent an important minority of familial melanoma cases. In these patients, the accumulation of sequence alterations in essential genes may prelude the risk of internal malignancies, in addition to melanoma. Although several host and environmental factors have been implicated in familial melanoma, the exact mechanisms of cancer predisposition—particularly in the context of mixed cancer syndromes—still remain unclear. In this paper, we review new insights into MTS and elucidate recent efforts that guide individualized prognostication and treatment for these diseases in the past quarter century.

INTRODUCTION
Melanoma, the most lethal form of skin cancer, is driven by the complex interplay between genotype and environment. Because UVR exposure remains to be the most significant adverse risk factor for melanoma (Jhappan et al., 2003), one can argue that most melanomas are environmentally induced by excessive sun exposure, with subsequent somatic mutagenesis of melanocytes. However, the risk of exposure is profoundly shaped by inherited factors, such as skin color and the tanning response, which are both genetically determined. Heritable risk for melanoma has been estimated as 58% on the basis of a large twin study comparing melanoma rates in identical (monozygotic) twins with those in nonidentical (dizygotic) twins (Mucci et al., 2016). Despite this largerisk attribution to inheritance, only a fraction has been characterized.

The earliest attempts to explore these questions were focused on clusters of melanoma cases in families.

UPDATE ON MELANOMA RISK LOCI
Retinoblastoma pathway genes

CDKN2A/CDK4. Dysplastic nevus syndrome or familial atypical (multiple) mole melanoma (FAMMM) syndrome is a hereditary cancer syndrome resulting from germline variants of several genes, including CDKN2A. Patients will clinically...
present with numerous atypical nevi (>50, as determined by the ABCDE [asymmetry, border, colors, diameter, evolution] criteria), concerning histologic features (e.g., lymphocytic infiltration, lentiginous melanocytic hyperplasia, and architectural disorder with asymmetry), and a positive family history of melanoma in first- or second-degree relatives (Eckerle et al., 2009) (Figure 2). Although these criteria have been established for clinical diagnosis of FAMMM, it does not describe lesions exclusive to the disorder.

CDKN2A and CDK4 are high-penetration genes associated with an increased risk of familial melanoma. Early genetic linkage analysis proposed at least two high-risk susceptibility loci for melanoma on chromosomal bands 9p21 (Cannon-Albright et al., 1992) and 1p22 (Bale et al., 1989). Shortly after, CDKN2A located in the 9p21 locus was established as a key regulator of cell cycle proteins (CDK4, D-type cyclins, and Rb) (Serrano et al., 1993). Homozygous deletions found in numerous malignant cell lines were finally established as an important factor for cancer susceptibility (Nobori et al., 1994).

The CDKN2A gene encodes isoforms 1 and 4. The CDKN2A gene encodes for two widely studied proteins p16/INK4A and p14/ARF. The protein p16 inhibits cyclin-dependent protein kinases CDK4 and CDK6, which form a protein complex with cyclin D that functions to phosphorylate the Rb tumor suppressor gene product (Ruas and Peters, 1998). Phosphorylation of the Rb/E2 factor subsequently causes the release of E2F transcription factors that enter the nucleus. These E2F transcription factors then regulate the expression of genes involved in cell cycle progression, including cyclin E and cyclin A, which in turn contribute to the proliferation of melanoma cells.

Figure 1. Integrated molecular pathways in melanoma tumor syndromes. (a) CDKN2A consists of two splice products in alternate reading frames. p16, encoded by exons 1a, 2, and 3, inhibits CDK4, thereby permitting its binding to CYCD. This complex subsequently phosphorylates the Rb protein which releases E2F and ultimately facilitates G1–S cell cycle progression. ARF is encoded by exons 1b, 2, and 3 and inhibits HDM2-mediated ubiquitination of p53 (Eskandarpour et al., 2003; Foulkes et al., 1997; Ruas and Peters, 1998). (b) As the catalytic subunit of the PR-DUB complex, BAP1 deubiquitinates the H2A complex to regulate cell proliferation, differentiation, metabolism, and apoptosis (Pilarski et al., 2020; Rai et al., 2016a). (c) PTEN functions to negatively regulate PI3K signaling through dephosphorylation of PIP3 to PIP2. Receptor Y kinase– and Ras-mediated activation of protein kinases PDK1 and Akt in turn regulates many important proliferative functions (Roh et al., 2016; Wu et al., 2003; Zhou et al., 2003). (d) TERT and the shelterin complex serve important roles in the regulation of telomere length and chromosomal protection. Recruitment of GABP transcription factor to a mutant TERT promoter region may promote a variety of cancers. Akt, protein kinase B; CYCD, cyclin D; E2F, E2 factor; P3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5 bi-phosphate; PIP3, phosphatidylinositol 3,4,5 tri-phosphate; PR-DUB, polycomb repressive deubiquitinase; RB, retinoblastoma; TERT, telomerase reverse transcriptase (Fan et al., 2016; Halezi and Perez Bercoff, 2020).
transcription factors are critical regulators of S-phase entry, DNA replication, and cell proliferation (Wu et al., 2001). Derepression of E2F-dependent transcription is thus a hallmark of many human cancers (Johnson and Schneider-Broussard, 1998). In addition to germline CDKN2A inactivation, dysfunction of the Rb pathway may also result from UVR, which is estimated to cause 60–70% of cutaneous malignant melanomas (Sample and He, 2018). The second principle CDKN2A product, p14ARF, functions through the inhibition of proto-oncogene MDM2 to prevent degradation and ubiquitination of p53 in proliferating cells (Weber et al., 2002). The majority of germline variants in CDKN2A tend to occur in p16/INK4A rather than in p14/ARF, with a specific preference for exons 1a and 2 (Tsao et al., 2012).

Germline CDKN2A sequence variants most frequently occur in exons 1–3 (Foulkes et al., 1997). In exon 2, c.225-243del and c.301G>T are among the most frequent variants in FAMMM kindreds (Foulkes et al., 1997). Hussussian et al. (1994) described eight p16 germline variants—one splice donor-site, one nonsense, and six missense variants—occurring in 13 of 18 familial melanoma kindreds. Of these variants, six were reported in 33 of 36 melanoma cases in nine families. Another Dutch study reported a germline deletion (19 basepair length) in 13 of 15 families with FAMMM (Gruis et al., 1995). This deletion produces a shift in reading frame, thereby truncating the p16 protein. Strikingly, heterozygous patients in this group exhibited a more severe phenotype than homozygous family members, suggesting a clinically relevant compensatory mechanism in p16 deficiency, which requires further exploration (McWilliams et al., 2011). Finally, an Italian study showed three cases of PC detected in seven melanoma-prone families containing a Gly101Trp missense variant (Ciotti et al., 1996).

The association between germline CDKN2A variants and PC is well-established. In a previous study, 28% of melanoma-prone families harboring a germline CDKN2A variants were found to have PC (compared with 6% of families harboring no CDKN2A variant) (Goldstein et al., 2006). From this sample, 45% of CDKN2A-mutant families with neural system tumors reported at least one case of PC, although these studies utilize small patient samples. The frequency of PC was found to be greatest (>60%) in patients with p.R112_L113insR and c.225_24del19 CDKN2A variants and to be least (<11%) in patients with p.M53I, c.IVS2-105A>G, and c.32_33ins9-32 variants (Eckerle et al., 2009). Results from the GenoMEL study show that CDKN2A variants in kindreds with melanoma with PC are more likely to affect both p16 and p14ARF (49%) than p16 alone (26%) (Goldstein et al., 2006; McWilliams et al., 2011). Outside of the melanoma phenotype, between 1.5% and 3.3% of patients with familial PC harbor germline CDKN2A variants (Kimura et al., 2021).

Inactivating CDKN2A germline variants may also confer an increased risk of astrocytoma in addition to melanoma, for example, in familial melanoma–astrocytoma syndrome (Chan et al., 2017). In a 1993 case report, Kaufman et al. (1993) first described a family affected by cutaneous melanoma and cerebral astrocytoma over three successive generations. Through linkage analysis, this disorder was later characterized by deletions of chromosome 9p21.3 at the INK4 locus, which encodes tumor suppressor genes CDKN2A and CDKN2B (Bahuau et al., 1998, 4). The full spectrum and histology of nervous-system tumors in familial melanoma–astrocytoma syndrome is not currently well-described.

CDK4, the cognate target of p16, is also mutationally activated in a small number of FAMMM kindreds. All sequence variants of CDK4 have been described to occur in exon 2, which is the site of the p16:CDK4 interaction; mutagenesis of this site abrogates p16 binding (Rossi et al., 2019; Zuo et al., 1996). Patients with germline CDK4 variants cannot be differentiated phenotypically from those with germline CDKN2A variants (Puntervoll et al., 2013).

Although a single consensus that covers the clinical management of patients with FAMMM has yet to be determined, regular total body skin examinations are essential. Depending on the number of atypical nevi, individuals with FAMMM should be examined at least every 6–12 months, and self-surveillance measures should be emphasized by the dermatologist. For PC, the National Comprehensive Cancer Network screening guidelines (www.nccn.org, version 2.2022) recommend that individuals with a known
pathogenic germline variant in a PC susceptibility gene (e.g., CDKN2A) and a family history of PC undergo surveillance with magnetic resonance imaging and/or endoscopic ultrasound. Whether CDKN2A variant carriers from hereditary melanoma kindreds, in the absence of any PC affected, require the same rigorous PC screening has not been fully established.

**RB1.** Multiple publications have reported an increased risk of melanoma among patients with retinoblastoma who carry germline variants in the *RB1* gene. In a survey of 1,927 patients with retinoblastoma (MacCarthy et al., 2013) diagnosed in Britain between 1951 and 2004, there were 12 cases of melanoma among patients with heritable retinoblastoma, yielding a standardized incidence ratio of 18.6 (9.6–32.4). Thus, a consensus panel convened in 2020 strongly recommended an annual skin examination for survivors of retinoblastoma with a single-skin examination before age 8 years and annual skin examinations with adequate sun protection measures after adolescence (Tonorezos et al., 2020).

**BAP1**

In 1998, Jensen et al. (1998) discovered a novel ubiquitin carboxy-terminal hydrolase that attached to the wild-type BRCA1-RING finger in certain breast cancers. Since then, BAP1 has been established as a tumor suppressor gene involved in transcription modulation (YY1, FOXX1, FOXX2), response to extracellular stress and DNA-damage repair (MBD5, MBD6), and chromatin modification (ASXL1, ASXL3, KDM1B, OG1T) through independent mechanisms (Baymaz and Irem, 2014; Campagne et al., 2019; Ji et al., 2014; Yu et al., 2010). Subsequent experiments by Venti et al. (2008) suggested tumor growth suppression of BAP1-restored lung cancers in animal models. Suppression of tumorgenicity may be due to cell cycle disruption, at the G1/S checkpoint for example, or induction of apoptosis (Venti et al., 2008). Germline sequence variants in BAP1 have been linked to increased risks for renal cell carcinoma, mesothelioma, and melanoma (uveal and cutaneous) (Louie and Kurzrock, 2020). The exact nature of BAP1's molecular function remains unclear given the diverse role of ubiquitination in physiologic maintenance.

A connection between BAP1 and melanoma was first established through somatic analyses of uveal melanoma (UM) specimens. Harbour et al. (2010) found inactivating BAP1 variants in 84% of metastatic UM cases. Shortly thereafter, germline variants of BAP1 were detected in kindreds with mixed tumors, including peritoneal and pulmonary mesotheliomas, meningiomas, UM and cutaneous melanoma, and renal cell carcinomas (Abdel-Rahman et al., 2011; Carbone et al., 2013; Testa et al., 2011).

Germline variants in the BAP1 gene are inherited in an autosomal dominant pattern (Masoomian et al., 2018). The incidence of de novo sequence alterations in BAP1 tumor predisposition syndrome (TPDS) has yet to be established (Pilarski et al., 2020). The gene exhibits incomplete penetrance, and incidence and tumor type may vary among members of the same family (Carbone et al., 2013).

From the skin perspective, inactivation of this gene may predispose an individual to BAP1-inactivated melanocytic tumors, formerly called atypical Spitz tumors, and a subsequent diagnosis of BAP1 TPDS (Masoomian et al., 2018). BAP1-inactivated melanocytic tumors clinically appear as dome-shaped papules or nodules located on the face or extremities (Masoomian et al., 2018). These tumors may show absent mitotic figures and the presence of Kamino bodies (Wiesner et al., 2011). Because the lesion carries a diverse histopathological spectrum that closely resembles that of melanoma, high interobserver variability has been reported among dermatologists (Filiberto et al., 2015). However, UM is the most common cancer found in BAP1 TPDS (36.2% occurrence in probands compared with 23.4 and 15.0% occurrence in probands for cutaneous melanoma and nonmelanoma skin cancers, respectively) (Walpole et al., 2018). Tumors with this allelic variant may be more aggressive, with a high propensity to metastasize (Rai et al., 2016). Altogether, germline BAP1 variants can be designated by a phenotypic complex containing cutaneous and ocular melanomas, characteristic melanocytic proliferations, and other internal neoplasms; for this reason, BAP1 TPDS is sometimes referred to as COMMON syndrome (Njauw et al., 2012). These tumors, although present in other germline susceptibilities, have reportedly worse outcomes (Gupta et al., 2015) than tumors without the sequence variant.

Given the rarity of individuals with germline BAP1 variants, there is currently no consensus for medical management—although annual skin and eye examinations may be plausible in addition to routine imaging surveillance of the abdomen and chest (Pilarski et al., 2020).

**Human telomerase reverse transcriptase promoter sequence alterations and the shelterin complex**

**Human telomerase reverse transcriptase promoter.** Telomerase reactivation or re-expression is a common process in tumorigenesis (Vinagre et al., 2013). The absence of telomerase in normal tissue causes progressive telomeric decay owing to DNA polymerase activity. As telomeric length decreases, thereby losing its function, the DNA damage response pathway is activated. Replicative senescence is subsequently induced to mitigate uncontrolled proliferation in precancerous cells (Yuan et al., 2019). Therefore, telomerase activation is an important mechanism used to bypass physiologic brakes involved in cell growth.

Germline variants in the telomerase reverse transcriptase (TERT) gene TERT promoter region have been identified (chr5:1295161 T>G, GRCh37/hg19) in a single family with familial melanoma using linkage analysis followed by next-generation sequencing (NGS) (Horn et al., 2013); a second independent family with the identical promoter variant was also reported in a cohort screen of 675 families with melanoma (Harland et al., 2016). This sequence variant generated a new binding motif for ETS domain proteins, which link transcription to the MAPK signaling pathway. Family members showed early onset melanoma (mean = 34 years) and high susceptibility to other primary tumors affecting the ovaries, kidneys, breast, and lungs. A recent report found TERT promoter CpG dinucleotide methylation to be associated with decreased recurrence-free melanoma survival in adolescents and young adults (Seynaeve et al., 2017). TERT hypermethylation has been associated with tumor progression and poorer prognosis in previous brain and prostate
tumor studies (Castelo-Branco et al., 2013; 2016). Benign tissue should show minimal methylation of CpG dinucleotides (Lee et al., 2017), which serves as an important factor for diagnostic purposes.

Somatic germline alterations of the TERT promoter region are relatively common in cutaneous melanomas and are associated with decreased disease-free survival and increased rate of metastasis, particularly when coupled to BRAF and NRAS alterations (Hugdahl et al., 2018; Nagore et al., 2016; Chang et al., 2020). The most commonly observed sequence variant, TERTp C>T transition), has been associated with poor prognosis in multiple studies (Campos et al., 2019; Hafezi and Perez Bercoff, 2020). The hypermethylation status of CpG islands may also serve as a molecular landmark to discriminate advanced melanocytic nevi (Fan et al., 2016). In this study, TERT promoter variants or hypermethylation were harbored exclusively in melanomas and were notably absent in benign or low-grade melanocytic lesions. More recently, Thomas et al. (2019) reported TERT promoter variants in 77.9% of confirmed melanomas. In contrast, only 5.0% of diagnostically uncertain melanomas contained such sequence alterations. Future improvements in methylation assays, together with high-throughput sequencing, may allow for increased clinical prognostication for patients with melanoma with TERT alterations.

POT1. Telomeres consist of repeated DNA sequences and proteins that comprise the terminal ends of each chromosome. In somatic cells, progressive telomeric elongation is thought to contribute to genomic damage and the immortal phenotype of cancer cells (Henry et al., 2020). The shelterin complex or telosome binds both single-strand DNA (ssDNA) and double-strand DNA regions of telomeres to downregulate physiologic DNA damage signaling (Lim and Cech, 2021). Shelterin is composed of six protein subunits: TRF1, TRF2, POT1, RAP1, TIN2, and TPP1. After binding to DNA, this assembly may yield various DNA-protective conformations such as the end-capped telomere and telomere loop (Lim and Cech, 2021).

The POT1 gene is critical for shelterin complex formation and binding to telomeric ssDNA through its interaction with TPP1 (Henry et al., 2020). POT1 is located at 7q31.33, and variants have been reported at isoform 1 of the protein (Müller et al., 2018). Germline variants in this gene have been implicated in familial melanoma predisposition in addition to the development of other tumors such as chronic lymphocytic leukemia, angiosarcomas, and gliomas (Calvete et al., 2017). In 2014, a POT1 founder sequence alteration (chromosome 7: g.124493086C>T; p.Ser270Asn) was found in five melanoma-prone families from Romagna, Italy (Shi et al., 2014). In another study, four additional POT1 variants were identified in melanoma families: (i) g.124503684T>C, (ii) g.124465412C>T, (iii) g.124503670G>C, and (iv) g.124493077C>A (Robles-Espinoza et al., 2014). Eight high-risk melanoma POT1 variants were also observed in Austrian patients in a more recent study (Müller et al., 2018). Variants associated with different tumor types are observed to be randomly distributed along the gene (Calvete et al., 2017). Owing to the wide spectrum of POT1 variants and associated cancers, further study of this gene is required to elucidate the putative relationship between melanoma and POT1 dysfunction.

ACD gene. Adrenocortical dysplasia gene ACD encodes a second shelterin complex protein factor called TPP1, which has been implicated in telomerase recruitment and activity (Henslee et al., 2021). When bound to POT1, ACD inhibits the elongation of telomeric chromosomal ends and increases the affinity for POT1 to bind ssDNA (Loayza and De Lange, 2003). Whole-exome sequencing of 113 families with familial melanoma revealed six families with ACD variants (Aoude et al., 2014). The majority of cases were observed to be superficial spreading or lentigo maligna melanomas. A p.N249S variant was observed in two families, which has also been shown to occur in the POT1-binding domain.

TER2F1P. A third gene implicated in the shelterin complex, TERF2IP, acts to regulate telomere length by repressing homology-directed repair (Rai et al., 2016). In the cytoplasm, TERF2IP associates with the Ik-B kinase complex to activate the expression of proinflammatory NF-kB-target genes (Teo et al., 2010). Aoude et al. (2014) found TERF2IP variants in 4 of 510 families, with the majority of cases again resembling either superficial spreading or lentigo maligna melanomas.

MITF. MITF encodes a bHLH-Zip (basic-helix-loop-helix-leucine zipper) motif and is a key factor in melanocyte regulation (McGill et al., 2002). In 2005, Garraway et al. (2005) observed that MITF alterations may predict metastatic disease, patient survival, and chemotherapeutic response. Autosomal dominant variants of this gene have been linked to Waardenburg syndrome type IIA, a genetic disorder characterized by deafness and pigmentation abnormalities of the skin, eyes, and hair (Nobukuni et al., 1996). The MITF(E318K) variant is of particular interest because it carries at least a two-fold increased risk of melanoma (Bertolotto et al., 2011; Guhan et al., 2020). In normoxia, SUMO proteins bind to MITF, thereby decreasing the transcription of the HIF1A. Sequence alterations at codon 318 downregulate SUMOylation of MITF and consequently increase binding to the HIF1A promoter when compared with that of wild-type MITF. Patients with this variant are observed to have higher median nevus count and melanoma incidence (Ciccarese et al., 2020). Histologically, a greater proportion of nodular melanomas were observed in tumors containing this variant. A meta-analysis of nine studies conducted on both sporadic and hereditary melanoma families revealed a significant correlation of the MITF(E318K) variant with melanoma risk (OR = 2.37, 95% confidence interval [CI] = 1.89–2.97) and uterine sarcoma (OR = 9.24, 95% CI = 2.08–37.17) (Guhan et al., 2020). There are inconsistent findings to date regarding the association of this variant with PC and renal cell carcinoma.

ATM gene. Variants in ataxia–telangiectasia mutated gene ATM have been linked to multiple cancers in GWASs, including melanoma (Landi et al., 2020). ATM encodes for a kinase involved in double-stranded break repair in DNA and has been linked to a broad spectrum of cell processes such as cell metabolism, oxidative stress, and genome stability (Cremona and Behrens, 2014). The role of ATM as a tumor
PTEN

PTEN is an important tumor suppressor and modifier of the host immune response in many cancers (Chen et al., 2018; PTEN is an important tumor suppressor and modifier of the host immune response in many cancers (Chen et al., 2018; PTEN is an important tumor suppressor and modifier of the host immune response in many cancers (Chen et al., 2018; PTEN is an important tumor suppressor and modifier of the host immune response in many cancers (Chen et al., 2018; PTEN is an important tumor suppressor and modifier of the host immune response in many cancers (Chen et al., 2018; PTEN is an important tumor suppressor and modifier of the host immune response in many cancers (Chen et al., 2018;). Autosomal recessive inactivation of PTEN may cause ataxia–telangiectasia, also known as Louisa–Bar syndrome, which is characterized by ataxia, telangiectasias, immunodeficiencies, and increased cancer predisposition (Riboldi et al., 2022). A recent analysis of the Genome Aggregation Database found that loss-of-function (LOF) variants were more prevalent in melanoma patients (0.95% in the whole cohort) than in a subset of non-Finnish European control patients (0.36% in the control sample) (Dalmasso et al., 2021). A slightly increased prevalence of ATM LOF variants was observed in familial and multiple primary melanoma cases (1.08% in the subset of non)

DEFINING MIXED-TUMOR SYNDROMES WITH INCREASED MELANOMA RISK

PTEN

PTEN loss manifests as a complex spectrum of disorders called PTEN hamartoma tumor syndrome (PHTS) (Innella et al., 2021). Patients with PHTS will primarily exhibit numerous hamartomas and a high risk of multisystem tumor development, although they may suffer from rarer genetic disorders such as Cowden syndrome (CS), Lhermitte–Duclos disease, Bannayan–Riley–Ruvalcaba syndrome, and autism spectrum disorders (Pilarski, 2019) (Table 1). More than 100 germline variations for PTEN have been suspected in patients suffering from CS and Bannayan–Riley–Ruvalcaba syndrome (Bonneau and Longy, 2000). Despite large genetic heterogeneity, 10% of patients with CS without coding region variants harbor identifiable promoter variants (Zhou et al., 2003). Approximately 20–30% of germline and somatic PTEN alterations occur on exon 5, which encodes for a phosphatase core domain (Wu et al., 2003).

A number of skin lesions have been reported in PHTS. Skin involvement may occur before the age of 40 years as facial trichilemmomas (Brownstein et al., 1979), mucocutaneous neuromas (Schaffer et al., 2006), benign acral keratoses (Brownstein et al., 1979), and cutaneous lipomas (Buisson et al., 2006; Haibach et al., 1992). Some early case reports suggest an increased risk for melanomas in individuals with PTEN variants (Greene et al., 1984; Reifenberger et al., 2003), although melanoma is not part of the diagnostic criteria for PHTS. More recently, Innella et al. (2021) identified an atypical mole/melanoma syndrome phenotype in patients with pathogenic PTEN variants containing a rare truncating sequence alteration (c.495G>A) in the CDH13 gene. The lifetime risk for acquiring melanoma is estimated at 6% (Tan et al., 2012), which is substantially less than the estimated risk for breast, thyroid, endometrial, colorectal, and kidney carcinomas. Although the evidence is limited, patients with pathogenic PTEN variants should undergo careful clinical evaluation (and if necessary, routine skin examinations) for adequate management of PHTS.

TP53

TP53 mutagenesis is one of the most frequently encountered events in cancer (Olivier et al., 2010). Somatic TP53 variants occur in up to 19% of cutaneous melanoma cases (Hodis et al., 2012). These somatic variants may occur through single-base substitution, loss of alleles, and inactivation by cellular or viral compounds (Olivier et al., 2010). Germline variants of the TP53 gene cause Li–Fraumeni syndrome (LFS), a rare cancer syndrome conferring a high lifetime risk for a wide range of cancers, including melanoma (Table 1). TP53 is a melanoma-promoting target of UV (Hocker and Tsao, 2007). Downregulation of HD2 by p14ARF further

| Subtype | Gene | Syndrome | Inheritance Pattern | Associated Nonmelanoma Tumors |
|---------|------|----------|---------------------|-----------------------------|
| Melanoma-dominant syndromes | CDRN2A and CD4 | Familial atypical multiple mole melanoma syndrome or dysplastic nevus syndrome | Autosomal dominant | Pancreatic cancer, astrocytoma (familial melanoma-astrocytoma syndrome) |
| Melanoma-associated syndromes | BAP1 | BAP1 tumor predisposition syndrome or COMMON syndrome | Autosomal dominant | BAP1-inactivated melanocytic tumors (Spitz tumors), basal cell carcinoma, renal cell carcinoma, mesothelioma |
| Melanoma-associated syndromes | PTEN | PTEN hamartoma tumor syndrome | Autosomal dominant | Hamartomas, Cowden syndrome, Lhermitte–Duclos disease, Bannayan–Riley–Ruvalcaba syndrome, facial trichilemmomas, mucocutaneous neuromas, cutaneous lipomas |
| Melanoma-associated syndromes | TERT | — | Both | Ovarian cancer, kidney cancer, breast cancer, bladder cancer, lung cancer |
| Melanoma-associated syndromes | TP53 | Li–Fraumeni syndrome | Autosomal dominant | Breast cancer, soft tissue sarcoma, Osteosarcoma, leukemia, adrenal cortical tumors |
suggests that p53 inactivation results from CDKN2A/p14ARF loss (Kamijo et al., 1998). More recently, germline TP53 p.I254V variants causing p53 inactivation were found in two unrelated patients with UM (Hajkova et al., 2018). Approximately 70% of TP53 pathogenic variants in LFS arise as missense variants interspersed in six hotspot regions of the DNA-binding domain (Ali-Harbi et al., 2018; Leroy et al., 2014). For such patients, routine skin examinations should be considered alongside interdisciplinary clinical management.

**FUTURE PERSPECTIVES**

**Gene, phenotype, and environmental interactions**

Penetrance of CDKN2A variants—ranging from 50 to 90%—appears to vary by geography and general population incidence rates, suggesting that factors that influence the general population also modify the risk with CDKN2A variants (Bishop et al., 2002). Clearly, context matters, and gene–gene and gene–environment interactions continue to be studied in how specific variants may shape individual risk. Polygenic background is known to modify penetrance for monogenic conditions (Fahed et al., 2020). Among individuals with monogenic variants, significant variation in disease penetrance has been associated with polygenic background. The probability of colon cancer by age 75 years ranged from 11 to 80% in individuals with a pathogenic Lynch syndrome sequence alteration. Similarly, the probability of developing breast cancer ranged from 13 to 76% for individuals with BRCA1 and BRCA2 variants on the basis of polygenic background (Fahed et al., 2020). For individuals with CDKN2A variants, carrying MC1R variants has been associated with the diagnosis of melanoma at a younger age and the development of more melanomas than for those with CDKN2A variants alone (Begg et al., 2005; Goldstein et al., 2005). Developing a robust polygenic risk predictor to contextualize individual risk in those with MTS sequence variants may prove informative in counseling, screening, and prognostication.

In addition to the interacting genetic background, environment may also substantially modify the penetrance of an MTS variant. For instance, among patients with CDKN2A variants, sun burns, increased sun exposure, and nevus phenotype have been associated with increased melanoma risk (Chaudru et al., 2004). Studies aimed to adequately describe gene–environment interactions are limited and have been historically underpowered. In individuals with CDKN2A variants, activating NRAS variants were found in 95% of familial melanoma cases but in only 10% of sporadic melanomas (no reported family history of melanoma) (Eskandarpour et al., 2003). These allelic variants were found both in primary melanomas and precancerous dysplastic nevi. The NRAS gene has previously been established as a target for UV-induced transformation, suggesting a possible hypermutability mechanism from this exposure (Pierceall et al., 1992). Cultivating pooled databases across health and research institutions has the potential to allow for more robust comparisons and validation of existing studies. Moreover, natural language processing may be applied to electronic health records for phenotype and risk factor extraction. This information can then be coupled to gene prioritization algorithms to curate mechanistic associations (Parikh et al., 2021). Additional studies untangling the complex interaction between driver syndromic sequence variants in the context of other heritable traits and environmental exposures are needed.

**Multiomics approaches**

In more than half of melanoma cases clustered in families, a molecular predisposition for cancer has not been elucidated (Goldstein et al., 2006) (Table 1). Recent progress in NGS has revolutionized the detection of causative genes in MTS that may be screened for in individual patients. In particular, NGS has elucidated previously underappreciated overlaps between melanoma-dominant tumor syndromes (i.e., those caused by CDK2NA or BAP1 alterations) and melanoma-associated tumor syndromes. However, there are numerous variants with an unknown significance of pathogenicity in familial melanoma cases that have yet to be classified. In 2017, a rare variant germline association study using whole-exome sequencing revealed strong signals in CDKN2A ($P = 6.6 \times 10^{-5}$) and BAP1 ($P = 3.83 \times 10^{-5}$) as well as in 11 borderline genes ($P < 1 \times 10^{-4}$), including EBF3 (Artomov et al., 2017). More recently, whole-genome sequencing of a subset of acral melanomas revealed significant somatic variants in BRAF, NRAS, NF1, NOTCH2, PTEN, TYRP1, and KIT (Newell et al., 2020). Variances in structural rearrangements and copy number signatures were also shown in TERT, CDK4, MDM2, CCND1, PAK1, and GAB2. These studies have identified the potential of NGS in the subclassification of melanoma and the identification of therapeutic targets.

Given the missing heritable driver in half of familial melanoma cases, contributions from numerous low-risk, more common variants have been explored. A recent study explored the association of a 46 SNP polygenic risk score in explaining melanoma risk in Dutch patients with familial melanoma (Potjer et al., 2021). Identifying and assembling contributing risk variants is an ongoing research effort. Large GWASs have identified 21 susceptibility loci for melanoma (Ransohoff et al., 2017). The contribution of rare yet significant coding variants remains understated in melanoma. Recent attempts at rare-variant gene-based association studies have identified additional melanoma susceptibility genes such as EBF3 (Artomov et al., 2017). When compared with canonical gene association studies (e.g., for common rather than rare variants), rare-variant studies require a targeted approach to enrich for pathogenic variants below a certain frequency threshold. Individual samples must be sequenced rather than genotyped using an existing set of cataloged sequence variants owing to a large number of potential variants. Once a rare-variant case is identified, the study requires aggregation of these samples into sets to examine frequency distribution against the control samples (Zuk et al., 2014). Another report analyzed the contribution of rare melanoma variants toward Parkinson’s disease using whole-exome sequencing data from 6,065 control and 6,875 Parkinson-positive samples. Parkinson’s disease samples were found more likely than melanoma to harbor an unusually rare TYR p.V275F variant, although this finding had limited statistical power even after combining sets (Lubbe et al., 2016). Rare-variant association studies may enable the discovery of
previously undetected signals in the exome and enable more refined polygenic risk scores for melanoma.

Epigenetic modifications—heritable changes in gene function that cannot be explained by changes in DNA sequence (Felsenfeld, 2014)—play a significant role in melanoma pathogenesis. For instance, PTEN promoter methylation has been associated as an independent predictor of impaired survival with patients with melanoma (Roh et al., 2016). Epigenetic alterations in germline inheritance have been reported in some familial cancer syndromes. Perhaps, the best described example is Lynch syndrome, which is canonically caused by germline variants in mismatch repair genes, including MLH1, MSH2, MSH6, PMS2, and EPCAM. In some families presenting with Lynch syndrome, no variants mutations in these genes could be identified. Rather, epigenetic silencing of MLH1 and MSH2 by DNA methylation in promoter regions was implicated (Lee, 2019). To date, epimutations in CDKN2A have not been observed in familial melanoma (Erlandson et al., 2008; van Doorn et al., 2009). A more recent report analyzed five Dutch families, with at least three melanoma cases in different generations, for associated DNA methylation alterations. The authors concluded that despite several clustered epimutations discovered, these candidates were unlikely driving the predisposition (Salgado et al., 2020). Limitations of this study include the small number of families studied, and any causative epimutation may occur in a subset of melanoma families (and unlikely to be common in all). In addition, samples were interrogated on a 450K Illumina array that interrogated the methylation status of CpG sites in all gene promoters but did not cover other possible regulatory sequences (Salgado et al., 2020). Future research focused on additional epigenetic mechanisms, including noncoding RNA, will continue to help elucidate unexplained predisposition to hereditary melanoma.

### Precision medicine

Current guidelines for genetic testing in melanoma are restricted to CDKN2A screening and employ the rule of twos, threes, and fours (Delanay et al., 2017). According to this rule, genetic testing is indicated for subjects with ≥2, ≥3, or ≥4 primary melanomas or genetically related cancers depending on the general population incidence. Penetration of CDKN2A variants may be influenced by intense and intermittent UV exposure in conjunction with certain high-risk phenotypes—such as pale skin, tanning ability, and red hair color. Therefore, regional context may be used to supplement the rule of twos, threes, and fours (Leachman et al., 2009). Regions with low background incidence may consider two instances of melanoma or PC in first- or second-degree relatives to qualify for a genetic referral. In contrast, a moderate-to-high background incidence may require three or more instances of disease. In families with no detectable CDKN2A variant, gene panel testing that includes CDK4 testing should be considered (Leachman et al., 2017). Furthermore, clinical prediction algorithms such as MELPREDICT (Niendorf et al., 2006; Taylor et al., 2019) and MelaPRO (Wang et al., 2010) may be useful for estimating the presence of a CDKN2A variant and overall melanoma risk.

To our knowledge, there are more than 20 commercial laboratories that offer NGS panels, which include genes implicated in hereditary melanoma. The genes included on these panels may vary, but most typically include BAP1, BRCA2, CDK4, CDKN2A, MITF (E318K), POT1, PTEN, RB1, and TP53. Genetic testing should therefore be ordered by specialists who can select the most appropriate laboratory test. Providers must obtain informed consent before ordering genetic testing, a process that requires adequate education related to the risks and benefits of genetic testing, potential outcomes of testing, and implications for both the patient and family members. Interpretation of test results should be done in the context of the patient’s personal and family history of cancer so that appropriate medical management guidance can be provided in the event of positive, negative, and uncertain test results. Testing in commercial laboratories typically includes multigene panel testing as long as criteria are met for CDKN2A. Most laboratories preform insurance preauthorization before running clinical testing. In most cases, commercial insurance will cover the cost of genetic testing even if no insurance criteria exist for CDKN2A. Out-of-pocket costs for gene panel testing are now approximately $250 in many laboratories, which has significantly removed the financial barrier of these tests.

Total body surveillance is an important component of clinical management in patients predisposed to melanoma. Image-based diagnostics such as deep neural networks have enabled rapid diagnosis and triaging of skin cancer (Esteva et al., 2017; Tschandl et al., 2020). Full-body imaging (or three-dimensional imaging) is an emerging technique for patients predisposed to numerous atypical pigmented lesions, a previous diagnosis of melanoma, or a positive family history of melanoma. The apparatus catalogs an interactive image of the patient’s skin using an array of cameras integrated with software. Such technology may be used to monitor the onset and development of dysplastic nevi, which presents an increased risk for melanoma. Acquired nevi often serve as precursors to these lesions, although they are most commonly benign (Elder, 2006). These lesions exhibit a dynamic life cycle containing the following stages: inception, growth, senescence, and involution (Terushkin et al., 2010). Inception occurs when a nevus progenitor cell acquires a sequence alteration to facilitate proliferation. Growth defines active nevus proliferation. Senescence involves a series of cellular brakes that stop proliferation. Nevi are then relatively stable for a period of time before the lesion regresses and eventually disappears (Ross et al., 2011).

A previous cohort study determined that patients at risk for melanoma underwent significantly fewer biopsies after full-body imaging (Truong et al., 2016). Younger patients were found to have higher rates of biopsy, suggesting that full-body imaging may be less effective in those with increasing or changing nevi (Rayner et al., 2018; Truong et al., 2016). These digital skin models can be easily accessed by either the patient or dermatologist during follow-up, thereby increasing the potential to reinforce self-surveillance behaviors. Furthermore, full-body imaging may also enable the early detection of lesions specific to MTSs, for example, in BAP1 tumor disposition syndrome. Patients with this disorder may uniquely present with reddish–brown and dome-shaped papules that are 2–10 mm in diameter (Souriau et al., 2016). Computerized magnification may also enable the detection
of BAP1-mutated atypical intradermal tumors on the basis of histological features. Further studies that compare the appearance of nevi associated with MTS with those associated with sporadic tumors are required. Altogether, clinical guidelines for skin surveillance—regardless of technology—should be routinely monitored to reflect our collective knowledge of the disease.

CONCLUSION
Over the past few decades, tremendous strides have been made in the field of MTS. Early linkage attempts to decipher familial clusters resulted in the discovery of melanomas enriched in families with pathogenic CDKN2A and CD4 allelic variants. Since then, our understanding of heritable melanoma has been enriched with a more nuanced understanding of genetic and environmental context. In the era of personalized medicine, a more refined understanding of how high-risk sequence alterations interact with polygenic backgrounds and environmental exposures can help clinicians to deliver patient-centered, risk-stratified care.

Data availability statement
No datasets were generated or analyzed during this study.

ORCID
Sarem Rashid: http://orcid.org/0000-0002-3902-2155
Sameer Gupta: http://orcid.org/0000-0002-1812-6555
Shelley R. McCormick: http://orcid.org/0000-0003-2974-2633
Hensin Tsao: http://orcid.org/0000-0002-2204-2071

CONFLICT OF INTEREST
SRM and HT are authors of the chapter, “Inherited susceptibility to melanoma” in UpToDate. The remaining authors state no conflict of interest.

AUTHOR CONTRIBUTIONS
Conceptualization: SR, SG, HT; Writing - Original Draft Preparation: SR, SG, SRM, HT; Writing - Review and Editing: SR, SG, SRM, HT

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