Microcystic Adnexal Carcinoma–like Neoplasm in a Patient With *POT1* Mutation

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PRACTICE **POINTS**

- Dermatologists should consider referring patients with both a history of skin cancer and a strong family history of internal malignancy for genetic testing for *POT1* (protection of telomeres 1) mutations.
- Although melanoma, chronic lymphocytic leukemia, angiosarcoma, and gliomas are most commonly associated with *POT1* mutations, this case suggests a broader and more heterogeneous malignancy spectrum than previously recognized.

A 72-year-old man with a history of multiple cancers, including melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), presented to the dermatology clinic for a regularly scheduled full-body skin examination and subsequently was diagnosed with microcystic adnexal carcinoma (MAC). He previously had been referred to a medical geneticist and was found to have a *POT1* (protection of telomeres 1) mutation. While a connection between melanoma and *POT1* mutations has been established, further research may clarify the relationship between *POT1* mutations and specific skin cancer susceptibility.

A 72-year-old man with a history of multiple cancers, including melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), presented to the dermatology clinic for a regularly scheduled full-body skin examination. His family history was negative for malignancy, but due to his personal history of both primary internal cancers and skin cancers, the patient previously had been referred by dermatology to a medical geneticist for evaluation. He tested positive for a pathogenic *POT1* (protection of telomeres 1) variant associated with tumor predisposition, which most often is associated with cutaneous melanoma, chronic lymphocytic leukemia (CLL), angiosarcoma, and gliomas.[1]

At the current presentation, physical examination revealed a small, asymmetric, pink papule on the superior thoracic spine. A biopsy of the lesion was performed (Figure 1). Pathology demonstrated cornifying cystic structures with a granulomatous response at the surface of the tumor, ductal differentiation with depth, and infiltrative

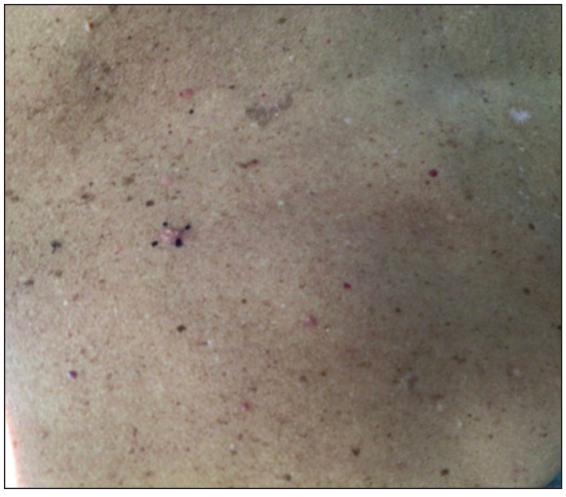

FIGURE 1. Microcystic adnexal carcinoma manifesting as a small, asymmetric, pink papule on the superior thoracic spine in a 72-year-old man with a history of multiple cancers and confirmed *POT1* mutation.

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strands and cords of hyperchromatic cells within a collagenous stroma at the base of the specimen (Figures 2A and 2B). One unusual finding was the presence of prominent clear-cell change within the superficial portion of the neoplasm (Figure 2C). Immunohistochemical stains revealed strong p63 and p40 positivity. Epithelial membrane antigen staining was positive in the hyperchromatic strands and cords with depth but not in the clear-cell superficial portion. Similarly, periodic acid–Schiff–positive material increased within tumor cells in proportion to depth of infiltration. Additional immunohistochemical staining showed carcinoembryonic antigen was largely negative (with rare positivity in a few ductal lumina), with negative results for S100, SOX10, CD117, BerEP4, factor XIIIa, CD34, and cytokeratin 7 (Figures 2D and 2E).

The differential diagnoses included trichilemmal carcinoma (which may manifest with CD34 expression),[2] clear cell BCC, adenoid cystic carcinoma (tubular variant), sebaceous carcinoma, and eccrine carcinoma. Importantly, the patient was under continuous oncologic surveillance, with no evidence of a primary internal tumor to suggest metastasis. Despite negative carcinoembryonic antigen staining, the immunohistochemical and histopathologic findings fit best with a primary cutaneous malignant eccrine tumor, specifically microcystic adnexal carcinoma (MAC), in which p63 typically stains peripheral cells but solid variants have been described.[3]

Eccrine carcinoma is exceedingly rare, reported in 0.01% of diagnosed cutaneous malignancies, and demonstrates overlapping features to other malignant eccrine

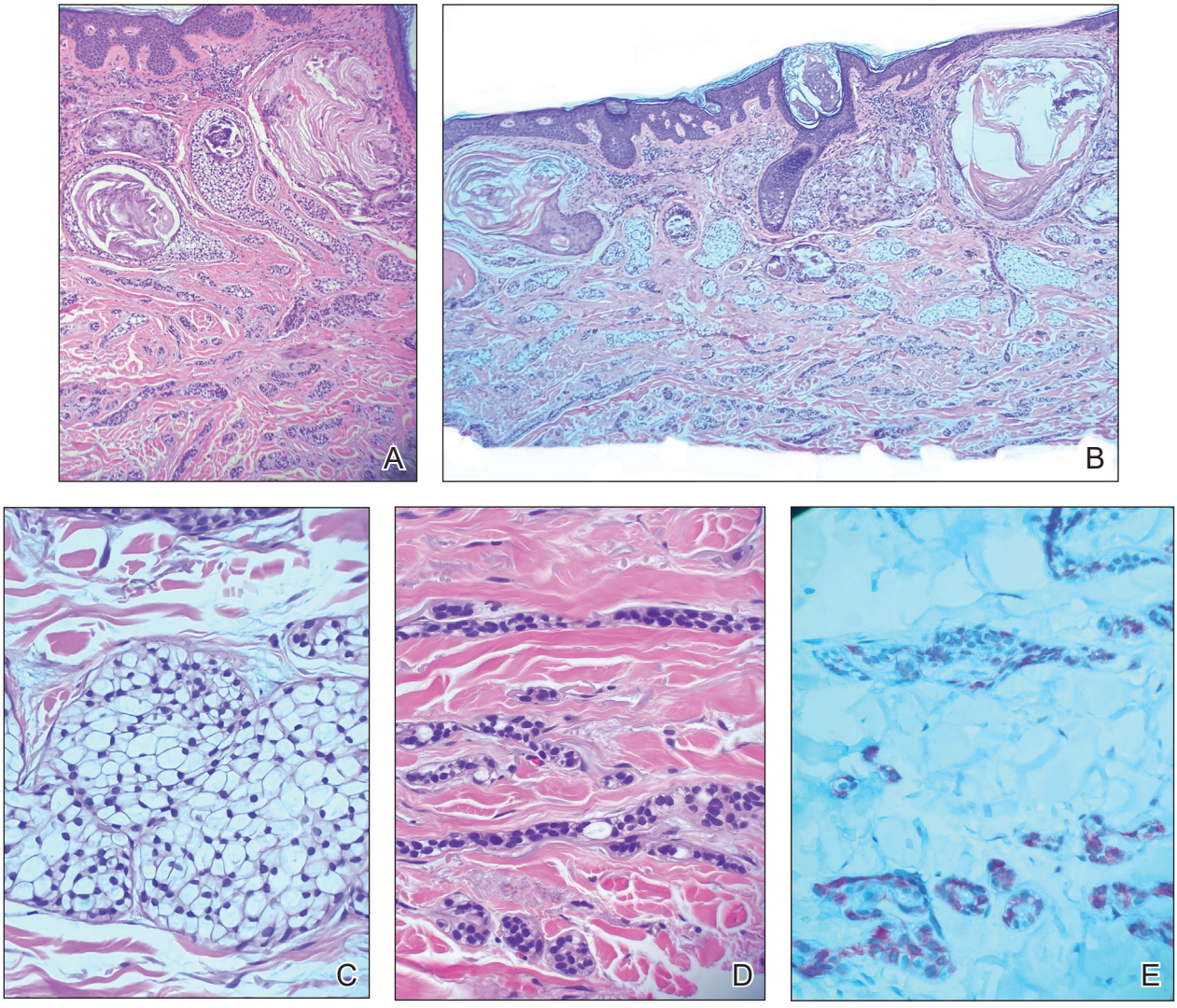

FIGURE 2. A and B, Cornifying cystic structures with clear-cell change superficially, focal foreign body granulomas, and strands and cords of infiltrative hyperchromatic cells with depth (H&E, original magnification ×4). C, High-power view of the superficial portion of the tumor with prominent clear-cell change (H&E, original magnification ×40). D, Ductal lumen noted within the infiltrative strands of tumor (H&E, original magnification ×40). E, Immunohistochemical stain with epithelial membrane antigen demonstrates positivity in the deeper desmoplastic and infiltrative tumor cells but not in the superficial component with clear-cell change (original magnification ×40).

tumors. It possesses an inconsistent immunohistochemical staining profile, making the distinction from other malignant sweat gland tumors challenging.[4] Given that the morphologic features were otherwise classic for MAC in our patient, we favored a clear-cell variant.

Sixteen years prior to the current presentation, our patient presented to urology with a history of prostatitis and increasing prostate-specific antigen levels. Biopsies were negative until prostate-specific antigen reached 13 ng/mL, confirming stage 1A prostate cancer. The patient subsequently underwent a robot-assisted radical prostatectomy. At age 63 years, dysphagia that was unresponsive to antibiotics led to a tonsillar biopsy revealing T2N2bM0 stage IVA SCC of the right tonsil with confirmed HPV type 16 with extracapsular extension. The patient underwent transoral robotic radical tonsillectomy and right neck dissection, followed by adjuvant chemoradiation consisting of intensity-modulated radiation therapy (IMRT) to a total dose of 63 Gy in 33 fractions, with concurrent weekly cisplatin. At age 67 years, dyspepsia, dysphagia, pyrosis, and gastroesophageal reflux prompted endoscopy, revealing T1aNxMx esophageal adenocarcinoma. Three months later, the patient underwent laparoscopic-assisted esophagectomy, with no recurrence. At age 68 years, an atypical intramelanocytic proliferation was found on the left cheek and was treated with Mohs micrographic surgery.

At age 71 years, acral lentiginous malignant melanoma (Breslow thickness 0.8 mm; Clark level IV; American Joint Committee on Cancer T1b) was diagnosed on the left plantar foot and treated with Mohs micrographic surgery. Sentinel lymph node biopsy was negative. Squamous cell carcinoma in situ on the frontal scalp and nodular BCC on the right upper back also were diagnosed.

While there are no guidelines for surveillance of individuals with *POT1*, recommendations were given in consensus from a medical genetics team,[1] including comprehensive monitoring—specifically baseline imaging utilizing brain and full-body magnetic resonance imaging. Furthermore, considering the crucial role of *POT1* in maintaining telomeres, it was advised to measure telomere length as part of the surveillance process. Given the patient's susceptibility to CLL, routine complete blood count assessments were recommended. Additionally, we advised close monitoring for seizures and consideration of genetic testing in first-degree relatives.

Literature Review

Given our patient's history of multiple skin cancers, including the most recent MAC, we sought to conduct a review of the literature to evaluate existing skin cancer associations and reports for patients with known *POT1* mutations to guide recommendations for dermatologic surveillance (Table). A search of PubMed articles indexed for MEDLINE through April 2023 using the terms *microcystic adnexal carcinoma*, POT1, *melanoma*, *basal cell carcinoma*, *squamous cell carcinoma*, and *skin cancer* yielded no reported cases of MAC associated with *POT1* mutations. POT1 is one of 6 proteins (TERF1, TERF2, RAP1, TIN2, TPP1, and POT1) belonging to the shelterin complex, which plays a crucial role in telomeric DNA remodeling and regulation of telomere length.[5] Mutation in the *POT1* gene disrupts the shelterin complex, causing telomeres to become elongated and unstable, resulting in chromosomal abnormalities and promoting cancer development.[5]

While our literature review did not reveal any associations between the shelterin complex genes and MAC, mutations in the *POT1* gene have been studied in other types of skin cancer, particularly melanoma.[1] One of the earliest studies was conducted in 2014 by Shi et al,[6] in which whole-exome sequencing was performed on families with a history of melanoma. Multiple *POT1* gene pathogenic variants associated with increased telomere length and fragility were identified in unrelated families. Subsequent studies have confirmed *POT1* variants in melanoma-prone families,[7] supporting an association between increased telomere length and melanoma risk[8-11]; however, other studies have yielded nonsignificant findings.[12,13] Further investigation also has identified morphologic characteristics consistent with *POT1* mutation, including spitzoid morphology.[14]

The association between *POT1* mutations and nonmelanoma skin cancers has been relatively understudied. While a few studies have explored this link, results have shown mixed findings. Some studies have suggested a potential role for *POT1* mutations in cutaneous SCC risk,[15] while other studies have shown no significant associations for both BCC and SCC risk and telomere gene mutations.[16] Additionally, mRNA levels of *POT1* were upregulated in BCC cases compared to normal tissue in a gene expression.[17]

Comment

In the literature, *POT1* mutations are well established as high-penetrance alterations associated with melanoma.[9,18,19] However, the correlation between *POT1* and other forms of skin cancer is not yet delineated. Recent insights suggest that *POT1* mutations play a major role in promoting melanoma progression through telomere elongation, an established driver of melanoma progression, thereby extending the proliferative capacity of incipient cancer cells.[20] This notion is supported by observations of increased telomere length in melanoma-prone families with *POT1* mutations. Given this association, research has focused on examining the relationship between telomere length and skin cancer.

Several studies have examined the relationship between telomere length and the risk for various types of skin cancer, including melanoma, BCC, and SCC. Prior investigations have suggested that shorter telomere length is associated with a decreased risk for melanoma and an increased risk for BCC, while no significant association has been observed for SCC.[16] However, subsequent

reports analyzing *POT1* variants have failed to reveal any conclusive associations between BCC and SCC and telomere length.[16,21]

In contrast, other genetic variants associated with melanoma susceptibility have demonstrated notable associations with BCC and SCC; for instance, the *CDKN2A* (cyclin-dependent kinase inhibitor 2A) gene, which is the first gene linked to high-risk familial melanoma, exhibits an increased presence of mutations in individuals with BCC and SCC.[22] Similarly, the *MC1R* (melanocortin 1 receptor) variant, a gene involved in human pigmentation and known to increase the risk for melanoma, carries a statistically significantly higher risk for BCC (summary odds ratio, 1.39; 95% CI, 1.15-1.69) and SCC (summary odds ratio, 1.61; 95% CI, 1.35-1.91) when at least one variant is present and an even greater risk with 2 or more variants.[23]

Considering the potential importance of *POT1* mutations and their association with melanoma, as well as the inconsistencies surrounding *POT1* mutations

TABLE. Existing Studies Examining the Relationship Between *POT1* Mutations and Skin Cancer

Reference (Year)	Relevant cancer assessed	Results
Müller et al[8] (2018)	Melanoma	Discovered 54 variants, 8 of which were exclusive in high-risk melanoma patients; 2 of the variants were nonsynonymous: g.124510982 G>A (p.R80C) and g.124491977 T>G (p.N300H)
Robles-Espinoza[9] (2014)	Melanoma	Determined germline variants in *POT1* were present in approximately 4% of familial melanoma pedigrees (negative for *CDKN2A* and *CDK4* mutations) and 2 of 34 pedigrees with ≥5 cases; found that loss-of-function variants in *POT1* led to increased telomere length
Shi et al[6] (2014)	Melanoma	Identified a rare variant in the *POT1* gene that was associated with increased telomere length and fragile telomeres
Wilson et al[7] (2017)	Melanoma	Uncovered a novel *POT1* germline mutation within a family with multiple primary melanomas: g.124503682 T>C
Potrony et al[19] (2019)	Melanoma	Identified *POT1* germline mutations in 1.75% of families; detected in 4 of 228 *CDKN2A* wild-type melanoma-prone families
Wong et al[10] (2019)	Melanoma	Identified *POT1* p.I78T variant and demonstrated how it disrupts *POT1*-telomere binding and promotes telomere lengthening
Sargen et al[14] (2020)	Spitzoid melanoma	Determined spitzoid morphology associated with *POT1* mutation
Pastorino et al[18] (2020)	Melanoma	Identified multiple variants in the *POT1* gene, including 2 pathogenic splicing variants and 6 missense VUS; found *POT1* variants demonstrated a higher frequency than the other genes
Potjer et al[12] (2019)	Melanoma	Detected no pathogenic variants in *POT1* gene in the families
Pellegrini et al[13] (2022)	Melanoma	Found that none of the patients carried a pathogenic *POT1* S270N variant
Simonin-Wilmer et al[11] (2023)	Melanoma	Found that approximately 0.5% of melanoma cases carried pathogenic variants that were associated with increased telomere length
Zhang et al[17] (2016)	BCC	Found upregulated mRNA levels of multiple *POT1* proteins while TIN2 was downregulated in BCC
Nan et al[16] (2011)	Melanoma, BCC, SCC	Observed no significant associations for BCC and SCC risk and single nucleotide polymorphisms in the *POT1* gene
Shen et al[15] (2020)	Melanoma, BCC, SCC	Found that 3.7% of melanoma cases examined possessed nonbenign *POT1* variants, whereas 9% of SCC and 2.7% of BCC contained nonbenign *POT1* variants

Abbreviations: BCC, basal cell carcinoma; CDK4, cyclin-dependent kinase 4; *POT1*, protection of telomeres 1; SCC, squamous cell carcinoma; TIN2, TERF1-interacting nuclear factor 2; VUS, variants of uncertain significance.

and their associations with BCC and SCC, further research may clarify the impact of *POT1* mutations on the development and progression of different types of skin cancers and improve understanding of the complex interplay among telomere length, genetic variants, and skin cancer susceptibility. Given the established risk for melanoma with *POT1* mutations, regular dermatology surveillance seems prudent. Dermatologists should consider referring patients with multiple skin cancers (especially melanoma) and any strong family history of internal malignancies to genetic testing for *POT1*. Though melanoma, CLL, angiosarcoma, and gliomas are the most commonly associated malignancies with *POT1* mutations, as our case demonstrates, presentations can be heterogeneous, and the spectrum of malignancies associated with *POT1* may be more expansive than previously thought.

For our patient, the current surveillance plan is full-body skin examinations every 3 months. Given no prior family history of malignancies, presumably our patient's case was a spontaneous mutation. Interestingly, despite his many primary cancer diagnoses and metastases, our patient has responded well to all treatments without recurrence. It is unclear if these characteristics and treatment successes are features of *POT1*-associated cancers. Further research is needed to refine recommendations for screening and management of patients with identified *POT1* mutations.

Conclusion

This case report highlights a rare occurrence of MAC in a patient with a *POT1* mutation. Given the limited research conducted on investigating *POT1* mutations and skin cancer, it is important to consider various forms of skin cancer, in addition to melanoma, when treating patients with a *POT1* mutation.

REFERENCES

1. Accardo ML, Osborne J, Else T. *POT1* tumor predisposition. *GeneReviews®*. October 29, 2020. Updated December 4, 2025. University of Washington.
2. Chaichamnan K, Satayasoontorn K, Puttanupaab S, et al. Malignant proliferating trichilemmal tumors with CD34 expression. *J Med Assoc Thai*. 2010;93(suppl 6):S28-S34.
3. Kavand S, Cassarino DS. "Squamoid eccrine ductal carcinoma": an unusual low-grade case with follicular differentiation. are these tumors squamoid variants of microcystic adnexal carcinoma? *Am J Dermatopathol*. 2009;31:849-852.
4. Kaseb H, Babiker HM. Eccrine carcinoma. *StatPearls [Internet]*. Updated June 26, 2023. Accessed May 11, 2026. https://www.ncbi.nlm.nih.gov/books/NBK541042/
5. Ye JZ, Hockemeyer D, Krutchinsky AN, et al. POT1-interacting protein PIP1: a telomere length regulator that recruits POT1 to the TIN2/TRF1 complex. *Genes Dev*. 2004;18:1649-1654. doi:10.1101/gad.1215404
6. Shi J, Yang XR, Ballew B, et al. Rare missense variants in POT1 predispose to familial cutaneous malignant melanoma. *Nat Genet*. 2014;46:482-486. doi:10.1038/ng.2941
7. Wilson TL, Hattangady N, Lerario AM, et al. A new POT1 germline mutation-expanding the spectrum of POT1-associated cancers. *Fam Cancer*. 2017;16:561-566. doi:10.1007/s10689-017-9984-y
8. Müller C, Krunic M, Wendt J, et al. Germline variants in the POT1-gene in high-risk melanoma patients in Austria. *G3 (Bethesda)*. 2018;8:1475-1480. doi:10.1534/g3.117.300394
9. Robles-Espinoza CD, Harland M, Ramsay AJ, et al. POT1 loss-of-function variants predispose to familial melanoma. *Nat Genet*. 2014;46:478-481. doi:10.1038/ng.2947
10. Wong K, Robles-Espinoza CD, Rodriguez D, et al. Association of the POT1 germline missense variant p.I78T with familial melanoma. *JAMA Dermatol*. 2019;155:604-609. doi:10.1001/jamadermatol.2018.3662
11. Simonin-Wilmer I, Ossio R, Leddin EM, et al. Population-based analysis of *POT1* variants in a cutaneous melanoma case-control cohort. *J Med Genet*. 2023;60:692-696. doi:10.1136/jmg-2022-108776
12. Potjer TP, Bollen S, Grimbergen AJEM, et al; Dutch Working Group for Clinical Oncogenetics. Multigene panel sequencing of established and candidate melanoma susceptibility genes in a large cohort of Dutch non-CDKN2A/CDK4 melanoma families. *Int J Cancer*. 2019;144:2453-2464. doi:10.1002/ijc.31984
13. Pellegrini C, Raimondi S, Di Nardo L, et al; Italian Melanoma Intergroup (IMI). Melanoma in children and adolescents: analysis of susceptibility genes in 123 Italian patients. *J Eur Acad Dermatol Venereol*. 2022;36:213-221. doi:10.1111/jdv.17735
14. Sargen MR, Calista D, Elder DE, et al. Histologic features of melanoma associated with germline mutations of CDKN2A, CDK4, and POT1 in melanoma-prone families from the United States, Italy, and Spain. *J Am Acad Dermatol*. 2020;83:860-869. doi:10.1016/j.jaad.2020.03.100
15. Shen E, Xiu J, Lopez GY, et al. *POT1* mutation spectrum in tumour types commonly diagnosed among *POT1*-associated hereditary cancer syndrome families. *J Med Genet*. 2020;57:664-670. doi:10.1136/jmedgenet-2019-106657
16. Nan H, Qureshi AA, Prescott J, et al. Genetic variants in telomere-maintaining genes and skin cancer risk. *Hum Genet*. 2011;129:247-253. doi:10.1007/s00439-010-0921-5
17. Zhang L, Huang X, Zhu X, et al. Differential senescence capacities in meibomian gland carcinoma and basal cell carcinoma. *Int J Cancer*. 2016;138:1442-1452. doi:10.1002/ijc.29882
18. Pastorino L, Andreotti V, Dalmasso B, et al. Insights into genetic susceptibility to melanoma by gene panel testing: potential pathogenic variants in *ACD*, *ATM*, *BAP1*, and *POT1*. *Cancers (Basel)*. 2020;12:1007. doi:10.3390/cancers12041007
19. Potrony M, Puig-Butille JA, Ribera-Sola M, et al. POT1 germline mutations but not TERT promoter mutations are implicated in melanoma susceptibility in a large cohort of Spanish melanoma families. *Br J Dermatol*. 2019;181:105-113. doi:10.1111/bjd.17443
20. Kim WT, Hennick K, Johnson J, et al. Cancer-associated POT1 mutations lead to telomere elongation without induction of a DNA damage response. *EMBO J*. 2021;40:e107346.
21. Ventura A, Pellegrini C, Cardelli L, et al. Telomeres and telomerase in cutaneous squamous cell carcinoma. *Int J Mol Sci*. 2019;20:1333. doi:10.3390/ijms20061333
22. Helgadottir H, Höiom V, Jönsson G, et al. High risk of tobacco-related cancers in CDKN2A mutation-positive melanoma families. *J Med Genet*. 2014;51:545-552. doi:10.1136/jmedgenet-2014-102320
23. Tagliabue E, Fargnoli MC, Gandini S, et al; M-SKIP Study Group. MC1R gene variants and non-melanoma skin cancer: a pooled-analysis from the M-SKIP project. *Br J Cancer*. 2015;113:354-363. doi:10.1038/bjc.2015.231