OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

Melanoma: A Disease For All Ages

Laya Thangamani
dethx.567@gmail.com

ABSTRACT

Melanoma is an aggressive malignancy of melanocytes that accounts for a small proportion of skin cancer diagnoses yet contributes disproportionately to skin cancer–related mortality. While traditionally associated with older adults, melanoma represents one of the most frequently diagnosed cancers among adolescents and young adults (AYAs), highlighting the need for age-specific scientific and clinical perspectives. This review synthesizes current literature on the biology of melanoma, with particular emphasis on molecular signaling pathways, recurrent genetic mutations, patterns of disease detection in AYA populations, and emerging therapeutic strategies. Key oncogenic drivers—including mutations in BRAF, NRAS, and KIT—are examined in the context of aberrant MAPK pathway activation and melanoma progression. Additionally, this review evaluates diagnostic challenges unique to AYAs and discusses how advances in targeted therapy and immunotherapy have reshaped treatment outcomes. By integrating molecular mechanisms with age-relevant clinical considerations, this review aims to provide a focused framework for understanding melanoma pathogenesis and management in adolescent and young adult populations.

INTRODUCTION

Melanoma is an aggressive malignancy originating from melanocytes, the pigment-producing cells responsible for synthesizing melanin. Although it accounts for approximately 1% of all skin cancer diagnoses, melanoma contributes disproportionately to skin cancer–related mortality due to its high potential for metastasis, therapeutic resistance, and recurrence following treatment [1]. Advances in molecular oncology over recent decades have substantially improved understanding of the biological mechanisms that drive melanoma progression, particularly the role of recurrent genetic mutations in oncogenes such as BRAF, NRAS, and KIT. These mutations lead to dysregulation of critical signaling pathways, most notably the mitogen-activated protein kinase (MAPK/ERK) pathway, resulting in uncontrolled cellular proliferation and tumor formation [2]. Concurrently, the development of targeted therapies and immune checkpoint inhibitors has transformed treatment outcomes for many patients with advanced disease.

While melanoma has historically been regarded as a cancer predominantly affecting older adults, its increasing incidence among adolescents and young adults (AYAs) has prompted renewed scientific and clinical attention. In medical research, AYAs are commonly defined as individuals aged 15 to 39 years [3]. Within this population, melanoma ranks among the most frequently diagnosed cancers, particularly in females aged 15 to 29 years. Epidemiologic studies have identified intermittent ultraviolet (UV) exposure and indoor tanning as major risk factors in this age group. Data from the Surveillance, Epidemiology, and End Results (SEER) Program indicate that melanoma incidence in young women rose significantly from the 1990s through the early 2010s, even as rates in older adults began to stabilize [4]. Consistent with these findings, the Skin Cancer Foundation reports that melanoma is the second most common cancer in women under 30 years of age and that indoor tanning before age 35 increases melanoma risk by up to 75% [5].

The etiology of early-onset melanoma is multifactorial, reflecting an interplay between biological susceptibility and behavioral exposure. Despite widespread public health messaging, many adolescents and young adults underestimate their personal risk for melanoma and engage inconsistently in preventive behaviors such as routine skin self-examination or timely clinical evaluation of suspicious lesions. These patterns contribute to delays in detection and underscore the importance of understanding how melanoma presents and is identified in younger populations.

At the molecular level, the relationship between ultraviolet radiation and melanoma development is well established. UVB radiation induces direct DNA damage through the formation of cyclobutane pyrimidine dimers, while UVA exposure generates reactive oxygen species that cause indirect oxidative damage to DNA and other cellular components. In response, cells activate the DNA damage response (DDR), a coordinated network of repair mechanisms and cell cycle checkpoints that function to preserve genomic integrity. When DNA damage is extensive or repair mechanisms fail, mutations may become permanently fixed within the genome, increasing the likelihood of malignant transformation.

This review examines melanoma through the integrated lenses of molecular biology and age-specific clinical relevance. By synthesizing current literature on melanoma biology, recurrent genetic mutations, patterns of disease detection in adolescent and young adult populations, and therapeutic implications, this article aims to provide a focused framework for understanding melanoma pathogenesis and management in AYAs. Emphasizing both mechanistic insight and clinical application, this review highlights key considerations for advancing research and improving outcomes in this increasingly affected population.

METHODOLOGY

This review was conducted using a literature search of the PubMed, Google Scholar, and MPDI databases. Searches were conducted using keywords such as *"melanoma," "AYA," "BRAF mutation," "NRAS mutation," "melanoma therapy," and "melanoma stages."* Articles that have been published between 2013 and 2023 were used to examine both older and new studies. Only peer-reviewed articles were considered. Studies were included if they mentioned the genetic background of melanoma, occurrence in the AYA category, detection, epidemiology, and therapeutic strategies. Articles focusing on skin cancers other than melanoma and lacking relevance to pathogenesis were not considered. After reading the abstracts and titles, the articles were selected and read entirely. Key information collected from each article was compared across multiple sources based on mutation, diagnostics, and treatment results. The information that was extracted was then summarized and arranged into categories corresponding to melanoma biology, genetic mutations, diagnosis in AYA, and treatment options.

BIOLOGY OF MELANOMA

Melanoma arises from melanocytes, specialized cells located primarily in the basal layer of the epidermis that synthesize melanin to protect the skin from ultraviolet (UV) radiation. Under normal physiological conditions, melanocyte proliferation and survival are tightly regulated by signaling pathways that respond to environmental cues and cellular stress. Multiple studies indicate that malignant transformation occurs when this regulatory balance is disrupted, allowing melanocytes to evade growth control mechanisms, resist apoptosis, and acquire invasive properties.[21] This matters for AYAs since studies report higher prevalence of UV-related risk behaviors such as indoor tanning.[26] Studies suggest that this disruption is

triggered by DNA damage from chronic exposure to UV radiation.[14] However, not all individuals show the same susceptibility due to genetic differences.[9] These genetic differences include variation in pigmentation, gene mutations such as CDKN2A, and differences in DNA repair capacity.[9] Although indoor tanning increases the risk of developing melanoma, the magnitude varies among individuals.[26] It remains difficult to determine the relative contribution of UV exposure versus genetic factors.[14] This matters clinically because it complicates prevention as well as assessing the risk of the lesion for AYAs.[26] The most frequently observed genetic alterations in melanoma and their associated signaling pathways are summarized in Table 1.

A central feature of melanoma biology is aberrant activation of intracellular signaling pathways that govern cell growth and survival.[9] Among these, the mitogen-activated protein kinase (MAPK) pathway plays a dominant role.[7] In healthy cells, MAPK signaling is transiently activated in response to external growth signals, leading to controlled cell division. In melanoma, however, persistent activation of this pathway promotes sustained proliferation and contributes to tumor progression.[7] Melanoma is distinguished from many other solid tumors by a high mutational burden, reflecting both the intrinsic biology of melanocytes and cumulative exposure to ultraviolet (UV) radiation.[10] Genomic analyses have revealed that melanoma is driven by recurrent activating mutations in genes regulating cell signaling pathways, as well as inactivating alterations in tumor suppressor genes that normally constrain cell growth and maintain genomic stability.[10] These genetic changes do not act independently; rather, they converge on a limited number of core pathways that promote sustained proliferation, survival, and resistance to cellular stress.[10] Many studies show that melanoma has a higher amount of mutations than most other skin cancers.[10] This helps explain why melanoma grows quickly and how it can quickly adapt to stress or treatment.[10] A high amount of mutations can result in increasing the chances of resisting therapeutic agents.[18] This factor partially explains why melanoma is aggressive and how it can be compared to other skin cancers.[10]

The most common oncogenic alteration in cutaneous melanoma involves mutations in the BRAF gene, which are present in approximately 40–50% of cases.[7] The BRAF V600E mutation results in constitutive activation of the BRAF kinase, leading to persistent downstream signaling through the mitogen-activated protein kinase (MAPK) pathway independent of upstream growth factor stimulation.[7] This continuous signaling promotes unchecked cell division and supports early tumor development.[7] BRAF mutations are particularly prevalent in melanomas arising on intermittently sun-exposed skin and are frequently detected in younger patients, suggesting a distinct molecular pattern in adolescent and young adult populations.[10] Most studies suggest that BRAF mutations are the most common genetic difference in melanoma.[7] This is primarily important for AYAs since they are more prone to show BRAF-supported tumors compared to individuals aged older than 21.[22] These findings show that BRAF mutations play an important role in melanoma developing early.[10] This has guided the growth of more targeted therapeutic agents for younger patients.[35] The prevalence helps target therapeutic strategies on MAPK inhibition in the younger generation.[35]

In melanomas lacking BRAF mutations, activating alterations in NRAS represent another major oncogenic driver.[9] NRAS mutations occur in approximately 15–25% of melanomas and similarly activate the MAPK pathway, while also engaging parallel signaling networks such as the phosphoinositide 3-kinase (PI3K)/AKT pathway.[9] Compared with BRAF-mutant melanomas, NRAS-mutant tumors are often associated with greater genomic instability and a more aggressive clinical course.[8] These differences highlight the molecular heterogeneity of melanoma and underscore the importance of mutation-specific classification in both biological and clinical contexts.[10] Unlike BRAF-mutant melanomas, NRAS-mutant tumors lean towards more than one signaling pathway.[9] This may explain why NRAS-mutant melanomas are harder to treat and are aggressive.[8] Relying on more

than one signaling pathway can diminish the effect of single-agent targeted therapies.[18] Additionally, this contributes to poor treatment outcomes.[8]

Less frequently, mutations in KIT are observed, particularly in distinct melanoma subtypes such as acral and mucosal melanomas.[9] KIT encodes a receptor tyrosine kinase involved in melanocyte development and survival, and activating mutations can lead to aberrant growth signaling.[9] Although KIT mutations are uncommon in cutaneous melanoma overall, their presence in specific subtypes illustrates how melanoma biology varies by anatomic site and developmental origin, further complicating disease classification and management.[12] These variations make it harder to classify and to use a single or general model.[12]

In addition to oncogenic drivers, loss-of-function mutations in tumor suppressor genes play a critical role in melanoma progression.[10] Alterations in genes such as CDKN2A, which regulates cell cycle progression through the p16INK4A and p14ARF pathways, impair normal growth control and facilitate malignant transformation.[9] Mutations in PTEN, a negative regulator of the PI3K/AKT pathway, further enhance cell survival and contribute to resistance to apoptosis.[11] Together, these alterations enable melanoma cells to bypass multiple layers of cellular regulation.[10] Research suggests that when tumor suppressor genes are minimal, they remove important cell growth functions.[11] This allows the melanoma cells to keep growing without stopping.[11] If and when tumor suppressor genes stop functioning, the cancer cells will lose control and keep multiplying allowing them to be persistent.[11]

The coexistence of activating oncogenic mutations and inactivated tumor suppressor pathways contributes to the biological aggressiveness of melanoma and its capacity to adapt to therapeutic pressure.[10] Importantly, this genetic landscape has direct clinical implications, informing both diagnostic classification and treatment selection.[35] Understanding how specific mutations shape melanoma behavior provides a critical foundation for interpreting patterns of disease detection and for evaluating targeted and immune-based therapeutic strategies discussed in subsequent sections.[35] These mutations show that melanoma is driven by various genetic factors all at the same time.[10] Together, these findings imply that melanoma is mainly driven by different mutation types making it harder to diagnose and identify a singular cause.[10] These factors all work together to prompt cancer growth.[10]

DETECTION AND DIAGNOSIS IN THE ADOLESCENT AND YOUNG ADULT POPULATION

Early detection remains one of the most important determinants of melanoma prognosis, yet diagnosis in adolescents and young adults (AYAs) presents unique clinical challenges.[26] Although melanoma in this age group is often detected at earlier stages than in older adults, delays in recognition and diagnosis still occur, influenced by age-specific clinical presentation, behavioral factors, and lower perceived risk among both patients and clinicians.[26] Most studies imply that early detection is an effective way to improve survival rates and to quickly recognize the affected area.[25] However, they also suggest that diagnosis can be delayed or inaccurate in AYAs.[26] Non-biological factors such as awareness and clinical suspicion play a significant role in this age group.[27] Delayed diagnosis lowers survival rates mainly due to it not being expected in the AYA population.[26]

The clinical evaluation of suspected melanoma typically relies on visual inspection and pattern recognition, most commonly guided by the ABCDE criteria: asymmetry, border irregularity, color variation, diameter greater than 6 mm, and evolution over time.[25] While these criteria remain valuable

screening tools, their application in AYAs can be limited.[25] Melanomas in younger patients may present as smaller lesions, exhibit less obvious asymmetry, or demonstrate subtle changes that do not immediately meet classic ABCDE thresholds.[25] As a result, lesions in AYAs may be misclassified as benign nevi, particularly when clinical suspicion is low.[25] Melanoma is more likely to appear smaller and won't adhere to the ABCDE guidelines in AYAs than older adults.[25] This means that standard screening rules will miss the lesion in early melanomas or younger cases.[25]

Histopathologic evaluation following biopsy remains the gold standard for melanoma diagnosis.[25] In AYAs, distinguishing between benign atypical nevi and early melanoma can be particularly challenging due to overlapping morphological features.[26] Pediatric and AYA melanomas may display distinct histologic patterns, including spitzoid morphology, which can complicate diagnostic interpretation and contribute to interobserver variability among pathologists.[26] These diagnostic ambiguities highlight the importance of experienced dermatopathologic assessment and, when appropriate, adjunctive molecular testing.[26] Many studies support that benign lesions are harder to recognize under a microscope in younger patients.[26] Even among skillful pathologists, there is uncertainty and disagreement while evaluating marginal cases.[26] This suggests that diagnosing AYA patients not only relies on technology but also on specialized professionals.[26]

Advances in molecular diagnostics have begun to supplement traditional histopathology in melanoma detection and classification.[10] Identification of driver mutations, such as BRAF or NRAS, can provide supportive evidence in diagnostically uncertain cases and assist in risk stratification.[10] In AYAs, molecular profiling may be especially valuable, as tumors often arise in the context of fewer accumulated genetic alterations compared with melanomas in older adults.[22] However, the routine use of molecular testing in early-stage melanoma remains an area of ongoing investigation.[10] While most cases use traditional histology as the basis of most diagnosis, some cases benefit from molecular testing as it provides additional information.[10] However, there is still partial agreement on when molecular testing should be used for earlier detected melanoma.[10] As a result, molecular testing can be used but not as a standard for all patients.[10]

Behavioral factors also influence diagnostic timing in AYAs.[27] Studies indicate that adolescents and young adults are less likely to perform routine skin self-examinations and may delay seeking medical evaluation for changing lesions.[27] Additionally, melanoma risk is frequently underestimated in this age group, contributing to missed opportunities for early detection.[27] These factors underscore the need for age-appropriate diagnostic awareness among clinicians, particularly in primary care and pediatric settings where early lesions may first be observed.[28] The behavior of not getting a regular skin check may contribute to a higher long-term risk of delayed diagnosis even when tumors could be still treated.[27]

Collectively, these challenges emphasize that melanoma detection in AYAs requires heightened clinical vigilance and an appreciation of age-specific presentation patterns.[26] Improved understanding of diagnostic limitations in younger populations is essential for reducing delays in diagnosis and optimizing outcomes.[26] As diagnostic strategies evolve, integrating clinical assessment with histopathologic and molecular tools may enhance early detection and inform therapeutic decision-making in adolescent and young adult patients.[26] Ultimately, this research shows that delayed diagnosis is caused by biological variations in individuals and age-related behaviors.[26] More research is needed to establish which diagnostic tools and rules work best and give accurate results in AYAs.[40]

THERAPEUTIC IMPLICATIONS: AGE-SPECIFIC STRATEGIES AND CHALLENGES

Advances in melanoma treatment have increasingly emphasized precision medicine, with therapeutic strategies guided by molecular profiling and immune responsiveness.[35] For adolescents and young adults (AYAs), however, the application of these therapies presents distinct challenges that extend beyond tumor control alone.[22] Differences in disease biology, treatment tolerance, and long-term survivorship considerations necessitate an age-specific approach to therapeutic decision-making.[22] Collectively, these data indicate that if younger patients such as AYAs consider treatment options, they should consider long-term effects and not short-term.[39]

Targeted therapies exemplify the importance of molecular stratification in melanoma treatment.[35] In AYAs, BRAF-mutant melanomas are relatively common, making BRAF and MEK inhibitors a frequent first-line option in advanced disease.[36] These agents can produce rapid tumor regression, which is particularly beneficial in younger patients with high disease burden or symptomatic metastases.[36] However, the development of acquired resistance remains a significant limitation.[18] In AYAs, prolonged life expectancy increases the clinical relevance of resistance mechanisms, as treatment failure may occur years after initial response.[22] This underscores the need for combination strategies and ongoing molecular monitoring to adapt therapy over time.[18] Most studies accept that BRAF and MEK inhibitors are beneficial in decreasing the size of the tumor primarily in BRAF-mutant melanoma.[36] However, studies show that the tumor develops resistance to the treatment which limits long-term control of the cancer.[18] This conveys that early treatment does not always guarantee long-term benefit for AYAs.[22]

Immunotherapy has further expanded treatment options and has demonstrated durable responses across age groups.[37] In AYAs, immune checkpoint inhibitors may be especially effective due to generally intact immune function and fewer age-related comorbidities.[22] Nevertheless, immune-related adverse events pose unique concerns in younger patients.[22] Endocrine toxicities, such as thyroid dysfunction or hypophysitis, may result in lifelong hormone replacement, introducing long-term health management challenges.[22] Balancing the potential for durable remission against the risk of chronic toxicity is therefore a central consideration in AYA melanoma care.[22] While immunotherapy can bring long-term remission, it also leads to higher risk in immune related side effects in comparison to targeted therapy.[35] This creates a trade-off between long-lasting control and the risk of treatment conditions that could be permanent in AYAs.[22]

Another age-specific challenge lies in clinical trial participation.[40] Despite being biologically well suited for experimental therapies, AYAs remain underrepresented in melanoma clinical trials.[40] Barriers include restrictive age eligibility criteria, limited access to specialized centers, and gaps between pediatric and adult oncology care.[40] This underrepresentation restricts the availability of age-specific efficacy and safety data, limiting the ability to optimize therapeutic strategies for this population.[40] Expanding AYA inclusion in trials is essential for refining treatment algorithms and improving outcomes.[40] Multiple studies show that AYAs are underrepresented in melanoma clinical trials.[40] Due to this, many treatment diagnoses are based on older patients and can be inaccurate as it is not age-specific.[40]

Long-term survivorship further distinguishes therapeutic decision-making in AYAs.[39] Many patients diagnosed in adolescence or early adulthood will live for decades following treatment, making late effects of therapy a critical concern.[39] Potential consequences include secondary malignancies, chronic immune dysregulation, and impacts on fertility and reproductive health.[39] Integrating survivorship planning into initial treatment discussions is therefore particularly important for AYAs, ensuring that therapeutic success is measured not only by survival but also by long-term quality of life.[39] These long-term risks make it primarily important to balance treatment options that are aggressive with quality of life considerations in AYAs.[39]

Taken together, the therapeutic management of melanoma in adolescents and young adults requires strategies that account for both biological efficacy and life-stage–specific challenges.[22] As treatment options continue to evolve, incorporating age-specific considerations into therapeutic planning will be essential for delivering effective, durable, and patient-centered melanoma care in this population.[22] All in all, these findings show that even if therapies are effective and beneficial in older patients, it may not be the same for younger patients as they will have different long-term consequences.[22] There is still a narrow amount of data directly comparing treatment results between AYAs and older patients.[22]

CONCLUSION

Melanoma in adolescents and young adults represents a distinct clinical and biological challenge that is not fully captured by frameworks developed for older adult populations.[22] Evidence from large-scale genomic studies has demonstrated that while the core oncogenic drivers of melanoma—such as activating mutations in BRAF and NRAS—are shared across age groups, younger patients often present with differences in mutation burden, tumor evolution, and immune responsiveness.[10] These findings suggest that age influences not only melanoma incidence but also its underlying biology and clinical behavior.[22]

Epidemiologic studies further reinforce the need for age-specific approaches.[31] Importantly, these trends persist despite stabilization or decline in older cohorts, indicating that prevention and early detection strategies effective in older adults may be insufficient for younger populations.[31] Clinical studies have also highlighted diagnostic challenges in AYAs, where melanomas may present with atypical features that fall outside classic screening criteria, increasing the risk of delayed diagnosis.[25]

Therapeutic outcomes provide additional insight into age-specific considerations.[22] Clinical trials evaluating BRAF and MEK inhibitors, as well as immune checkpoint inhibitors, demonstrate substantial survival benefits across age groups.[36][37] However, subgroup analyses and retrospective studies suggest that AYAs may experience distinct toxicity profiles and long-term treatment consequences.[22] For example, immune-related endocrine adverse events, while manageable in the short term, carry greater lifelong implications for younger patients.[22] These findings underscore the importance of integrating survivorship considerations into initial treatment planning for AYAs.[39]

Collectively, the literature indicates that melanoma in adolescents and young adults cannot be optimally managed through a one-size-fits-all approach.[22] Instead, effective care requires integration of molecular classification, age-aware diagnostic strategies, and therapeutic planning that accounts for long-term outcomes.[22] Future research should prioritize increased representation of AYAs in clinical trials, longitudinal studies of treatment-related toxicities, and refined molecular analyses to better define age-associated biological differences.[40] By aligning mechanistic insight with age-specific clinical evidence, the field can move toward more precise and durable melanoma management strategies for this increasingly affected population.[22]

ACKNOWLEDGEMENTS

This work was supported by the *College Impact* program, which provided mentorship, guidance, and academic resources that contributed to the development of this review. I gratefully acknowledge the support and feedback received throughout the research and writing process.

REFERENCES

1. American Cancer Society. Key Statistics for Melanoma Skin Cancer. 2024. Available at: https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html

2. Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. Cell. 2015;161(7):1681–1696. doi:10.1016/j.cell.2015.05.044

3. National Cancer Institute. Adolescent and Young Adult Oncology Program Review Group Report. Bethesda, MD: NIH; 2006. Available at: https://www.cancer.gov/types/aya

4. Surveillance, Epidemiology, and End Results (SEER) Program. SEER Cancer Stat Facts: Cancer Among Adolescents and Young Adults (Ages 15–39). National Cancer Institute. Updated 2025. Available at: https://seer.cancer.gov/statfacts/html/aya.html

5. Skin Cancer Foundation. Melanoma in Young People. Available at: https://www.skincancer.org/skin-cancer-information/melanoma/melanoma-in-young-people/

6. Davies H, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417(6892):949–954. doi:10.1038/nature00766

7. Jakob JA, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer. 2012;118(16):4014–4023. doi:10.1002/cncr.26724

8. Curtin JA, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005;353(20):2135–2147. doi:10.1056/NEJMoa050092

9. Hayward NK, et al. Whole-genome landscapes of major melanoma subtypes. Nature. 2017;545(7653):175–180. doi:10.1038/nature22071

10. Wu H, Goel V, Haluska FG. PTEN signaling pathways in melanoma. Oncogene. 2003;22(20):3113–3122. doi:10.1038/sj.onc.1206451

11. Bradford PT, et al. Acral lentiginous melanoma: Incidence and survival patterns in the United States, 1986–2005. Arch Dermatol. 2009;145(4):427–434. doi:10.1001/archdermatol.2008.609

12. Trucco LD, et al. Molecular and clinical characterization of melanoma in adolescents and young adults. J Clin Oncol. 2020;38(18_suppl):10050–10050. doi:10.1200/JCO.2020.38.18_suppl.10050

13. Mar VJ, Wong SQ, Li J, Scolyer RA, McLean C, Papenfuss AT, et al. BRAF/NRAS Wild-Type Melanomas Have a High Mutation Load Correlating with Histologic and Molecular Signatures of UV Damage. Clinical Cancer Research [Internet]. 2013 Jul 6;19(17):4589–98. Available from: https://aacrjournals.org/clincancerres/article/19/17/4589/78119/BRAF-NRAS-Wild-Type-Melanomas-Have-a-High-Mutation

14. Castellani G, Buccarelli M, Arasi MB, Rossi S, Pisanu ME, Bellenghi M, et al. BRAF mutations in melanoma: biological aspects, therapeutic implications, and circulating biomarkers. Cancers [Internet]. 2023 Aug 8;15(16):4026. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10452867/

15. Box NF, Vukmer TO, Terzian T. Targeting p53 in melanoma. Pigment Cell & Melanoma Research [Internet]. 2013 Oct 12;27(1):8–10. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4112749/

16. TP53 gene: MedlinePlus Genetics [Internet]. Available from: https://medlineplus.gov/genetics/gene/tp53/

17. Irvine M, Stewart A, Pedersen B, Boyd S, Kefford R, Rizos H. Oncogenic PI3K/AKT promotes the step-wise evolution of combination BRAF/MEK inhibitor resistance in melanoma. Oncogenesis [Internet]. 2018 Sep 20;7(9). Available from: https://www.nature.com/articles/s41389-018-0081-3

18. Corrales E, Levit-Zerdoun E, Metzger P, Mertes R, Lehmann A, Münch J, et al. PI3K/AKT signaling allows for MAPK/ERK pathway independency mediating dedifferentiation-driven treatment resistance in melanoma. Cell Communication and Signaling [Internet]. 2022 Nov 24;20(1). Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9700886/

19. Brown TA. Mutation, repair and recombination [Internet]. Genomes - NCBI Bookshelf. 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK21114/

20. Van Der Kooij MK, Wetzels MJAL, Aarts MJB, Van Den Berkmortel FWPJ, Blank CU, Boers-Sonderen MJ, et al. Age Does Matter in Adolescents and Young Adults versus Older Adults with Advanced Melanoma; A National Cohort Study Comparing Tumor Characteristics, Treatment Pattern, Toxicity and Response. Cancers [Internet]. 2020 Jul 27;12(8):2072. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7464956/

21. Tas F, Erturk K. Clinical and prognostic significance of BRAF V600E mutation in non-metastatic cutaneous melanoma patients. Neoplasma [Internet]. 2019 Jan 1;66(04):631–6. Available from: https://pubmed.ncbi.nlm.nih.gov/31058533/

22. Tas F, Erturk K. BRAF V600E mutation as a prognostic factor in cutaneous melanoma patients. Dermatologic Therapy [Internet]. 2020 Feb 15;33(2). Available from: https://pubmed.ncbi.nlm.nih.gov/32061008/

23. Abbasi NR, et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. JAMA. 2004;292(22):2771–2776. doi:10.1001/jama.292.22.2771

24. Whiteman DC, et al. Melanoma in adolescents and young adults: epidemiology and clinical outcomes. Eur J Cancer. 2015;51(18):2725–2733. doi:10.1016/j.ejca.2015.08.024

25. Kasparian NA, et al. Skin examination practices among individuals at high risk of melanoma. Arch Dermatol. 2009;145(8):922–928. doi:10.1001/archdermatol.2009.152

26. Geller AC, et al. Physician screening for melanoma: prevalence and predictors. Arch Dermatol. 1999;135(3):313–318. doi:10.1001/archderm.135.3.313

27. Agbai ON, et al. Skin cancer and photoprotection in people of color: a review and recommendations. J Am Acad Dermatol. 2014;70(4):748–762. doi:10.1016/j.jaad.2013.11.038

28. SEER Cancer Stat Facts: Melanoma of the skin. National Cancer Institute. Updated 2025. Available at: https://seer.cancer.gov/statfacts/html/melan.html

29. Dawes SM, et al. Racial disparities in melanoma survival. J Am Acad Dermatol. 2016;75(5):983–991. doi:10.1016/j.jaad.2016.06.029

30. Robinson JK, et al. Use of multimedia to increase melanoma awareness in minority populations. Arch Dermatol. 2011;147(7):804–810. doi:10.1001/archdermatol.2011.172

31. Lester JC, et al. Lack of diversity in dermatology images: comparison of textbooks and the internet. J Am Acad Dermatol. 2019;80(2):514–515. doi:10.1016/j.jaad.2018.07.046

32. Luke JJ et al. "Targeted agents and immunotherapies: optimizing outcomes in melanoma." Nat Rev Clin Oncol. 2017.

33. Long GV et al. "Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma." N Engl J Med.2014.

34. Larkin J et al. "Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma." N Engl J Med. 2019.

35. Johnson DB et al. "Tumor mutational burden and age-related response to immunotherapy in melanoma." J Immunother Cancer. 2018.

36. Benedict C et al. "Young adult cancer survivorship: Fertility and psychosocial health." Cancer Treat Res. 2020.

37. Shaw PH et al. "Adolescent and young adult (AYA) oncology: The first decades." Pediatr Blood Cancer. 2015.

Table 1: Key Genetic Mutations in Melanoma and Their Functional Impact

Gene	Mutation Frequency	Affected Pathway(s)	Functional Impact	Associated Melanoma Subtypes
BRAF (V600E)	~40–50% of melanomas	MAPK/ERK	Constitutive activation of MEK/ERK → uncontrolled proliferation	Most common in superficial spreading melanoma; especially prevalent in adolescents and young adults (AYAs)
NRAS	~15–30%	MAPK/ERK, PI3K/AKT	Persistent RAS signaling → proliferation + survival	Common in older adults; seen across subtypes
KIT	~10% (higher in acral/mucosal)	MAPK/ERK, PI3K/AKT	Activates downstream signaling via receptor tyrosine kinase	Acral lentiginous and mucosal melanoma
NF1	~10–15%	MAPK/ERK	Loss of negative regulation of RAS → pathway hyperactivation	Often in chronically sun-damaged skin
TP53	~10–20%	DNA damage response, apoptosis	Loss of cell cycle arrest and apoptosis → genomic instability	Associated with poor prognosis and resistance
CDKN2A	~30–50% (variable)	Cell cycle regulation	Loss of p16/ARF → unchecked cell cycle progression	Familial melanoma; various subtypes
TERT promoter	~70% in cutaneous melanomas	Telomerase activation	Extends replicative lifespan via telomere maintenance	Cutaneous melanoma (broadly across subtypes)
PTEN	~10%	PI3K/AKT	Loss leads to increased survival signaling	Seen in therapy resistance contexts