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Forecasting Melanoma with Precision Emerging Technologies and Biomarker-Based Risk Stratification

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Abstract

Accurate prediction and early identification of melanoma remain central challenges in dermatologic oncology, with traditional clinical tools—such as the ABCDE criteria and dermoscopy—limited by subjective interpretation and insufficient sensitivity for detecting early or atypical lesions. Advances in technology, including AI-driven image analysis, total body 3D imaging, and multispectral reflectance devices, have begun to standardize lesion assessment and enable more refined surveillance of high-risk individuals. Concurrently, biomarker-based risk stratification approaches—such as polygenic risk scoring, germline mutation profiling (CDKN2A, BAP1, MC1R), circulating tumor DNA, and microRNA signatures—are reshaping melanoma evaluation from morphology-based triage to biologically informed risk modeling. The integration of these diagnostic innovations with clinical phenotyping, environmental exposure data, and patient history offers a pathway toward individualized melanoma surveillance and prevention. In populations with genetic predispositions, chronic immunosuppression, or cumulative UV damage, multimodal tools can detect early malignant transformation, inform timing of intervention, and stratify follow-up intensity with greater precision. Implementation challenges persist, including inequitable access to genomic tools, underrepresentation of diverse skin types in training datasets, and a lag in provider readiness to interpret complex molecular outputs. Realizing the full potential of precision melanoma diagnostics will depend on reconceptualizing early detection as a biologically continuous process—anchored in molecular insight, enhanced by technological sophistication, and governed by a commitment to equity, accuracy, and anticipatory care.

1. Introduction

Skin cancer is the most common cancer in the United States, with melanoma, an aggressive skin cancer, occupying 1% of skin cancer diagnoses yet accounting for the majority of skin cancer deaths. (American Cancer Society, 2025) Melanoma cases demonstrate a rising global incidence and dangerous rates of mortality, especially when its diagnosis is delayed. A recent study by Wang et al. on global patterns in skin cancer incidence, mortality, and prevalence found that approximately 17% (58,667/331,722) of patients diagnosed with melanoma die from the disease. (Wang et al., 2025) Early detection remains imperative to improving prognosis, yet current frontline diagnostic tools often fall short of their promise to offer early detection. Traditional clinical tools, such as the ABCDE criteria and dermoscopy, are limited by variable sensitivity, (Garrison et al., 2023) especially for early-stage, atypical, or amelanotic lesions, and are heavily reliant on subjective interpretation.

These limitations underline a central challenge in melanoma care: not only the importance of identifying malignant transformation at its earliest stage, but also identifying them at more treatable stages with greater accuracy as well as consistency. Recent advances in technology and molecular diagnostics offer promising solutions. From AI-enhanced image analysis and total-body 3D photography to polygenic risk scores and circulating biomarkers, innovative tools are shifting melanoma evaluation beyond visual inspection and more so toward a more integrated, precision-based approach.

This paper delves into how novel technologies and biomarker-based stratification are reshaping melanoma surveillance--enabling individualized risk modeling, improving early detection in high-risk populations, and addressing longstanding gaps in sensitivity and equity across diverse patient groups.

2. Technological Advances in Imaging and Surveillance

Though notable advancements have been made in the early detection and treatment of skin cancer, it remains the most common type of cancer worldwide. Of its subtypes, melanoma is of greatest clinical concern, due to its likelihood of metastasis and malignancy. Currently, keen ophthalmological examinations, skin biopsies, and dermoscopic imaging are primarily used to assess skin lesions and derive treatment plans. These methods, when integrated with deep learning algorithms, hold considerable value in the detection of early-stage melanoma (Kwiatkowska et al., 2021). Convolutional Neural Networks (CNNs) is a specific, deep learning model architecture that successfully analyzes and learns intricate visual information from dermoscopic images. Using raw input, these models progressively extract advanced features from images until a feature map is generated. Notably, a novel FCDS-CNN architecture extracts knowledge from large datasets while utilizing transfer learning from pre-trained models (ResNet152V2, EfficientNetV2B0, InceptionResNetV2, and MobileNetV3). This data augmentation allowed for the accurate identification of rare and progressive cutaneous lesions (Nawaz et al., 2025). Due to its ability to extract discriminative features of skin lesions to 96%, the FCDS-CNN model may be paramount in early-stage melanoma detection, which will thereby improve patient outcomes and reduce mortality rates.

Convolutional Neural Networks (CNNs) have also been influential in the utilization of a 3D whole-body imaging system for skin lesion screening. Whole-body imaging modalities capture the complete epidermis, allowing for longitudinal assessments of old and new lesions that evolve over time (Ahmedt-Aristizabal et al., 2023). After 2D images of a whole-body surface are captured, images are processed for 3D reconstruction, where deep learning models localize the lesions and map them to their corresponding anatomical locations. This 3D imaging allows for a 360-degree view of images from all angles, and the ability to examine curved surfaces and lesion borders, features that dermoscopy alone cannot provide. In a randomized clinical trial with subjects high-risk for developing melanoma, however, usage of 3D total-body photography did not show significant outcomes without the use of AI (Lindsay et al., 2025). Compared to the control group, intervention group participants had more benign excisions and more biopsy specimens, with similar total quality-adjusted life-years per person between the two. Other literature suggests that total-body photography succeeded in identifying a greater amount of in situ tumors and melanoma, while also noting the unconventional potential AI can have in image analysis and pattern recognition (Hornung et al., 2021). These assessments further underscore the role of CNNs in early-stage melanoma detection and the power of AI in shaping clinical outcomes.

Non-invasive optical imaging techniques can further aid in the early detection of melanoma. Confocal microscopy (CM) is further divided into reflectance CM (RCM), which utilizes reflectance contrast from skin tissue, and ex vivo CM (EVCM), which relies on fluorescent nuclear dye to image tissue (Atak et al., 2023). RCM is especially useful in the detection of melanocytic lesions, as melanin has a high refractive index, thus appearing bright on the device. RCM has significant clinical value when detecting melanomas such as lentigo maligna melanoma on sun-damaged skin, namely the head and neck. When compared to dermoscopy alone, RCM showed greater sensitivity and specificity for suspicious melanoma (Dinnes et al., 2018). Because RCM is non-invasive, such findings are especially promising for patients who may not be surgical candidates, or who cannot afford such procedures. For physicians, RCM may help reduce unnecessary excisions while ensuring the detection of malignant melanomas. EVCM proves to be clinically useful for the real-time assessment of tumor margins from freshly excised cutaneous tissue. This tool would allow physicians to accurately measure melanoma thickness and then correctly determine surgical margins before excision (Cinotti et al., 2018). In

addition to truncating histological evaluation time, EVCM would be especially beneficial in resource-poor countries lacking formal laboratory equipment and personnel.

3. Molecular and Genetic Risk Stratification

Traditional melanoma diagnostics have relied mainly on visual and morphological criteria, but emerging biomarker-based strategies are helping shift risk assessment toward molecular precision. Among high-penetrance genetic contributors, mutations in the CDKN2A gene, responsible for encoding tumor suppressors p16INK4a and p14ARF, are the most commonly identified germline alterations in familial melanoma (Fargnoli et al., 2010). However, CDKN2A alone does not fully explain observed melanoma clustering within families, prompting investigations into genetic modifiers such as melanocortin 1 receptor (MC1R). MC1R variants, particularly red hair color, not only increase melanoma risk independently but also significantly enhance CDKN2A penetrance and lower age of onset when co-inherited (Fargnoli et al., 2010). These interactions illustrate how polygenic and additive effects influence risk, calling for the importance of polygenic risk scores (PRS). PRSs aggregate common variants, including low-to-moderate-risk alleles in pigmentation genes like MC1R and ASIP, and have demonstrated 2–3-fold increases in melanoma risk across populations (Roberts et al., 2019). While the clinical utility of PRS remains modest in isolation, its integration with germline mutation profiling provides a multi-tiered approach to individualized surveillance. Beyond CDKN2A and MC1R, BAP1 mutations define a tumor predisposition syndrome encompassing uveal, mesothelioma, and cutaneous melanomas, further emphasizing the inclusion of diverse germline alterations in melanoma risk modeling (Papakostas et al., 2020). Collectively, these biomarkers move risk assessment beyond phenotype alone, supporting a biologically informed and preemptive strategy for high-risk individuals.

Complementing genetic risk stratification, liquid biopsy technologies are transforming melanoma detection by providing minimally invasive, real-time insights into tumor dynamics. Circulating tumor DNA (ctDNA), which is released into the bloodstream as tumors grow and mutate, can be detected even in early stages and has been linked to tumor burden and patient outcomes, including progression-free survival (Slusher et al., 2024). This allows clinicians to monitor disease activity over time without repeated surgical biopsies, making it especially useful for high-risk patients. In parallel, microRNAs (miRNAs), small regulatory RNA molecules found in blood, have emerged as another promising marker, particularly when enclosed in exosomes that protect them from degradation (Friedman et al., 2023). Their expression patterns often reflect tumor stage and aggressiveness, with specific miRNAs like miR-221 and miR-150-5p associated with worse survival outcomes. These findings suggest that miRNAs can play a crucial role in refining diagnosis and guiding early intervention, empowering clinicians to take proactive measures. Notably, the packaging of these markers in extracellular vesicles does more than enhance stability; it also reflects ongoing communication between tumor cells and the immune system. For example, some melanoma-derived exosomes carry PD-L1, a protein that can interfere with immune response and signal resistance to immunotherapy (Slusher et al., 2024). When used together, ctDNA and miRNAs offer a broader picture of tumor behavior, enabling earlier and more tailored care than a clinical exam alone. Integrating liquid biopsy markers into routine practice could shift melanoma care from waiting for symptoms to appear toward continuous, tailored surveillance and timely intervention.

Integrating molecular diagnostics with liquid biopsy technologies and computational tools reshapes melanoma surveillance. In a prospective clinical trial of patients with advanced solid tumors, early changes in ctDNA levels were strongly linked to treatment outcomes. Notably, patients who achieved ctDNA clearance had 100% overall survival at 25 months, demonstrating the potential of ctDNA as a sensitive, non-invasive marker of therapeutic response in melanoma (Bratman et al., 2020). Researchers developed the Molecular Oncology Almanac (MOAlmanac) to expand the utility of molecular data. This clinical interpretation platform analyzes well-known genomic mutations, like BRAF, and broader features such as tumor burden and mutational signatures. When tested in a retrospective cohort of patients with metastatic melanoma, MOAlmanac identified meaningful molecular features in every case (Reardon et al., 2021). It often uncovered treatment options that traditional sequencing did not detect. The platform matches patient data to similar cancer models and helps guide risk stratification and personalized surveillance planning. This approach is beneficial in cases where few standard treatment targets are available. These tools support shifting from fixed staging systems to adaptive, biology-driven melanoma care.

4. Multimodal Integration for Individualized Melanoma Monitoring

Deep-learning fusion architectures are now piloting true cross-modal melanoma surveillance by integrating three complementary layers of data into continuously updated risk malignancy-probability scores. In the imaging layer, AI-assisted 2-D dermoscopy and 3-D total-body photography construct a longitudinal "digital skin," with convolutional-neural-network (CNN) classifiers spotting new or evolving lesions earlier and more reproducibly than physician exam alone (Cerminara et al, 2023; Winkler et al., 2024). Notably, in an eight-center prospective study of over 20,000 lesions, an ensemble CNN reached 79% balanced accuracy and 92% sensitivity – surpassing dermatologist sensitivity (73%) on the same images – albeit with a lower specificity (67% vs. 83%), highlighting the familiar trade-off of increased melanoma detection at the expense of false-positives (Heilein et al., 2024). For equivocal lesions or high-risk individuals, reflectance confocal microscopy (RCM) offers a noninvasive, *in vivo* "optical biopsy" that enables cellular-resolution evaluation, reducing benign excisions and aiding early detection in atypical presentations. In the molecular layer, tumor-informed liquid biopsies (circulating-tumor DNA, melanoma-specific microRNAs, methylation signatures) flag malignant transformations months before morphologic change and predict recurrence in stage II-III disease (Marchisio et al., 2024). Genta et al. (2024) reported that ctDNA surveillance identified recurrence a median of 128 days earlier than standard radiologic or clinical evaluation. This lead time not only facilitates earlier intervention but may also enable curative resection or timely immunotherapy escalation before widespread disease progression.

The clinical-genomic layer leverages polygenic-risk scores (PRS) combining common pigmentation variants (e.g., MC1R) with high-penetrance melanoma genes (CDKN2A, BAP1) to improve risk assessment in clinical cohorts (Pellegrini et al., 2024). Early efforts to enrich these models with environmental context have paired PRS with self-reported UV exposure to enhance disease-risk predictions (Fontanillas et al., 2021). Enrichment with dynamic, real-world exposures remains under active investigation. Two variables show particular promise: (i) continuous, erythemally weighted UV-dose logs from wearable dosimeters (Dumont et al., 2024); and (ii) the current class of immunosuppressive medication used in solid-organ-transplant care. In a study involving the UK Biobank, adding a 68-SNP PRS to routine clinical factors raised discrimination from an AUC (Area Under the Receiver-Operating-Characteristic Curve) of 0.629 to 0.685 – about a 9% relative gain across 54,799 participants (Wong et al., 2023). Separately, transplant data illustrate the impact of immunosuppression: among 444,497 U.S. solid-organ-transplant recipients, melanoma incidence was 52% higher than expected, yet regimens that substituted calcineurin inhibitors with mammalian-target-of-rapamycin (mTOR) inhibitors cut that excess by ~25% (Sargen et al., 2022). Together, these observations suggest that precision surveillance must go beyond genetic predisposition to dynamically incorporate modifiable environmental and pharmacologic factors—tracking personal UV exposure in real time and adjusting risk thresholds based on changing immunosuppression regimens. When the imaging, molecular, and clinical-genomic layers are combined, they enable tailored care – for example, a top-decile PRS patient with stable imaging and undetectable ctDNA can be appropriately managed with six-monthly photo-mapping and annual liquid biopsy (Chan et al., 2024; Wong et al., 2023), whereas a *CDKN2A* carrier – already monitored with total-body photography and RCM – would likely warrant immediate escalation to RCM-guided biopsy and surgical review if their ctDNA variant allele fraction begins to rise. At the opposite end of the care continuum, even low-tech teledermatology accelerates melanoma detection: in primary-care settings, general practitioners who transmitted smartphone images of suspicious lesions to dermatologists shortened time to consultation by an average of 18.5 days compared to standard referrals (Bouton et al., 2024). Ongoing programs aim to integrate these high-frequency image streams with quarterly ctDNA monitoring and immunosuppression metadata (e.g., calcineurin vs mTOR inhibitors) into adaptive loops that modulate follow-up intensity in real time. Although full validation remains ongoing, these platforms demonstrate how AI-driven imaging, molecular biomarkers, genomic data, and medication metadata can be integrated into an adaptive surveillance loop – signaling a shift toward truly multimodal, data-driven dermatologic oncology.

5. Barriers to Implementation and Equity in Precision Diagnostics

While precision diagnostics are reshaping how melanoma is detected and monitored, their integration into real-world care settings continues to reveal major gaps in equity and implementation. Tools such as polygenic risk scores, total body imaging, and circulating tumor DNA testing often require clinical

interpretation by specialists and depend on decision-support systems that are more accessible in academic centers than in community or rural clinics[1] [2]. Molecular tumor boards have helped bridge this gap by providing interdisciplinary guidance, but many providers still report uncertainty when acting on complex molecular outputs. At the same time, the datasets used to train artificial intelligence algorithms and construct genomic risk models are largely derived from individuals with lighter skin types and those of European ancestry, limiting their diagnostic accuracy in patients with skin of color[3] [4]. These limitations are compounded by access barriers, including cost, inconsistent insurance coverage, and the geographic distribution of advanced testing infrastructure[5]. Addressing these disparities will require a coordinated response that includes more inclusive data practices, investments in genomics education, and national policies that support thoughtful, widespread implementation of precision tools in dermatology[6].

6. Reconceptualizing Early Detection in Melanoma

Early detection of Melanoma is essential to improve patient outcome. However, current diagnostics rely on dermoscopy and skin biopsies as the primary screening tests (Czerw et al., 2024). Traditional methods, which involve pattern recognition and the ABCDE criteria, are insufficient to assess the complex nature of Melanoma. Blundo et al. reported multiple non-invasive diagnostic techniques with higher efficacy than traditional dermoscopy (Blundo et. al. 2021), highlighting the need to adopt new diagnostic and screening approaches. Melanoma detection should be a continuous, dynamic process utilizing a multi-modal approach. This new strategy allows for the detection of subclinical transformations and personalized risk-stratification, rather than relying solely on visual changes.

The future of Melanoma detection will move beyond periodic skin assessments to continuous monitoring, incorporating AI detection, adaptive risk assessment with molecular monitoring, and proactive intervention such as lifestyle modifications. Despite the improved care offered by new diagnostic techniques, digital advancement often increases healthcare inequalities (Yao et al. 2022). Therefore, innovations must be implemented in a system that guarantees fair access and availability to prevent worsening inequalities in dermatologic care. Precision diagnostics not only represent technological advancement but also a fundamental shift in dermatologic oncology. New methods of early detection may redefine the standards for Melanoma screening and can extend into other fields of oncology.

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