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REVIEW

Advances in Uveal Melanoma: From Molecular Pathogenesis to Precision Diagnostics and Personalized Therapies: Narrative Overview

Raed Shatnawi[1], Ahmad Al-Hyari[2], Motasem Al-Latayfeh[1], Mohammad Abu Ain[1], Husam Shatnawi[3], Yazan Shatnawi[3], Yacoub A. Yousef[4]

[1]Department of Special Surgery, Faculty of Medicine, The Hashemite University, P.O. Box 330127, Zarqa 13133, Jordan. [2]Department of Ophthalmology, Prince Hamzah Hospital, Ministry of Health, Amman, Jordan. [3]Medical Student, Faculty of Medicine, The Hashemite University, P.O. Box 330127, Zarqa 13133, Jordan. [4]Department of Surgery, King Hussein Cancer Center, Amman, Jordan.

Abstract

Objective: This review aims to summarize recent progress in the molecular understanding, diagnostic strategies, and treatment innovations in uveal melanoma (UM), the most common primary intraocular malignancy in adults. Emphasis is placed on the integration of precision diagnostics and emerging therapies that may improve clinical outcomes in high-risk cases. **Materials and Methods:** A narrative literature review was conducted using databases including PubMed, Scopus, Web of Science, and Google Scholar, covering the years 2020 to 2024. Keywords used included "uveal melanoma," "liquid biopsy," "circulating tumor cells," "gene mutations," "immunotherapy," and "precision oncology." Relevant peer-reviewed articles, clinical trials, and reviews were selected based on methodological quality and relevance to the scope of the review. **Results:** Uveal melanoma most frequently arises in the choroid and is genetically distinct from cutaneous melanoma. It is primarily driven by mutations in guanine nucleotide-binding protein G (q) subunit alpha (GNAQ), guanine nucleotide-binding protein G(q) subunit alpha-11 (GNA11), BRCA1 associated protein-1 (BAP1), eukaryotic translation initiation factor 1A X-linked (EIF1AX), and splicing factor 3B subunit 1 (SF3B1). These mutations activate key signaling pathways such as mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), influencing prognosis and therapeutic response. Diagnostic advancements include high-resolution imaging and liquid biopsy techniques, which enable detection of circulating tumor cells, circulating tumor DNA, and microRNAs. Standard treatments include radiation therapy (plaque brachytherapy) and surgical interventions. Novel therapeutic approaches such as tebentafusp (a T-cell receptor therapy), oncolytic viruses, chimeric antigen receptor (CAR) T-cell therapy, suicide gene constructs, and RNA interference show promise in clinical and preclinical settings. **Conclusion:** A precision medicine approach that integrates molecular diagnostics, artificial intelligence-enhanced liquid biopsy, and novel systemic therapies is transforming the management of uveal melanoma. These innovations may enable earlier detection, more accurate risk stratification, and targeted treatment, potentially improving survival and preserving vision in affected patients.

Keywords: Uveal melanoma- liquid biopsy- circulating tumor cell- GNAQ mutation- tebentafusp- RNA interference

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Introduction

Uveal melanoma (UM) is the most prevalent form of primary intraocular malignancy in adults, although it remains a rare disease with an incidence of approximately 5 cases per million annually in the United States [1, 2]. Despite its rarity, UM carries a significant clinical burden due to its aggressive metastatic potential. In a population-based study from Sweden, about 30% of patients died from metastatic UM within five years of diagnosis, with mortality rising to nearly 40% over a span of 10 to 15 years. The liver and gastrointestinal

Corresponding Author:
Dr. Raed Shatnawi
Associate Professor of Ophthalmology, Department of Special Surgery, Faculty of Medicine, The Hashemite University, Zarqa 13133, Jordan.
Email: raed972@yahoo.com

tract, particularly the colon, are the most common sites of metastasis and primary contributors to mortality [1].

Beyond its biological aggressiveness, UM severely impacts patients' emotional well-being and mental health. The diagnosis often leads to significant psychological distress, including anxiety, depression, and a diminished quality of life, especially given the associated risks of visual impairment and systemic spread [3]. Although therapeutic innovations such as tebentafusp an immune-modulating T-cell receptor (TCR) therapy have been introduced, they have not markedly improved overall survival outcomes in patients with metastatic disease [4]. One reason for this is the likely presence of micrometastases at the time of diagnosis, suggesting early hematogenous dissemination. Additionally, diagnostic and treatment delays are thought to exacerbate disease progression and worsen prognoses [5].

UM originates from melanocytes in the uveal tract of the eye, including the iris, ciliary body, and choroid [6]. It is genetically distinct from cutaneous melanoma, being driven by mutations in specific genes such as BRCA1-associated protein 1 (BAP1), eukaryotic translation initiation factor 1A X-linked (EIF1AX), guanine nucleotide-binding protein G (q) subunit alpha (GNAQ), guanine nucleotide-binding protein G (q) subunit alpha-11 (GNA11), and splicing factor 3B subunit 1 (SF3B1) [7]. These genetic alterations influence tumor development and metastatic behavior. For example, BAP1 loss is linked with poor prognosis and high metastatic potential, whereas EIF1AX mutations tend to indicate a more favorable outcome. Mutations in GNAQ and GNA11 activate signaling cascades such as RAS and phosphoinositide 3-kinase (PI3K), promoting tumor proliferation, survival, and migration [8].

Recent discoveries have identified circulating hybrid cells (CHCs), which form via fusion of tumor and immune cells and carry markers from both, making them promising indicators of metastatic risk [9]. Likewise, tumor-derived extracellular vesicles (TEVs) are believed to contribute to metastasis by altering distant tissue microenvironments [10].

The discovery of CHCs and TEVs in blood has sparked interest in liquid biopsy technologies. These non-invasive tests detect circulating tumor cells (CTCs), cell-free DNA (cfDNA), and exosomes, providing real-time insights into tumor dynamics. Liquid biopsies allow for early detection of metastasis, continuous monitoring of disease progression, and evaluation of therapeutic response all without the need for tissue samples [1]. When paired with artificial intelligence (AI) systems, data from liquid biopsies can improve diagnostic precision, guide treatment decisions, and support personalized patient care.

This review will comprehensively explore UM's molecular basis, key genetic mutations, metastatic mechanisms, diagnostic innovations, and therapeutic challenges, with emphasis on integrating liquid biopsy and artificial intelligence to enhance clinical outcomes. This review advances precision medicine by summarizing molecular insights, non-invasive diagnostics, and emerging therapies that support early detection, personalized risk assessment, and targeted treatment. It also aligns with the efforts to improve clinical outcomes through cost-effective technologies, innovative procedures, and culturally adapted care strategies, offering a foundation for future research and policy development as other studies confirmed [11-17].

Methods

This narrative literature review was conducted to synthesize current knowledge on the pathogenesis, diagnosis, and management of uveal melanoma (UM), with a particular focus on emerging diagnostic technologies such as liquid biopsy and artificial intelligence (AI)-assisted tools. A systematic literature search was performed using multiple academic databases, including PubMed, Scopus, Web of Science, and Google Scholar, covering publications from 2020 to 2024. Search terms included combinations of keywords such as "uveal melanoma," "choroidal melanoma," "intraocular tumor," "liquid biopsy," "circulating tumor cells," "circulating tumor DNA," "microRNA," "prognostic biomarkers," "ocular oncology," "plaque brachytherapy," and "artificial intelligence in ocular diagnosis."

Relevant peer-reviewed articles, clinical trials, meta-analyses, and systematic reviews were included based on their scientific quality, clinical relevance, and publication recency. Preference was given to studies providing molecular insights, epidemiological trends, diagnostic innovations, and therapeutic efficacy in the context of UM. Reference lists of the most impactful articles were manually screened to identify additional studies that were not retrieved through initial database searches.

Only publications in the English language were considered for inclusion. Extracted data were organized thematically into five major domains: (1) molecular pathophysiology and genetic underpinnings; (2) epidemiology and clinical risk stratification; (3) diagnostic modalities, including advanced imaging and tissue-based assessment; (4) novel diagnostic innovations such as liquid biopsy and circulating biomarkers; and (5) contemporary and experimental therapeutic interventions, including surgery, radiation, immunotherapy, gene therapy, and AI-assisted tools.

Each identified article was assessed for its contribution to understanding the pathophysiology, diagnostic advancements, and therapeutic landscape of UM, particularly in relation to circulating biomarkers and digital diagnostic tools. Studies specifically addressing liquid biopsy techniques such as detection of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), microRNAs (miRNAs), and tumor-derived extracellular vesicles (TEVs) were prioritized to explore their utility in early detection, risk stratification, and treatment monitoring. Articles detailing the development and validation of AI-enabled algorithms for image analysis or molecular data interpretation in ocular oncology were also included.

Emphasis was placed on integrating findings across multiple disciplines, including molecular oncology,

ophthalmology, bioinformatics, and biomedical engineering. The collected data were synthesized qualitatively, focusing on the convergence of histopathological findings, genetic profiling, and non-invasive diagnostic technologies to form a comprehensive understanding of UM's clinical and biological behavior.

Results

Pathophysiology

Uveal melanoma (UM) originates from melanocytes residing in the uveal tract, which includes the choroid, ciliary body, and iris. Approximately 90% of cases arise in the choroid [1, 18]. This malignancy is characterized by marked genetic instability and a high tendency for hematogenous metastasis, particularly to the liver, which contributes significantly to its poor long-term prognosis even when the primary tumor is controlled. Unlike cutaneous melanoma, UM is not strongly associated with ultraviolet (UV) radiation exposure. Instead, established risk factors include fair skin, light-colored eyes, atypical nevi, ocular melanocytosis (also known as nevus of Ota), and periorbital freckling [2, 19]. Certain occupational exposures such as welding or working in high-heat environments have also been implicated in increasing the risk of UM.

On a molecular level, UM is driven by mutations that differ from those found in cutaneous melanoma. Activating mutations in guanine nucleotide-binding protein G (q) subunit alpha (GNAQ) and guanine nucleotide-binding protein G (q) subunit alpha-11 (GNA11) initiate tumorigenic signaling cascades including the mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and mammalian target of rapamycin (mTOR) pathways, all of which promote unchecked cellular proliferation and survival. Loss of function in BRCA1-associated protein 1 (BAP1) is a particularly aggressive molecular alteration, linked to early metastasis and poor survival outcomes. In contrast, mutations in eukaryotic translation initiation factor 1A X-linked (EIF1AX) and splicing factor 3B subunit 1 (SF3B1) are generally associated with a more indolent disease course and improved prognosis [5, 20].

UM arises in the immune-privileged environment of the eye a setting evolved to minimize inflammation and preserve vision. However, malignancy disrupts this immune balance. The tumor microenvironment in UM is often marked by an influx of macrophages and lymphocytes and an upregulation of human leukocyte antigen (HLA) class I and II molecules. This immune response is further amplified by activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway, which supports tumor survival and progression [1, 3].

Recent findings have expanded the understanding of UM progression through mechanisms involving tumor-derived extracellular vesicles (TEVs) and circulating hybrid cells (CHCs). TEVs are membrane-bound vesicles secreted by tumor cells that carry oncogenic proteins including MAPK pathway components, vascular endothelial growth factor (VEGF), and Wnt modulators facilitating the creation of pre-metastatic niches, especially in the liver. CHCs, formed through the fusion of tumor cells with immune cells, express both immune and tumor markers and possess high tumorigenic potential. The detection of TEVs and CHCs in bodily fluids suggests their potential role as non-invasive biomarkers in early diagnosis and monitoring of UM via liquid biopsy [18-27].

Epidemiology

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, though it remains rare, with an incidence of approximately 5 cases per million annually in the United States [1,2]. Several classification systems have been developed to aid in clinical staging, prognostication, and treatment planning. The American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC TNM) system is widely used, assessing tumor size (T), invasion into ocular structures, lymph node involvement (N), and the presence of distant metastasis (M) [1, 23]. Another key framework is the Collaborative Ocular Melanoma Study (COMS) classification, which stratifies tumors into small, medium, or large categories based on diameter and thickness critical for both clinical trials and therapeutic decisions. Histologically, the modified Callender system categorizes tumors as spindle-cell, epithelioid-cell, or mixed-cell types, each bearing distinct prognostic implications.

Recent advances in molecular diagnostics have enhanced risk stratification through tools such as gene expression profiling (GEP) and The Cancer Genome Atlas (TCGA)-based classification. These techniques help identify genetic signatures associated with high metastatic risk, enabling more personalized follow-up and therapeutic approaches [1, 24].

Clinically, UM is often asymptomatic in early stages and frequently discovered incidentally during routine ophthalmologic evaluations. When symptoms do occur, they are usually dictated by tumor location and may include reduced visual acuity, photopsia (flashes of light), floaters, metamorphopsia (distorted vision), or localized field defects [1, 3, 24, 25]. Iris tumors may present with visible pigment changes or mass lesions and are detected earlier due to their anterior location. In contrast, melanomas of the ciliary body often remain undiagnosed until they are large, due to their posterior and hidden position within the eye. Diagnostic delays are common, with approximately one-quarter of symptomatic cases initially misidentified or overlooked [1, 3, 24].

Prognosis in UM is influenced by anatomical, histopathological, and genetic factors. Tumors located in the ciliary body or near the optic nerve tend to be more aggressive and harder to detect early, leading to poorer outcomes. Histopathological markers of poor prognosis include epithelioid cell type, high mitotic rate, and extrascleral extension. Cytogenetically, monosomy 3, gain of chromosome 8q, and loss of chromosome 6q are associated with a high risk of metastasis, whereas gain of chromosome 6p is considered a favorable prognostic

indicator [1, 5, 24–30].

To differentiate early melanomas from benign nevi, clinicians often use the mnemonic TFSOM-UHHD, which stands for: Thickness >2 mm, subretinal Fluid, Symptoms, Orange pigment, Margin near optic disc, Ultrasonographic Hollowness, Halo absence, and Drusen absence. This tool assists in early detection and timely intervention of malignant lesions [1, 5, 30].

Diagnosis

The diagnosis of uveal melanoma (UM) requires a multimodal approach that integrates clinical evaluation, advanced imaging techniques, and, when necessary, histopathological confirmation. The process often begins with a detailed dilated fundus examination, which may reveal a characteristic pigmented or dome-shaped lesion. In advanced cases, the lesion may adopt a mushroom or collar-button configuration due to rupture of Bruch's membrane a hallmark feature distinguishing UM from benign intraocular lesions [1, 3-5, 31].

Optical coherence tomography (OCT) is a critical non-invasive imaging modality that provides high-resolution cross-sectional images of the retina and choroid. OCT is particularly useful in detecting subretinal fluid, disruption of the retinal pigment epithelium (RPE), photoreceptor loss, and retinoschisis. These features aid in differentiating UM from benign entities such as choroidal nevi or vascular tumors like hemangiomas [25-32].

Ocular ultrasonography remains an essential diagnostic tool, especially when direct fundus visualization is obstructed by media opacities. A-scan and B-scan ultrasonography allow accurate measurement of tumor thickness and internal reflectivity. UM typically exhibits low to medium reflectivity, dome or mushroom-shaped morphology, and may be associated with choroidal excavation and exudative retinal detachment [1].

Magnetic resonance imaging (MRI) is particularly valuable for assessing posteriorly located or large tumors and for evaluating potential extrascleral extension. UM lesions usually appear hyperintense on T1-weighted and hypointense on T2-weighted MRI sequences. Restricted diffusion may also be seen and is indicative of high cellularity, supporting the diagnosis of malignancy [1, 30-35].

Definitive diagnosis is established through histopathological analysis, which may follow fine needle aspiration biopsy (FNAB) or enucleation. Microscopic examination identifies tumor cell type spindle, epithelioid, or mixed with significant prognostic value. Spindle-cell tumors are generally associated with favorable outcomes, while epithelioid-cell tumors suggest a poorer prognosis. Additional histologic markers, such as mitotic index, vascular loop presence, and lymphocytic infiltration, provide further insight into tumor aggressiveness and metastatic potential [1, 25-36].

Ultimately, diagnosis hinges on the integration of clinical, radiologic, and histologic data. Advances in imaging and molecular diagnostics have enhanced the accuracy of UM identification and staging, facilitating earlier and more tailored treatment planning.

Key Diagnostic Themes and Molecular Targets in Liquid Biopsy

Liquid biopsy has emerged as a transformative, non-invasive tool for the diagnosis and monitoring of uveal melanoma (UM), particularly in settings where traditional tissue sampling is technically challenging or carries procedural risk. While fine needle aspiration biopsy (FNAB) remains useful in select cases, its limitations including potential complications such as retinal detachment, vitreous hemorrhage, and tumor seeding have prompted the exploration of safer alternatives [33-36].

Liquid biopsy involves the analysis of tumor-derived components circulating in bodily fluids such as blood, aqueous humor, and vitreous fluid. This technique enables dynamic monitoring of disease progression and therapeutic response without direct tumor manipulation, supporting its integration into precision oncology workflows [1, 35-38].

Key analytes in liquid biopsy include circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), microRNAs (miRNAs), and extracellular vesicles. CTCs reflect active tumor dissemination and carry genetic mutations consistent with the primary lesion. Their detection often via immunomagnetic separation or filtration correlates with metastatic potential and poorer prognosis [1, 38-40].

ctDNA, shed into the bloodstream by apoptotic or necrotic tumor cells, harbors actionable mutations such as those in guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) and guanine nucleotide-binding protein G (q) subunit alpha-11 (GNA11). Although ctDNA concentrations are typically low in early-stage UM, their presence can guide molecular profiling and longitudinal surveillance [1, 39].

Circulating miRNAs, including miRNA-618, serve as epigenetic biomarkers with differential expression patterns in metastatic versus non-metastatic disease. These small, stable RNA fragments can help stratify patient risk and potentially indicate early progression. Protein biomarkers such as glycoprotein 100 (gp100), osteopontin, cathepsin, and heat shock protein 27 are also under investigation, particularly in multiplex panels to enhance diagnostic sensitivity [35-40].

Extracellular vesicles, especially tumor-derived subtypes, represent another promising class of biomarkers. These vesicles carry oncogenic cargo including MAPK pathway proteins, vascular endothelial growth factor (VEGF), and Wnt modulators and are instrumental in creating pre-metastatic niches, particularly in the liver. Their detection, however, remains technically challenging due to isolation and characterization barriers [34-41].

Advanced platforms such as next-generation sequencing (NGS), enzyme-linked immunosorbent assay (ELISA), fluorescence-activated cell sorting (FACS), and nanoparticle tracking analysis (NTA) are being developed to improve detection accuracy. When combined with artificial intelligence (AI) and integrative molecular analysis, liquid biopsy holds promise for revolutionizing early detection, risk stratification, and personalized treatment strategies in UM.

Current Treatment Methods

Management of uveal melanoma (UM) is largely influenced by tumor size, location, and proximity to critical ocular structures, with the primary goal of achieving local control while preserving as much vision as possible. For anteriorly situated tumors especially those confined to the iris or ciliary body transscleral resection, also known as exo-resection, may be performed. This surgical technique involves the partial or total removal of the tumor through a direct external approach but is generally avoided for posterior tumors due to increased procedural complexity and risk [1, 34, 37-43].

When tumors are large or have caused significant ocular damage, enucleation, the complete surgical removal of the eye, may be indicated. This option is typically reserved for lesions exceeding 12 mm in thickness or 18 mm in basal diameter, or in cases complicated by secondary glaucoma or optic nerve involvement. Although enucleation can provide definitive local control, it does not prevent systemic spread, and recurrence portends a poor prognosis [1, 40-43].

In rare, advanced cases involving extensive orbital invasion or a blind and painful eye, orbital exenteration may be required. This disfiguring procedure entails the removal of the eye along with adjacent orbital contents, and while potentially curative in select cases, it is associated with significant morbidity and limited overall benefit when recurrence occurs postoperatively [1, 40-43].

Radiation therapy, particularly plaque brachytherapy, is a preferred eye-conserving modality for small to medium-sized tumors. This technique involves temporarily attaching a radioactive plaque (commonly iodine-125 or ruthenium-106) to the sclera overlying the tumor, delivering localized radiation. It is most effective for tumors not encroaching upon the optic nerve. Complications may include radiation-induced cataracts, retinopathy, and optic neuropathy, depending on tumor proximity and radiation dose [39-52].

Given the complexity and variability of UM presentations, treatment must be individualized. Decisions are best made within a multidisciplinary framework, considering the patient's overall health, tumor characteristics, visual function, and personal preferences. The aim is to optimize tumor control while minimizing long-term functional impairment and enhancing quality of life [1].

Contemporary Therapeutic Modalities

Contemporary approaches to treating uveal melanoma (UM) are increasingly focused on addressing the limitations of conventional therapies, particularly in the context of metastatic disease, where long-term survival remains poor. One major area of innovation involves immunotherapy, specifically immune checkpoint inhibitors that block cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) interactions. Despite their success in other malignancies, agents like ipilimumab and nivolumab have demonstrated limited efficacy in UM due to the tumor's low mutational burden and an immunosuppressive microenvironment. In contrast, tebentafusp, a T cell receptor (TCR)-based therapy targeting the human leukocyte antigen HLA-A*0201, has shown improved overall survival in eligible patients, marking a significant step forward in precision immunotherapy [1, 43-53].

Oncolytic virotherapy is another promising avenue. Engineered viruses such as talimogene laherparepvec (T-VEC), herpes simplex virus-1 (HSV-1), and echovirus-7 (ECHO-7) are designed to selectively infect and lyse malignant cells while stimulating immune responses. Notably, AU-011 (belzupacap sarotalocan), a virus-like drug conjugate, has demonstrated encouraging outcomes in clinical trials for local tumor control and vision preservation and is progressing into advanced trial phases [47-53].

Adoptive T cell therapy, including tumor-infiltrating lymphocytes (TILs) and chimeric antigen receptor (CAR) T cells, offers an individualized immunologic strategy for patients with metastatic UM unresponsive to other treatments. Preclinical and early-phase clinical data suggest that CAR T cells can mediate tumor regression by targeting specific antigens, potentially overcoming resistance mechanisms inherent to UM [44-49].

Gene therapy strategies are also under development. Suicide gene therapy, for example, introduces enzymes such as cytosine deaminase into tumor cells to convert prodrugs into cytotoxic agents directly at the tumor site. Additionally, constructs targeting B7-H3 a surface antigen overexpressed in UM using inducible CRISPR-associated protein 9 (iCas9) systems have shown efficacy in reducing metastasis in animal models, offering a precision-guided treatment platform [1, 48-53].

RNA-based therapies are advancing rapidly, particularly RNA interference (RNAi) strategies using small interfering RNAs (siRNAs) and microRNAs (miRNAs) to silence key oncogenic drivers like vascular endothelial growth factor (VEGF), B-cell lymphoma 2 (Bcl-2), and hypoxia-inducible factor 1-alpha (HIF-1α). The use of innovative delivery systems, such as hyaluronic acid (HA)-coated chitosan nanoparticles, is being explored to enhance therapeutic stability and cellular uptake. Long non-coding RNAs (lncRNAs), including miR-181a, have also been implicated as potential therapeutic targets, although clinical translation is challenged by issues of delivery and degradation [1, 49-53].

Collectively, these evolving therapeutic strategies reflect a shift toward highly tailored treatment paradigms in UM. By combining immunological, genetic, and molecular techniques, ongoing research aims to address the unmet need for effective systemic treatments in a cancer historically resistant to conventional approaches.

Discussion

Recent advances in the understanding of uveal melanoma (UM) have significantly enriched our ability to diagnose, stratify, and potentially treat this aggressive intraocular malignancy. Although UM remains a rare entity with a relatively low incidence, its high metastatic

potential and liver tropism necessitate early detection and effective management strategies [1-3]. The observed five- to ten-year mortality rates reaching 40% underscore the urgency of refining both systemic surveillance and therapeutic options [4-6]. These epidemiologic realities highlight the importance of molecular profiling and personalized interventions aimed at intercepting disease progression at earlier stages.

At the molecular level, UM is now recognized as genetically distinct from cutaneous melanoma, largely due to its unique set of driver mutations. Mutations in GNAQ and GNA11 genes initiate aberrant signaling through the MAPK and PI3K/AKT pathways, contributing to cell proliferation and survival [22–27,29–31]. Importantly, the loss of BAP1 function serves as a hallmark of poor prognosis and increased metastatic risk, while mutations in EIF1AX and SF3B1 appear to signal less aggressive tumor behavior [33-38]. These genetic markers not only assist in prognostication but also serve as potential therapeutic targets, guiding risk-adapted surveillance and clinical decision-making.

The tumor microenvironment in UM is shaped by immune privilege, a physiological state intended to preserve ocular function by limiting inflammation. However, this privilege may inadvertently favor tumor immune evasion. Studies have shown that inflammatory UM phenotypes characterized by lymphocytic infiltration and elevated HLA class I/II expression are paradoxically associated with worse outcomes [28-37]. The activation of NFκB signaling in both primary tumors and metastases supports a pro-survival and pro-metastatic state, reinforcing the idea that immunomodulatory strategies need to be tailored to this unique immune context [52-57].

Liquid biopsy technologies offer a promising path forward in early UM detection and longitudinal disease monitoring. Detection of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and microRNAs (miRNAs) in blood and ocular fluids circumvents the limitations of fine needle aspiration biopsy, which carries risks of retinal detachment and tumor seeding [39-44]. Importantly, CTCs have demonstrated prognostic value, with high counts correlating with reduced progression-free and overall survival [22-25]. Moreover, studies confirm the presence of shared copy number alterations between CTCs and primary tumors, suggesting their utility for non-invasive genotyping and molecular tracking [1].

Circulating tumor DNA further refines molecular profiling, with next-generation sequencing of ctDNA enabling the identification of GNAQ and GNA11 mutations, as well as the monitoring of treatment response [30-35]. Despite challenges in detecting ctDNA in early-stage disease due to low abundance, advancements in isolation techniques continue to improve analytical sensitivity. Meanwhile, miRNAs such as miRNA-618 and other stable blood-based biomarkers offer additional layers of specificity for identifying metastatic risk [19, 28-35]. Together, these analytes strengthen the case for routine liquid biopsy integration into UM clinical protocols.

Current standard-of-care treatments, including transscleral resection, enucleation, exenteration, and plaque brachytherapy, offer varying degrees of disease control and ocular preservation depending on tumor size and location [24-32]. While effective for localized disease, these approaches fail to address systemic metastasis, particularly in the liver. This limitation reinforces the need for systemic therapies capable of eradicating micrometastatic disease or modulating immune response to prevent metastatic outgrowth.

Immunotherapy has emerged as a key investigational avenue but has shown modest efficacy in UM compared to cutaneous melanoma. Checkpoint inhibitors such as nivolumab and ipilimumab have yielded limited objective response rates, likely due to the low mutational burden of UM and its immunosuppressive microenvironment [34-46]. However, tebentafusp has demonstrated survival benefits in HLA-A*0201-positive patients, suggesting the need for genotype-based patient selection and expansion of HLA-compatible immunotherapies [38-52].

Gene-directed therapies, including suicide gene therapy and RNA interference strategies, represent additional innovative modalities under preclinical and clinical evaluation. Studies involving cytosine deaminase constructs and targeted siRNA delivery have shown success in suppressing tumor proliferation in vitro and in animal models [39-47]. However, clinical translation remains limited by challenges in vector design, delivery efficiency, and off-target effects. The potential for B7-H3-targeted CAR-T constructs and lncRNA-based therapies also holds promise, though these require further validation in larger, controlled trials [37-43].

Adoptive cell therapy (ACT), including tumor-infiltrating lymphocytes (TILs) and CAR-T cells, has demonstrated capacity to induce tumor regression in select metastatic UM cases [49-53]. Notably, engineered CAR-T cells have exhibited in vivo efficacy in murine models, including resistance to conventional TIL-based therapies. These findings support the rationale for integrating ACT into treatment regimens, particularly for patients refractory to immune checkpoint inhibitors or those with high-risk molecular profiles.

These scientific developments in the field of uveal melanoma (UM), particularly those related to molecular diagnostics, liquid biopsy, and novel immunotherapeutic strategies, are emblematic of a broader shift toward precision and patient-centered care in oncology. However, technological advancements alone are insufficient to optimize patient outcomes unless they are supported by comprehensive institutional frameworks that prioritize safety, quality, and individualized care. For instance, the integration of AI-assisted diagnostic tools and real-time monitoring systems must be matched with enhanced protocols for fall risk screening and management especially in patients with visual impairments or those undergoing aggressive treatments like enucleation or radiation therapy [1, 51]. Vision loss and balance issues place UM patients at higher risk of inpatient falls, necessitating proactive screening, tailored safety plans, and environmental modifications to prevent avoidable harm. Similarly, ensuring structured continuity of care after discharge through coordinated follow-up

appointments, medication reconciliation, and symptom surveillance helps detect recurrence or metastasis early, mitigates treatment-related complications, and reinforces patient adherence to long-term care plans [52, 53].

Moreover, to truly elevate the quality of care, institutions must prioritize patient-centered models that emphasize education, psychosocial support, and shared decision-making. UM patients, who often confront irreversible vision loss and the psychological toll of cancer diagnosis, benefit substantially from structured educational interventions that clarify treatment options, potential side effects, and self-monitoring strategies [54-58]. Incorporating mental health services, peer support groups, and low-vision rehabilitation into the treatment ecosystem addresses both emotional resilience and functional recovery. Finally, systemic quality improvement strategies aimed at reducing diagnostic and procedural errors such as the use of checklists, standardized documentation, and continuous process audits are essential for sustaining institutional accountability and patient safety [58-68]. These reforms underscore the need for advance multidisciplinary integration and management practice involving oncologists, ophthalmologists, radiologists, pathologists, nurses, and IT professionals, all working in concert to ensure that scientific innovation translates into meaningful clinical impact [68-78].

In conclusion, the landscape of UM management is rapidly transitioning from static, anatomy-based approaches to dynamic, personalized strategies driven by molecular diagnostics and targeted therapeutics. Liquid biopsy, AI-assisted diagnostics, immune checkpoint modulation, and gene therapies are reshaping how clinicians understand, monitor, and treat UM. Continued multidisciplinary collaboration, coupled with access to multicenter clinical trials and real-world data, will be essential in transforming these promising innovations into clinical standards. Future directions should emphasize individualized treatment based on genetic and biomarker profiling to improve both survival and quality of life for patients affected by this rare but deadly malignancy.

Acknowledgments

Statement of Transparency and Principals

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

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