HAYSTACK PROJECT
The Voices of Rare & Ultra Rare

POV
Patient Oriented Value

PATIENT ORIENTED VALUE (POV©) REPORT
UVEAL MELANOMA

MRF MELANOMA RESEARCH FOUNDATION
CURE OCULAR MELANOMA

Contents

Patient Oriented Value (POV©) Reports

POV© Reports are undertaken to provide insight into the patient journey, articulate disease burden from the patient perspective, reveal real-world care gaps and communication deficiencies, and better understand treatment priorities and perceived value from the patient perspective.

Health care systems seeking to transition from volume- to value-based payment have accelerated the use and relevance of methodological frameworks for assessing and assigning "value" to medical therapies. Entities that evaluate the clinical effectiveness and economic value of pharmaceuticals and other health care interventions in the US, including the Institute for Clinical and Economic Review (ICER), generally adopt a payer or societal perspective. Model designs, input selection, and metrics such as quality adjusted life years (QALY) were developed to aid payer decisions toward cost-effective care, primarily in highly prevalent conditions with multiple treatment options.

Treatments for exceedingly rare diseases and rare cancers present unique challenges for value frameworks given the high disease burden, limited treatment options, and potentially dire health consequences for patients if treatment access is delayed or denied due to payer-perception of low or questionable value. Similarly, a treatment option could have a high value from a payer or societal perspective yet be associated with an unacceptable side-effect or risk profile, or address outcomes that are not meaningful to patients living with the condition. This information may not be available within clinical trial data evaluating the safety and efficacy of new treatments. POV© Reports are designed to augment patient advocacy organizations' understanding of the patient journey, care gaps, unmet needs, and real-world disease burden, as well as patient preferences and value perception on treatment and symptom management options. This enables more robust participation from patient advocates so that the patient voice can be incorporated and integrated into the health care value frameworks that could drive access to new and evolving standards of care. Insights from POV© Reports can also identify gaps in patient-provider communication, support services, and access to care within and outside clinical trials.

Uveal melanoma (UM) is the most common form of ocular melanoma (OM), a very rare cancer with a substantial risk of metastasis (up to 50% in UM). No FDA-approved treatments have demonstrated improved overall survival in UM. Relatively recent introduction of genetic testing to identify high-risk UM tumors has enabled researchers and clinicians to stratify follow-up and surveillance to the patient's risk. As with most rare conditions, patients and their providers often struggle to obtain coverage for the standard of care, i.e., genetic testing for metastatic risk assessment, and appropriate surveillance regimens, including imaging studies, to detect metastatic disease as early as possible.

The potential for development of new treatments for metastatic disease and advances in addressing high-risk UM underscore the utility of prognostic genetic testing in devising treatment and surveillance plans tailored to the risk profile for the individual patient.

Accurately assessing value will be vital to ensuring that patients have access to prognostic genetic testing and treatments when these interventions can have greatest impact on survival.

The Melanoma Research Foundation (MRF)

The Melanoma Research Foundation (MRF) is a 501(c)(3) non-profit organization advocacy organization. Its mission is to eradicate melanoma by accelerating melanoma research while educating and advocating for the melanoma community. The foundation's goal is to transform melanoma from one of the deadliest cancers to one of the most treatable.

Research **--** Due to the remarkable development of both targeted therapy and immunotherapy, the national cutaneous melanoma death rates have decreased in both men and women by ~6%; however, the incidence rate in both men and women has increased by ~2%. Although we have achieved a number of important scientific milestones, much more work remains to be done in cutaneous melanoma as well as ocular and other rare melanoma subtypes. 2020 MRF Research and Science Brochure (flippingbook.com)

Education – The MRF's Education Institute creates general awareness about the dangers of melanoma and offers educational opportunities for the melanoma community on prevention, diagnosis, treatment, side effects, advances in research and clinical trials. The Institute provides in-depth training for melanoma advocates to participate in and actively support the medical, scientific and regulatory environments.

Advocacy **--** The MRF is dedicated to working with lawmakers on federal, state and local levels for increased melanoma research funding for all types of melanomas including, mucosal, ocular and pediatric, improved access to quality care, Centers for Disease Control (CDC) skin cancer prevention activities, preserving indoor tanning tax, age restricted indoor tanning, access to sunscreen in schools and more.

The MRF's CURE OM Initiative

Founded in 2011, CURE OM (the Community United for Research and Education of Ocular Melanoma) is the MRF's initiative to increase awareness, education, and research funding for ocular melanoma, while improving the lives of people affected by this disease.

OM Research **-** The MRF's CURE OM's scientific initiative includes research grants, the VISION patient registry, and biannual international scientific meetings. These efforts ensure continued collaboration, support and coordination to move OM research forward.

- The MRF has funded seventeen uveal melanoma grants totaling over $2.1 million. The *CURE OM Unite!* Campaign has spearheaded the incorporation of the patient/caregiver voice into its research grant and registry efforts. Research & Science Grants | Melanoma Research Foundation
- CURE OM's global patient-reported registry, the VISION Registry, developed under the

guidance of its Registry Steering Committee, will inform patient-centered research initiatives focused on policy, patient preferences and standards of care. In addition to collecting invaluable disease data, the registry will support the collaboration of patients, caregivers, clinicians, researchers, and the pharmaceutical industry to find a cure together.

- CURE OM hosts regular global science meetings to facilitate interdisciplinary and innovative collaboration focused on finding effective treatments and, ultimately, a cure for ocular melanoma. To date, CURE OM has held fourteen such scientific meetings. Scientific Meetings | Melanoma Research Foundation

OM Education **-** CURE OM partners with leading ocular melanoma clinicians and researchers to ensure that the ocular melanoma patient and caregiver communities always receives the best, most accurate information.

- Each year, the MRF's CURE OM initiative hosts the *Eyes on a Cure: Patient & Caregiver Symposium*, bringing together ocular melanoma patients, survivors and caregivers to learn about the latest advances in OM research and treatment. (776) 2020 Virtual Eyes on a Cure: Global Patient & Caregiver Symposium - YouTube; (776) 2021 Virtual Eyes on a Cure Mini Summit: Spring Updates - YouTube
- CURE OM's education program includes a variety of online educational and supportive resources for ocular melanoma patients and the people who support them, including webinars, support groups and a treatment center finder. Resources (Ocular) | Melanoma Research Foundation

OM Awareness - The MRF's CURE OM initiative aims to increase awareness by promoting the importance of early detection. Ocular melanoma is most often detected during a routine, dilated eye exam.

Colorado Retina

Colorado Retina Associates is a thirteen physician, owned and led, sub-specialty eye care practice providing medical and surgical care of vitreoretinal eye disease. Colorado Retina provides comprehensive retinal treatment for age-related macular degeneration (AMD), diabetic retinopathy, retinal vascular disease, retinal detachments, ocular tumors, uveitis/inflammatory eye disease, inherited retinal degenerations and numerous other vitreoretinal conditions.

Colorado Retina partners with many local and national foundations that support research and funding for finding a cure for blindness and vision related diseases. For the past decade, the practice has supported the Denver chapter's Foundation Fighting Blindness. Colorado Retina is also proud to support and partner with the Melanoma Research Foundation (MRF) and its advocacy programs and initiatives.

Haystack Project

Haystack Project is a 501(c)(3) non-profit organization enabling rare and ultra-rare disease patient advocacy organizations to coordinate efforts that address systemic value and access barriers. Our core mission is to evolve health care payment and delivery systems to make innovation and quality treatments accessible to all Americans living with or caring for someone with a rare or ultra-rare condition. We strive to amplify the patient and caregiver voice in disease states where unmet need is high, and treatment delays and inadequacies can be catastrophic.

The Rare Cancer Policy Coalition (RCPC) is a Haystack Project initiative, and the only rare cancer coalition developed to focus on and respond to access and value issues across the rare cancer community. RCPC also gives participants a platform for focusing on emerging landscape changes that impact new product development for rare cancers. Working within the Haystack Project enables RCPC participants to leverage synergies and common goals with other rare and ultra-rare patient advocates.

Support

A grant from Amgen to the Cutaneous Lymphoma Foundation supported the research, survey administration and analyses, and writing of this POV© Report.

Executive Summary

Ocular Melanoma. Ocular melanoma (OM) is a rare, non-cutaneous melanoma that occurs in all races and ages. Uveal melanoma (UM) accounts for 95% of OM cases and is the focus of this POV© Report. Primary UM tumors can be treated successfully with radiation therapy, but patients have up to a 50% risk of metastasis following treatment of their primary tumors. Post-treatment, UM patients enter into an uncertain period of "wait and see" surveillance where they undergo periodic or routine monitoring for metastases, which most often occur in the liver. Genetic or molecular prognostic testing of the primary tumor (e.g., DecisionDX-UM), capable of stratifying patients into high, medium or low risk for metastatic disease, has been commercially available since 2009 and can be used to inform surveillance protocols during the "wait and see" period.

As of this report, two adjuvant therapeutic regimens are under clinical development for patients at high risk for metastases from uveal melanoma (UM), the most common form of OM. Unfortunately, there are currently no FDA-approved effective treatments for metastatic UM and prognosis is poor. Median survival is approximately 4 months for those outside of clinical trials and approximately 10 months for patients participating in trials.

The POV© Report. The hope that comes with scientific advances in UM is tempered by concern that the costs associated with genetic testing and targeted treatments could drive coverage and payment constrictions that limit access for patients. As our health care system increasingly focuses on transforming from volume- to value-based frameworks, the patient voice in identifying what "value" means on a disease-specific basis is a crucial perspective that is often overlooked by entities evaluating the *economic* value of diagnostic and therapeutic interventions. These entities generally adopt a payer or societal perspective that may consider, but not fully incorporate, the patient perception of "value." Patient groups are increasingly interested in translating their understanding of value into the quantitative terms used by health economists so that treatment "value" incorporates the patient perspective.

UM patients, their clinicians, and payers face complex decisions on primary treatment of their tumor, determining whether or not to undergo biopsy and prognostic assessment, identifying a surveillance and follow-up plan for detecting metastatic disease, deciding to participate in a clinical trial, and, if needed, selecting a therapy for metastatic disease. Moreover, the potentially prolonged 'wait and see' period presents unique challenges likely to induce elevated levels of stress, uncertainty, and emotional distress, particularly within the context of a cancer that has a 50% risk of likely-fatal metastatic disease. From a patient perspective, decisions are not always based solely on clinical endpoints such as progression-free or overall survival; quality of life is an important consideration that may have a different meaning for each patient.

This Report was designed to enable insights into the real-world experience of UM patients throughout the treatment and surveillance processes, including:

- Participation in treatment decisions.

- Access to genetic or molecular prognostic testing.
- Understanding of metastatic risk.
- Access to specialists with disease-specific expertise.
- Impact of disease and its treatments on quality of life; and
- Priorities and preferences throughout the patient journey.

A survey instrument was developed through collaboration between Haystack Project and the MRF's CURE OM initiative to learn about UM disease burden and patient and/or caregiver preferences and perception of value for existing interventions as well as new tests and treatments. Survey responses were analyzed with statistical support from the Johns Hopkins Biostatistics Center and synthesized into a POV© Report.

Key Findings. As expected, treatment protocols recommended by their doctor and that successfully eradicate primary tumors while sparing the eye and vision are extremely important to UM patients. Factors such as involvement of pain/discomfort, repeat therapy administration or clinic visits, bothersome side effects, and the requirement for travel were less important in determining the primary tumor treatment.

Regarding genetic or molecular testing of the primary tumor to assess metastatic risk, patients desire reliable tests with low risk of side effects that can be performed locally by clinicians with expertise in their condition. Following treatment of the primary tumor, UM patients prefer a surveillance protocol tailored in frequency and intensity to their risk of metastatic disease. The results of this survey also revealed that newly diagnosed UM patients are not always informed that genetic testing for metastatic risk is available. In addition, a subset of respondents indicated that their metastatic risk was "unknown" despite reporting that genetic testing was performed. This finding suggests a gap in communication that could be addressed by augmenting clinician-led discussions on diagnosis, treatment planning and follow-up with resources that can be taken home and reviewed, such as the ***Ocular Melanoma Patient Guide*** developed by CURE OM (the guide can be downloaded from: Diagnosis (Ocular) | Melanoma Research Foundation).

The majority of survey respondents did not have to travel extensively for treatment and care following their primary diagnosis. Respondents felt that it was not important or only somewhat important- that treatment for their primary tumor, metastatic disease, and the blood tests and scans in the "wait and see" period be local or minimize travel; but, as noted above, they preferred that prognostic genetic testing be performed locally.

Changes in vision were not reported as having a significant impact on patients' employment or ability to live independently; however, approximately one third of patients across all risk groups for metastatic disease reported that activities of daily living were reduced due to changes in vision. As predicted, 50% or more of those with, or at known high risk for, metastatic disease reported less ability to plan for the future because of the uncertainty of their disease progression. However, those with known low risk expressed more confidence in this area. The majority of respondents at various risk for metastatic disease, and especially those with

metastatic disease, also reported occasional dependence on a spouse, partner, child and/or caregiver.

Although most respondents did not report receiving counseling or taking medication for anxiety or depression, the frequency of positive ("Yes") responses for anxiety (but not depression) in this cohort of patients did exceed that of the general population.

Low out-of-pocket expense for genetic testing, primary tumor treatment, and metastatic disease was either somewhat or very important to patients; cost considerations might also impact real-world access to care requiring travel. Additionally, these patients expressed that it is critically important that treatments for metastatic disease be prescribed and administered at first detection of metastasis.

Summary of Key Findings

✓	Treatment protocols for the primary tumor: protocols recommended by their doctor and that successfully eradicate the primary tumor while sparing the eye and vision are extremely important to patients
✓	For genetic or molecular prognostic testing of the primary tumor for metastatic risk: patients desire reliable tests with low risk of side effects that can be performed locally by clinicians with expertise in their disease
✓	Following treatment of the primary tumor: patients prefer a surveillance protocol tailored in frequency and intensity to their risk of metastatic disease
✓	Low out-of-pocket expense for genetic testing and treatments for primary tumors and metastatic disease was either somewhat or very important to patients
✓	It is critically important to patients that their treatments for metastatic disease be prescribed and administered at first detection of metastasis
✓	Reduction in activities of daily living due to changes in vision affects approximately one third of surveyed patients across all risk groups for metastatic disease
✓	Approximately one half those with, or at known high risk for, metastatic disease reported less ability to plan for the future because of the uncertainty of their disease progression
✓	The majority of respondents at various risk for metastatic disease, and especially those with metastatic disease, reported occasional dependence on a spouse, partner, child and/or caregiver
✓	The frequency of self-reported anxiety (but not depression) in this cohort of patients exceeded that of the general population

Implications. In addition to the above-referenced communication disconnect between providers and patients regarding genetic testing, coverage for genetic or molecular prognostic testing may vary from payer to payer and require UM patients to go through multiple appeal processes to secure coverage. Medicare covers the DecisionDX-UM test but requires that billing providers utilize a registry and implies a level of oversight on subsequent care, including referrals and follow-up surveillance intensity, which could deter utilization.

Although the majority of respondents prefer that "wait and see" surveillance protocols be tailored in frequency and intensity to their risk of metastatic disease, those patients unable or unwilling to have genetic testing performed may experience reduced access to follow-up tests and scans recommended for identifying metastatic disease before symptoms emerge.

Patients with high-risk or already developed metastatic disease who are interested in clinical trial participation have a limited set of interventional studies recruiting US patients; these studies are clustered in an extremely limited set of sites. Patients unable to afford repeated travel and/or travel for extended periods of time may lose the opportunity for early access to promising therapies in clinical development.

Access to clinical trials studying adjuvant therapy is even narrower than that for metastatic disease. These studies limit enrollment to patients who are within a 6-month window of their primary treatment for the UM tumor. High-risk patients potentially benefiting from adjuvant treatment in the years, or even decades, after their primary treatment are closed out of these clinical trials and may find that they have limited (or no) access if a treatment is approved but its label aligns with the clinical trial population. Additionally, the long timeline from diagnosis to emergence of metastatic disease suggests that clinical trial designs for potential adjuvant therapies could require durations to or beyond 5 years to demonstrate efficacy. This underscores the need for reliable surrogate biomarkers indicative of emerging metastatic disease for use in UM adjuvant clinical trials. Additionally, collaborative strategies between FDA, industry, researchers, clinicians, and patient advocacy organizations to expand early access to the full addressable population would offer hope to UM patients and may enable data collection outside the clinical trial context.

Because it is extremely important to patients that future treatments for metastatic disease be prescribed and administered at first detection of metastasis, any barriers that restrict access to treatments will necessarily add additional stress and anxiety to patients who have an extremely high unmet medical need, already carry the 24/7 burden of rare disease, and have lived through the inherent uncertainty of periodic surveillance for metastasis.

Introduction

Ocular melanoma (OM) is the most common non-cutaneous melanoma. It is a rare cancer that is diagnosed in approximately 2,000 individuals each year in the United States, most often occurs in lightly pigmented individuals, and has a median age at diagnosis of 62 years (MRF's CURE OM, Patient Guide; Aronow 2018). OM can, however, occur in all races and at any age. According to data from the Collaborative Ocular Melanoma Study (COMS), clinical examination alone could enable a diagnostic rate of approximately 99.5% (COMS 1990).

According to data from the Surveillance, Epidemiology, and End Results (SEER) database on the incidence, treatment, and survival of uveal melanoma in the United States from 1973 to 2013:

- There is a near-equal distribution of primary uveal melanoma by gender (males: 52.3%, females: 47.7%)
- The median age at diagnosis was 62 years (range: 5-100 years).
- The majority (98.0%) of cases occurred in the White population.
    - 0.6% of cases were reported in the Black population,
    - Race was unknown in the remaining 1.4% of patients.

(Aronow 2018).

The majority (95%) of OM tumors arise in the uvea (i.e., uveal melanoma). Uveal melanoma (UM) can be divided into posterior UM (arising in the choroid or ciliary body) and iris melanoma. The risk of developing metastasis for UM is much higher than for patients with a primary cutaneous melanoma; it can exceed 50% in high-risk tumors of the posterior uvea (Bol, 2020, Singh 2011, Kujala 2003, Jensen 1982).

Emerging treatment options have enabled improved survival for metastatic cutaneous melanoma patients. They are, however, not directly applicable to patients with UM, for whom existing treatments have failed to demonstrate improved overall survival. This POV© Report focuses on UM patients, their real-world experience, preferences and priorities.

Despite apparent ease in achieving timely diagnosis, metastatic disease will be observed in about half of patients with UM (Krantz 2017). For these patients, prognosis is poor and has not significantly improved from the survival observed in the 2006 Collaborative Ocular Melanoma Study (COMS) (Krantz 2017).

Diagnosis of the primary tumor. Approximately one-third of UM patients are asymptomatic at the time of diagnosis. Uveal melanoma is diagnosed through funduscopic examination by an experienced clinician, followed by further characterization with specialized noninvasive testing techniques, such as ultrasound, optical coherence tomography, and fluorescein angiography. UM cannot always be distinguished from a uveal nevus on clinical examination (Augsburger 2008) due to an overlap in size between small melanomas and large nevi. Magnetic resonance

imaging (MRI) of the orbit may be needed to confirm diagnosis and in patients with tumors that are large or suspicious for extraocular involvement. Diagnostic biopsy is required in approximately 5 percent of cases to differentiate an atypical uveal melanoma from a metastatic tumor, hemorrhagic lesion, or other simulating lesion (Augsburger 2008).

Although diagnostic biopsy is rarely required, most patients are now offered fine needle aspiration biopsy for genetic or molecular prognostic testing that can be useful in guiding customized metastatic surveillance and identifying high-risk patients for more frequent and intensive surveillance, and referral into clinical trials.

Primary treatment for UM. Asymptomatic patients with small uveal melanocytic tumors (<12 mm in diameter and <2 to 3 mm in height) may be managed initially through observation for evidence of growth, rather than immediate intervention (Lane 2010). This observation period would typically include two- to four-month intervals for imaging studies such as fundus photography, ultrasonography, optical coherence tomography, and fundus autofluorescence to identify evidence of tumor growth, subretinal fluid, orange lipofuscin pigmentation, and other risk factors for malignant transformation (Espinoza 2004, Gunduz 2007).

Radiation therapy (RT) is currently the most common treatment for primary UM (Ramaiya 2007). Since UM tumors are relatively radioresistant, they must be treated with high-dose radiation, usually in the form of plaque brachytherapy or charged-particle RT. Consensus opinion guidelines for the use of radioactive plaque therapy have been published by the American Brachytherapy Society (ABS) (ABS 2014), but research is ongoing into the optimal dosimetric parameters for uveal melanoma (Oellers 2018). Charged-particle RT (protons, carbon ions, helium ions) allow increased dose targeting at the end of the beam range and a sharp decrease in the dose of the radiation beam beyond the targeted area (the Bragg peak effect) but can result in collateral damage to ocular structures such as the lashes, lacrimal gland, cornea, iris, lens, retina, and optic nerve (Saunders 1985).

Local control rates are very similar for plaque brachytherapy and charged-particle RT, but differ on ocular radiation complications. Anterior eye complications are more commonly associated with charged-particle RT, while plaque brachytherapy tends to result in greater visual acuity loss and immediate procedural discomfort (Saunders 1985, Sikuade 2015). There is limited data from long-term follow-up on radiation modalities in treating UM, but it appears that plaque brachytherapy may have a higher complication rate with approximately two-thirds of patients developing ocular complications within five years after treatment (Dunavoelgyi 2012, Krema 2013).

Local tumor resection, i.e., resection of a UM tumor without removing the entire eye, is rarely used as primary treatment for UM due to risks of postoperative complications and local tumor recurrence. Enucleation had been the standard of care until the 1970s, but this surgical procedure has not demonstrated survival advantage over RT (Adams 1988, Seddon 1990, Augsburger 1998). The Collaborative Ocular Melanoma Study (COMS) compared 1317 patients with medium-sized choroidal UM tumors randomly assigned to enucleation versus 125I

assigned to brachytherapy with overall survival as the primary outcome measure (Collaborative Ocular Melanoma Study Group 2006). Five-, 10-, and 12-year mortality rates of with a histopathologically confirmed melanoma metastasis were 10, 18, and 21 percent, respectively, in the 125I brachytherapy arm and 11, 17, and 17 percent, respectively, in the enucleation arm. There was no statistically significant difference in survival between the two groups. Enucleation, therefore, is now generally reserved for patients who would not be expected to have a favorable outcome with RT, or for select patients who prefer enucleation. The COMS also confirmed that there is a lack of benefit to justify pre-enucleation RT to the eye and orbit for patients with large uveal melanomas (Hawkins 2004).

Metastatic risk assessment. After primary tumor treatment, patients are monitored for local recurrence and the development of metastasis. UM spreads almost solely hematogenously, given that fewer than 2% of patients experience extraocular growth and lymphatic spread does not occur from ***within*** the eye ((Bol, 2020, Singh 2011). The most common sites of metastasis for UM include liver (93%), lung (24%), bone (16%), and skin/subcutaneous tissue (11%); lymph node and brain metastasis are rare (Martin 2013).

Several genetic mutations have been identified in UM:

- GNAQ and GNA11: These mutations are found in over 80% of UM cases and are not predictive of patient outcomes or metastatic risk.
- Tumor BAP1: Approximately half of UM tumors contained the tumor BAP1 mutation. BAP1 is associated with a high metastatic risk.
- BRAF: This mutation is rarely found in UM, but common in cutaneous melanoma and found in approximately 30% of conjunctival melanoma cases.

(Correa 2016)

In newly-diagnosed UM patients, risk of metastatic disease can be assessed based on the size (larger tumors present higher metastatic risk) and location of the tumor as well as results of genetic testing on tumor. The most common genetic tests in UM are:

- Chromosome analysis (karotyping) – Approximately half of UM cases show abnormalities in chromosome 3; loss of chromosome 3 is associated with high metastatic risk. In addition, abnormalities in chromosomes 1, 6, and 8 may indicate increased metastatic risk.

- Genetic expression profile (GEP) testing – A 15-gene, qPCR-based assay groups the tumor into low-, medium- or high- 5-year risk of metastasis.

(Field 2014).

For patients undergoing enucleation as primary treatment, tumor tissue is readily available. The majority of patients, however, are now treated with an eye-conserving strategy, and pre-

treatment biopsy is required to utilize genetic testing to assess prognosis and risk of metastases (as outlined above). Tumor biopsies in posterior UM are considered a safe procedure and are not associated with increased risk of metastasis when performed by an experienced ocular surgeon (Bagger 2018).

- For patients undergoing eye-conserving local treatment, the option to perform a tumor biopsy to obtain tumor tissue for genetic testing should be discussed prior to treatment (Bol 2020).

- Genetic biomarkers improve the accuracy of predicting an individual prognosis and may guide decisions on:
    - schedule of monitoring during the "wait and see" period,
    - referral to clinical trials for adjuvant treatments

- The prognostic biomarkers are not currently useful in guiding treatment for metastatic disease (Bol 2020).

Follow-up and surveillance following treatment of primary UM tumor. Prior to development of genetic tests to aid in assessing risk of metastatic disease in UM patients, clinicians relied on traditional clinical and pathologic prognostic factors (tumor size and cytology, patient age, location of tumor) to guide and direct UM treatment and follow-up. The utility of these assessments in clinical management of UM patients was limited due to relatively low accuracy and lack of supporting evidence of improved outcomes (Harbour, 2013). Unfortunately, the inability to accurately assess risk of developing metastatic disease in UM had resulted in all patients receiving follow-up testing and surveillance with a frequency and intensity now recommended primarily for high-risk patients.

Currently, recommendations for follow-up vary widely and increasingly depend on the presence of high-risk features in the primary eye tumor, with typical follow-up regimens consisting of at least a full ophthalmological examination and imaging of the liver every 3–12 months for up to 10 years. Half-yearly screening of the liver by MRI can reveal metastases before symptoms in 92% of patients (Marshall 2013). A recent study contends that in patients with known low-risk features of the primary eye tumor, regular imaging of the liver may be omitted (Bol 2020).

The prevailing standard of care in newly diagnosed UM patients is to utilize the molecular prognostic testing discussed above to tailor metastatic surveillance intensity to the patient's risk of metastatic disease (Onken 2012, Gezgin 2017).

There is no consensus on UM surveillance modalities or frequency; the goal of surveillance is to aid in detecting metastatic disease as early as possible (Auburg 2014). Tailoring surveillance intensity to metastatic may enable patients with an identified low risk of metastatic disease to choose a regimen that is less burdensome and costly. A recent prospective registry study (89 enrolled patients) and meta-analysis reported on the impact of 15-GEP profiling for UM metastatic risk on physician-recommended management plans and outcomes (Aaberg 2020).

The prospective registry analysis on clinical use of 15-GEP testing in UM found that:

- Physician management plans for low-risk UM patients were of reduced intensity (annual surveillance by liver function testing and/or imaging)
    - 80% of Class 1 patients had low intensity surveillance
    - 70% of the Class 1 patients with higher-intensity surveillance (every 3-6 months) were Class 1B
- 100% of the UM patients identified as high-risk were managed a high-intensity schedule of surveillance (quarterly or biannual liver function testing and/or imaging).
- UM patients identified as low-risk do have low rates of metastasis within 5 years compared to high-risk UM patients (10% in low-risk; 58% in high-risk).

Treatment for Metastatic UM. Although local treatment for primary UM effectively prevents local recurrence in over 95 percent of cases, up to 50 percent of patients remain at risk for metastatic disease. Metastasis-related death occurs in patients initially diagnosed with early-stage cancer, as well as in patients many years after the initial tumor was successfully removed (Tura 2018). The high risk of metastatic disease is now thought to be due to UM tendency toward early micrometastasis, followed by a variable latency period, and finally emergence of overt metastatic disease (Eskelin 2000).

Approximately 20 to 30 percent of patients diagnosed with a primary UM die of systemic metastases within 5 years; 45 percent die within 15 years of diagnosis (Kujala 2003, Singh 2011). The median overall survival for patients with metastatic UM is approximately 4 months for those treated outside clinical trials and approximately 10 months in patients participating in clinical trials (Khoja 2019, Augsburger 2009). Predictors of survival in patients with metastatic UM include Karnofsky score, the size of largest metastasis, metastatic burden, and serum transaminase, lactate dehydrogenase, and alkaline phosphatase levels (Eskelin 2003).

There is currently no consensus standard-of-care therapy for patients with metastatic disease given the lack of FDA-approved therapies indicated for adjuvant use or in metastatic disease. While clinical trial participation is recommended for metastatic UM patients, enrollment in clinical trials has not been readily accessible due to the small number of UM-specific trials and exclusion of UM patients from larger (cutaneous) melanoma studies. It is worth noting, however, that several studies addressing metastatic UM treatments have been posted to clinicaltrials.gov within the past year, and two clinical trials are currently studying adjuvant therapies in high-risk UM patients (**Table 1**).

Table 1: US clinical trials recruiting (as of May 20, 2021) patients for studies involving adjuvant therapies and treatments for metastatic disease.

***Clinicaltrials.gov* studies of treatments for high-risk and/or metastatic uveal/ocular melanoma**	**Clinical Trial #**	**US Locations**	**Year Posted**
Transarterial Chemoembolization for the Treatment of Uveal Melanoma with Liver Metastases.	NCT04728633	Philadelphia, PA	2021
Defactinib and VS-6766 for the Treatment of Patients with Metastatic Uveal Melanoma	NCT04720417	Philadelphia, PA	2021
A Study of RO7293583 in Participants with Unresectable Metastatic Tyrosinase Related Protein 1 (TYRP1)-Positive Melanomas	NCT04551352	New York, NY; Philadelphia, PA; Nashville, TN (Boston and St. Louis not yet recruiting)	2020
Study of PAC-1 and Entrectinib for Patients with Metastatic Uveal Melanoma	NCT04589832	Minneapolis, MN	2020
Nivolumab Plus Relatlimab in Patients with Metastatic Uveal Melanoma	NCT04552223	Miami, FL	2020
Modified Virus VSV-IFNbetaTYRP1 in Treating Patients with Stage III-IV Melanoma	NCT03865212	Jacksonville, FL; Rochester, MN	2019
Adoptive Transfer of Tumor Infiltrating Lymphocytes for Metastatic Uveal Melanoma	NCT03467516	Pittsburgh, PA	2018
Study of **Adjuvant** Ipilimumab and Nivolumab in Subjects with High-risk Ocular Melanoma	NCT03528408	San Francisco, CA; DC; Chicago, IL; St. Louis, MO; New York, NY; Houston, TX	2018
Ipilimumab and Nivolumab with Immunoembolization in Treating Participants with Metastatic Uveal Melanoma in the Liver	NCT03472586	Philadelphia, PA	2018
Autologous CD8+ SLC45A2-Specific T Lymphocytes with Cyclophosphamide, Aldesleukin, and Ipilimumab in Treating Patients with Metastatic Uveal Melanoma	NCT03068624	Houston, TX	2017
Intermittent Selumetinib for Uveal Melanoma	NCT02768766	New York, NY; Houston, TX	2016
Adjuvant Sunitinib or Valproic Acid in High-Risk Patients with Uveal Melanoma	NCT02068586	Philadelphia, PA	2014
Vorinostat in Treating Patients with Metastatic Melanoma of the Eye	NCT01587352	New York, NY; Nashville, TN	2012

Access to clinical trials is likely all but impossible for UM patients not residing within proximity of the limited set of clinical trial sites unless they have the financial means to accommodate the travel requirements for clinical trial participation and are healthy enough to do so.

Immunocore presented interim data from a Phase 3 clinical trial of tebentafusp at the virtual American Association for Cancer Research (AACR) Annual Meeting 2021 (Abstract CT002).

Tebentafusp is an investigational bispecific fusion protein that has demonstrated promising results in Phase III metastatic UM clinical trials. An independent data monitoring committee unblinded the study at the first prespecified interim analysis, extracting data in November 2020. A total of 378 patients with metastatic uveal melanoma were randomized to tebentafusp (252 patients) or Investigator's choice – pembrolizumab (103 patients), ipilimumab (15 patients) or cacarbazine (7 patients). Estimated overall survival rate from the intention to treat population was 73.2% for pembrolizumab versus 57.5% for the Investigator's choice cohort (Piperno-Neumann 2021). No other Phase III study has shown a survival benefit in metastatic UM (Goodman 2021). Tebentafusp has been granted FDA Breakthrough Therapy Designation for unresectable or metastatic uveal melanoma, and its manufacturer anticipates working with the FDA toward submission of a BLA in the third quarter of 2021 (Immunocore 2021). If approved, it will be the first new therapeutic option for treating metastatic UM in 40 years. According to its policy on expanded access to investigational treatments, Immunocore considers requests for access to tebentafusp through an early access program for patients with metastatic uveal melanoma (Immunocore expanded access policy).

Adjuvant Treatment for High-Risk UM. Inability to access treatment options within clinical trials could become an increasingly important limitation driving divergence in care among UM patients at high risk of metastatic disease. Researchers and clinicians had previously concluded that it would be difficult to test survival benefit from adjuvant therapy or earlier diagnosis of metastatic disease, given the lack of progress on identifying a standard of care for metastatic UM with improved overall survival (Gragoudas 1991, Augsburger 2019, Augsburger 2011). Clinicians now increasingly incorporate prognostic biomarker testing into the standard of care, and a growing body of evidence has emerged suggesting that meaningful progress on survival may be achieved through adjuvant therapy in high-risk patients as well as earlier detection of, and intervention for, metastatic disease (Dayani 2009, Valsecchi 2018, Piperno-Neumann 2015).

Researchers at Wills Eye and Thomas Jefferson University conducted a study of sunitinib malate in 20 UM patients with metastasis who failed other treatment. The treatment showed a modest benefit with thirty percent of patients with confirmed metastatic disease achieving progression-free survival at six months. The researchers found, however, that using low-dose sunitinib malate in high-risk UM patients without detectable metastatic disease yielded improved survival of 85% at 6 years versus the 40% found in an institutional historical control cohort (Valsecchi 2018).

In addition, if approved in metastatic and nonresectable UM, tebentafusp may offer another treatment option for high-risk UM patients in the adjuvant setting, and spur additional research leading to development of new methods for accurate, early detection of metastatic disease. The long timeline from UM diagnosis to emergence of metastatic disease, however, suggests that promising adjuvant therapy options could require study designs with duration to or beyond 5 years to demonstrate improved progression-free survival, and be unavailable to patients outside of clinical trials for the foreseeable future. Moreover, the two adjuvant therapy clinical trials currently recruiting high-risk UM patients limit participation to individuals within the 6-

month window following successful primary treatment for the UM tumor. This not only limits access to treatments with a potential benefit in avoiding or delaying metastatic disease during the studies but could also drive any subsequent FDA-approved labeled indication and impede or exclude most high-risk patients from treatment access. Collaborative strategies between FDA, manufacturers, researchers, clinicians, and patient advocacy organizations to expand early access to the full addressable population would offer hope to this patient population and may enable data collection outside the clinical trial context.

Ensuring that all patients have the best set of options to address their disease state and risk will require proactive advocacy on the part of UM patients and their advocacy organizations, as well as researchers and clinicians specializing in UM.

POV© Report Objectives

Patient-centered care has been recognized as a key element in delivering high-quality, high-value treatment, and was incorporated into several initiatives within the Affordable Care Act legislation. Many studies have shown that placing patients at the center of care results in greater participation in clinical decision-making, as well as higher patient satisfaction and adherence to a treatment plan. Patient Oriented Value (POV©) reports provide critical information on patients' perspectives on disease burden, care gaps, priority outcomes, and other factors essential to understanding "value" for current standard(s) of care, treatments in development, or any FDA-approved therapies (on- or off-label).

Value frameworks have been developed to guide pricing and reimbursement decisions by key stakeholders in healthcare delivery, yet they are frequently criticized for not being sufficiently patient-centered and relying solely on data from randomized controlled trials to assess the comparative value of emerging therapies in disease states with multiple treatment options. When treatments emerge to address diseases that previously had no effective options to manage disease burden or improve survival, value frameworks focus instead on the incremental increase in survival, quality of life, and other metrics to determine whether the benefits of a treatment justify its price.

UM patients, their clinicians, and payers face complex decisions in valuing, comparing, and selecting a modality for primary treatment of a UM tumor, determining whether to undergo biopsy and prognostic assessment, identifying a surveillance and follow-up plan for detecting metastatic disease, deciding to participate in a clinical trial, and selecting a therapy for metastatic disease. From a patient perspective, these decisions are not based solely on clinical endpoints such as progression-free or overall survival; quality of life is an important consideration that may have different meanings for each patient.

The potential for near-term approval of a promising new treatment for metastatic disease and advances in addressing high-risk UM underscore the utility of prognostic genetic testing in devising treatment and surveillance plans tailored to the risk profile for the individual patient. Accurately assessing value will be vital to ensuring that patients have access to testing and treatments when these interventions can have greatest impact on survival.

This Report was designed to enable insights into the unique care gaps, unmet needs, and stressors patients experience throughout the treatment and surveillance processes, including:

- Participation in treatment decisions.
- Access to genetic or molecular prognostic testing.
- Understanding of metastatic risk based on genetic testing.
- Access to specialists with disease-specific expertise.
- Real-world care experience vs the standard of care.
- Impact of disease and its treatments on quality of life.
- Economic burdens of disease and its treatments; and
- Priorities and preferences in choosing a diagnostic and treatment options throughout the patient journey.

For UM patients, we hypothesized that the potentially prolonged 'wait and see' period presents unique challenges likely to induce high levels of stress, uncertainty, and emotional distress, particularly within the context of a cancer that has a 50% risk of likely-fatal metastatic disease. It was predicted that patients would:

- Perceive a value in knowing their tumor genetics and metastatic risk.
- Appreciate surveillance intensity that matches their risk profile; and
- Welcome opportunities to address metastatic disease earlier by starting adjuvant treatment based on risk of metastases rather than visualization of metastatic lesion(s).

A survey instrument was designed to test our hypothesis and learn from the patient and caregiver community about their journey through treatment for the primary tumor, "wait and see" surveillance, and metastatic disease, if applicable, as well as the preferences that drive treatment decisions, including perception of value on new and existing tests and treatment interventions.

Methods

Survey Instrument

Haystack Project in partnership with the MRF's CURE OM initiative, and its medical advisors developed a survey instrument to explore the preferences that drive decisions throughout the patient journey.

The survey instrument consisted of an introductory statement followed by an initial set of demographic questions, and inquiries into the individual's diagnosis, primary treatment modality, systemic and other anti-cancer treatments received, and current disease status. Participants were also asked about whether they had undergone biopsy or other biomarker testing, reasons for not having that testing done, if applicable, and whether their tumor was categorized as high- or low-risk for metastases. Finally, participants were presented with a series of inquiries and an opportunity for open-ended response, designed to illuminate disease

burden, impact on function and quality of life, and patient priorities and preferences throughout the "wait and see" and potential metastatic disease processes.

All participant responses were de-identified, without inclusion of participant email address or other contact information utilized in recruitment.

Participant Recruitment

The MRF and Colorado Retina distributed the survey to 1329 OM patients and/or their caregivers via an email invitation containing a link to Survey Monkey. Individuals electing to participate submitted responses electronically. The survey was open for three weeks, during which responses were received from 131 patients (9.9% response rate). No responses were received from self-identified OM caregivers. Three respondents were excluded from the analysis due to responses to survey questions indicating that the respondent's diagnosis was likely conjunctival, rather than uveal melanoma. Therefore, responses from **128** UM patients underwent statistical analyses and contributed to the Report.

For several of the analyses, participants were segmented into subgroups: 1) all participants; 2) participants with a known high- or low-risk of metastases; 3) participants with unknown metastatic risk, 4) patients with metastatic disease.

Statistical Analysis

Statistical analysis of the survey responses was performed by the Johns Hopkins Biostatistics Center (JHBC), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

The goal of statistical analyses was to inform understanding of UM patient experiences, disease impact and preferences for diagnosis and treatments.

Descriptive statistics, including frequencies and percentages for categorical variables and medians with ranges and means with standard deviations (SD) were calculated for ordinal rank variables.

Age was categorized as <50, 50 to <60, 60 to <70, 70 to <80 and 80 and older. Calendar year of diagnosis was calculated as the year of survey (i.e., 2020) minus disease duration. Disease duration was categorized as 0 to 2, >2 to 5, >5 to 8 and greater than 8 years. In addition, duration was combined with the wait-and-see indicator, to create a 3-category variable: 1) not in wait-and-see period, 2) wait-and-see with 5 or fewer years of duration, and 3) wait-and-see with greater than 5 years of duration. Finally, risk of metastatic disease variable in 4 categories was created from high- and low- self-reported risk questions and included 1) high risk, with positive response to the high-risk question, 2) low risk, with positive response to the low-risk question, 3) neither high nor low risk, with negative responses to both low-risk- and the high-risk questions, and 4) unknown risk, with missing or "don't know" response to the low-risk- or high-risk questions, but not missing both of the questions.

To assess associations between patient demographics and medical history characteristics and

disease impact and patient preferences using a priori defined questions, Fisher's exact test of association was performed with False Discovery Rate (FDR) adjustment for multiple comparisons using Benjamini & Hochberg's method that controls the expected proportion of false discoveries among the rejected hypotheses at 5%.

Statistical analysis was performed using RStudio version 3.6.3.

Results

Respondent Characteristics

The racial and ethnic demographic of the survey respondents was consistent with SEER data (95.3% of respondents self-identified as white, non-hispanic versus 98% in the SEER data) (Aronow 2018). The majority of respondents (88.3%) reported being in the "wait and see" surveillance period, also corresponding with the general UM patient population (personal communication, MRF).

Table 2. Respondent demographics and status of disease and genetic testing

	Overall (N=128)
CURRENT AGE	
Mean (SD)	59.4 (12.8)
Median [Min, Max]	61.0 [19.0, 89.0]
GENDER	
Female	84 (65.6%)
Male	44 (34.4%)
RACE AND ETHNICITY	
Asian (East Asian, South Asian, or Asian Indian)	2 (1.6%)
Latino or Hispanic	2 (1.6%)
Non-Hispanic White or Euro-American	122 (95.3%)
Other Race/Ethnicity	2 (1.6%)
AGE AT DIAGNOSIS	
Mean (SD)	52.8 (13.6)
Median [Min, Max]	54.0 [12.0, 86.0]
GENETIC TESTING FOR METASTATIC DISEASE	
No	52 (40.6%)
Yes	74 (57.8%)
Missing	2 (1.6%)
CURRENTLY IN "WAIT AND SEE?"	
No	15 (11.7%)

	Overall (N=128)
Yes	113 (88.3%)
HIGH RISK OF METASTATIC DISEASE?	
No	42 (32.8%)
Unknown	50 (39.1%)
Yes	35 (27.3%)
Missing	1 (0.8%)
LOW RISK OF METASTATIC DISEASE?	
No	42 (32.8%)
Unknown	49 (38.3%)
Yes	36 (28.1%)
Missing	1 (0.8%)
METASTATIC DISEASE?	
No	114 (89.1%)
Yes	14 (10.9%)

Medical Care Reported by Respondents

Care of Primary Tumor

As expected, the vast majority of patients received eye-preserving treatment (RT, brachytherapy) for the primary UM tumor, with just 12 of the 128 respondents (9.375%) indicating that their initial treatment was enucleation (Table 3). One patient, an 88-year-old male diagnosed at age 86, is being monitored rather than treated for the primary UM tumor.

Table 3. Primary treatment for tumor

Treatment	Responses
Enucleation (removal of eye)	12 (9.375%)
Radiation	109 (85.16%)
Other (please specify)	7 (5.46%)
TOTAL	**128**

The 12 patients treated with enucleation tended to be younger than the overall set of respondents, with 6 out of these 12 respondents (50%) under age 50 at diagnosis, and only 1

enucleation patient over age 65. This respondent subgroup also had a higher reported incidence of metastatic disease (3 of the 12 respondents: 25%), as well as more rapid progression to metastatic disease than the overall population. Metastatic disease was detected within one year in 2 of the 3 enucleation patients, with the other respondent reporting metastasis within 3 years of initial UM diagnosis. All 3 of these respondents are female; two are currently participating in clinical trials (data on file).

Genetic Testing and Metastatic Risk Potential

The survey responses demonstrated that most recently-diagnosed UM patients had biopsy and/or genetic testing for metastatic risk assessment. While patient understanding of their risk for metastatic UM has clearly improved since newly-developed assessments with greater predictive value have reached clinical practice (Table 4, "Unknown" risk column), inconsistencies still exist in patient awareness of their risk despite availability of this testing. Approximately 25% of the UM patients for whom testing was widely available responded that their risk was "Unknown."

Table 4. Respondent perceived/communicated understanding of their metastatic risk prior to or since commercial availability of genetic testing for UM prognosis.*

	High	Low	Neither	**Unknown**
Not Commercially Available (N=52)	5	12	2	33 (63.5%)
Commercially Available (N=73)	30	22	3	**18 (24.7%)**

*Diagnosis before/after 2009 based on current age of respondent and disease duration.

The majority of surveyed UM patients who did **not** have prognostic testing performed were either not aware of the testing and its use in guiding treatment planning or were diagnosed before the testing was available (Table 5). Six responses indicated that a patient had made an affirmative decision to decline genetic/prognostic testing, with the 6 participants citing "personal preference" spread across age groups. Only two respondents indicated that they declined to have their metastatic risk assessed through biopsy or genetic testing due to out-of-pocket costs.

Table 5. Respondent reason for not having primary tumor biopsied and/or genetically tested by respondent age.

	<50 (N=22)	**50-59 (N=40)**	**60-69 (N=37)**	**70-79 (N=26)**	**80+ (N=3)**	**Overall (N=128)**
Tumor size or location	0 (0%)	2 (5.0%)	5 (13.5%)	2 (7.7%)	0 (0%)	9 (7.0%)
Radiation therapy	1 (4.5%)	2 (5.0%)	1 (2.7%)	2 (7.7%)	1 (33.3%)	7 (5.5%)

	<50 (N=22)	50-59 (N=40)	60-69 (N=37)	70-79 (N=26)	80+ (N=3)	Overall (N=128)
Testing not available	0 (0%)	0 (0%)	7 (18.9%)	5 (19.2%)	0 (0%)	**12 (9.4%)**
Did not know about testing	5 (22.7%)	1 (2.5%)	2 (5.4%)	4 (15.4%)	0 (0%)	**12 (9.4%)**
Out-of-pocket costs	0 (0%)	1 (2.5%)	1 (2.7%)	0 (0%)	0 (0%)	2 (1.6%)
Personal preference	1 (4.5%)	1 (2.5%)	2 (5.4%)	1 (3.8%)	1 (33.3%)	6 (4.7%)
Unsure if offered	0 (0%)	2 (5.0%)	1 (2.7%)	3 (11.5%)	0 (0%)	6 (4.7%)

Medical Care Following Primary Tumor Diagnosis

Table 6 compiles the real-world care reported by respondents identifying as high- and low-risk for metastatic OM, as well as those reporting that they did not know their risk ("unknown"). Participants who did not report high, low, or unknown risk of metastatic disease are not included. The patients in the metastatic disease subpopulation responded to the metastatic risk inquiry and are, therefore included in both the metastatic group and the high, low, or unknown risk groups according to their survey responses. The total derived from the sum of respondents in each column, therefore, exceeds the total number of respondents (n=128).

Table 6: Treatment and care following primary tumor diagnosis.

	Unknown Risk N = 51	High-Risk N = 35	Low Risk N = 36	Metastatic N = 14
Received cancer medication **to address high risk of metastatic disease**	No 51 (100%)	No 21 (60.0%) **Yes 14 (40.0%)**	No 33 (91.67%) Yes 2 (5.56%)	No 11 (78.71%) Yes 3 (21.43%)
Metastatic disease detected (from date of primary treatment) **N=14**	>1 yr 1 (1.96%) 1-3 yrs 0 (0%) 3-5 yrs 0 (0%) 5-7 yrs 1 (1.96%) 10-15 yrs 0 (0%) 15 yrs 1 (1.96%) **Total 3 (5.88%)**	>1 yr 1 (2.86%) 1-3 yrs 2 (5.71%) 3-5 yrs 2 (5.71%) 5-7 yrs 2 (5.71%) 10-15 yrs 1 (2.86%) >15 yrs 0 (0%) **Total 8 (22.9%)**	>1 yr 1 (2.78%) 1-3 yrs 1 (2.78%) 3-5 yrs 0 (0%) 5-7 yrs 1 (2.78%) 10-15 yrs 0 (0%) >15 yrs 0 (0%) **Total 3 (8.57%)**	
A biopsy was performed.	No 27 (52.94% Unsure 3 (5.88%) Yes 21 (41.18%)	No 4 (11.4%) Unsure 1 (2.86%) Missing 1 (2.86%) Yes 29 (82.9%)	No 9 (25.00%) Yes 25 (69.44%) Missing 2 (5.56%)	No 4 (28.57%) Unsure 1 (7.14%) Yes 8 (57.14%) Missing 1 (7.14%)
A scan (MRI, CT or PET) was performed to check for metastases.	**No 6 (11.76%)** **Unsure 1 (1.96%)** Yes 44 (86.27%) Missing 0 (0.0%)	**No 1 (2.86%)** Unsure 0 (0.0%) Yes 34 (97.14%) Missing 0 (0.0%)	**No 4 (11.11%)** Unsure 0 (0.0%) Yes 30 (83.33%) Missing 2 (5.56%)	No 1 (7.14%) Unsure 0 (0.0%) Yes 12 (85.71%) Missing 1 (7.14%)

	Unknown Risk N = 51	High-Risk N = 35	Low Risk N = 36	Metastatic N = 14
Sought/received second opinion.	No 29 (56.87%) Unsure 0 (0.0%) Missing 0 (0.0%) Yes 22 (43.14%)	No 22 (62.86%) Unsure 1 (2.86%) Missing 0 (0.0%) Yes 13 (37.14%)	No 24 (66.67%) Unsure 0 (0.0%) Missing 1 (2.78%) Yes 10 (27.78%)	No 4 (28.57%) Unsure 1 (7.14%) Missing 1 (7.14%) Yes 8 (57.14%)
Genetic testing on tumor to assess risk of metastatic disease.	No 32 (62.74%) Yes 19 (37.25%)	No 5 (14.20%) Yes 30 (85.71%)	No 11 (30.56%) Yes 22 (61.11%) Missing 2 (5.56%)	No 4 (28.57%) Yes 9 (64.29%) Missing 1 (7.14%)
Care from out-of-town providers.	No 26 (50.98%) Consult 3 (5.88%) Travel for care 18 (35.3%)	No 14 (40.0%) Consult 7 (20.0%) Travel for care 14 (40%)	No 21 (58.3%) Consult 5 (13.9%) Travel for care 11 (30.6%)	No 4 (28.57%) Consult only 5 (35.7%) Travel for care 5 (35.7%)
Overnight travel requirements associated with receiving care.	<8 days 7 (13.72%) 8-14 days 1 (1.96%) 15-21 days 3 (5.89%) >21 days 0 (0%)	<8 days 8 (22.86%) **8-14 days 4 (11.43%)** **15-21 days 2 (5.71%)** **>21 days 3 (8.57%)**	<8 days 8 (22.22%) 8-14 days 0 (0%) 15-21 days 0 (0%) >21 days 0 (0%)	<8 days 4 (28.57%) **8-14 days 1 (7.14%)** **15-21 days 3 (21.43%)** **>21 days 2 (14.29%)**
Clinical trial interest and participation.	Seeking 1 (1.96%) **Enrolled 0 (0%)**	Seeking 4 (14.3%) **Enrolled 10 (28.6%)**	Seeking 2 (5.56%) Enrolled 2 (5.56%)	Seeking 2 (14.29%) Enrolled 5 (35.7%)

Clinical Trial Enrollment

Of the 12 participants reporting enrollment in a clinical trial at the time the survey was conducted, 5 have metastatic disease. Of the 10 clinical trial enrollees identified as high-risk for developing metastatic disease, 4 have metastatic disease and the remaining 6 have received or are receiving adjuvant treatment with anti-cancer medications to address that risk. Seven additional respondents reported that they are actively seeking to enroll in a clinical trial; 2 of these patients have metastatic disease and 4 report that they are at high risk of metastatic disease.

Help Navigating Care

Eight of the 128 participants (one male and 7 female) reported that they have "paid out-of-pocket to have someone help me navigate my UM care, including identifying specialists, treatment options and clinical trials that might help." Of these patients paying for assistance in navigating treatment options, 3 (21% of metastatic patients) report metastatic disease and the 5 remaining respondents (14.3% of high-risk patients) are at high risk of developing metastatic disease.

Adjuvant Therapy

Although there is no current consensus on a standard of care for adjuvant treatment in high-risk patients, 14 of the 35 high-risk respondents (40%) indicated that they have received adjuvant treatment, either within or outside of a clinical study. This contrasts sharply with the reported experience of patients with "unknown" risk of metastatic disease. None of these patients have received adjuvant treatment or have enrolled in a clinical trial.

Seeking and Receiving Medical Care

Approximately 1/3 of UM patients, across disease status and risk subgroups, reported seeking care from providers outside their geographic areas: 31.4% (low risk); 35.3% (unknown risk); 35.7% (metastatic); and 40% (high risk). As expected, individuals with known low risk of metastatic disease report the fewest number of overnight stays for medical care (all 8 patients reporting overnight travel indicated fewer than 8 days in the past year). For high-risk patients and those with metastatic disease, overnight travel can present a significant burden (25.71% of high-risk; 42.86% of metastatic disease patients report more than 8 days of overnight travel). It is unclear whether high-risk and metastatic disease patients receiving local care do so because they are receiving high-quality care or are unable to travel for medical care.

Open-ended responses from participants suggest that patients may face difficulties in securing coverage for follow-up appointments and imaging studies, and in ensuring that their clinicians are aware of and following the standard of care.

RESPONDENT COMMENTS ON BURDEN ASSOCIATED WITH NAVIGATING MEDICAL CARE

"It feels like there are no resources for having to travel and lodge but I probably don't qualify anyway because my salary is above poverty level." *(64-year-old patient)*

"I want to be able to choose the doctor and location of the treatment I desire when needed for survival." *(49-year-old patient)*

"Surgery and follow up was in NYC for first 5 years…from Virginia. required travel expenses…moved to Raleigh NC area and now go to Duke." *(73-year-old patient)*

"Currently health Insurance companies do not have OM on their list of prognoses and the need for follow-ups to be more frequent than 1-5 years after a 2-year period. They evaluate it the same as melanoma/skin cancer." (67-year-old patient)

In addition, the reported follow-up regimen in the unknown risk population closely mirrored that of the low-risk group with respect to whether imaging studies were performed. Of the 16 recently-diagnosed (within the last 7 years), unknown-risk respondents, 11 provided a reason for not having metastatic risk assessment testing performed:

- concerns about the risk to worsening vision (1)
- size or location of tumor (4)
- did not know about this testing until after tumor was removed/treated (3)
- out-of-pocket cost (1)
- personal preference (2)

Participant-Reported UM Disease Burden and Quality of Life Impact

Table 7 reports respondent perception of the real-world impact that UM has had on

employment, daily activities, mental health, and caregiver needs. As in the data reflecting responses on care experience (Table 6), respondents are sub-grouped into unknown, high- and low-risk, with an additional subgroup for individuals reporting metastatic disease. Participants who did not report high, low, or unknown risk of metastatic disease are not included. As with Table 6, the patients in the metastatic disease subpopulation are also included in the high, low, or unknown risk columns correlating with their survey responses.

Table 7. UM Impact on activity, employment and quality of life

	Unknown Risk N = 51	High-Risk N = 35	Low Risk N = 36	Metastatic N = 14
I have reduced my daily activities, such as driving, due to vision changes.	No 28 (54.9%) N/A 3 (5.89%) Unsure 1 (1.96%) **Yes 18 (35.3%)**	No 25 (71.4%) **Yes 10 (28.6%)**	No 20 (55.5%) N/A 4 (11.1%) Yes 10 (27.8%) Missing 4 ((11.1%)	No 12 (85.7%) **Yes 1 (7.1%)** Missing 1 (7.1%)
Changes in my vision have affected my employment.	No 25 (49.02%) N/A 14 (27.45%) Unsure 2 (3.92%) Yes 9 (17.64%)	No 22 (62.9%) N/A 8 (22.9%) Unsure 2 (5.7%) Yes 3 (8.6%)	No 24 (66.7%) N/A 4 (11.1%) Unsure 1 (0.0%) Yes 4 (11.1%) Missing 4 (11.1%)	No 9 (64.3%) N/A 3 (21.4%) Unsure 1 (7.1%) Yes 0 (0%) Missing 1 (7.1%)
Changes in my vision make it difficult for me to live independently.	No 40 (78.43%) N/A 5 (9.8%) Unsure 1 (1.96%) Yes 4 (7.84%)	No 32 (91.4%) N/A 3 (8.6%) Yes 0 (0%)	No 28 (77.8%) N/A 1 (2.78%) Yes 2 (5.55%) Missing 4 (11.11%)	No 12 (85.7%) N/A 1 (7.1%) Missing 1 (7.1%) Yes 0 (0%)
I currently wear an artificial eye prosthesis.	No 38 (74.51%) N/A 3 (5.88%) Yes 9 (17.64%)	No 23 (65.7%) N/A 5 (14.3%) Yes 7 (20.0%)	No 24 (66.7%)) N/A 2 (5.55%) Yes 5 (13.9%)	No 9 (35.7%) N/A 1 (7.1%) Yes 3 (21.4%) Missing 1 (7.1%)
The uncertainty of the progression of my illness has made me less able to plan for my future.	**No 31 (60.8%)** N/A 1 (1.96%) Unsure 3 (8.6.%) Yes 14 (27.45%)	No 10 (28.6%) Unsure 4 (11.4%) **Yes 21 (60.0%)**	**No 15 (41.67%)** N/A 1 (2.78%) **Yes 11 (30.5%)** Unsure 3 (8.33%)	No 5 (35.7%) Unsure 1 (7.1%) **Yes 7 (50.0%)** Missing 1 (7.1%)
I am receiving counseling or taking medication for anxiety.	No 38 (74.5%) N/A 2 (3.92%) Yes 10 (19.61%) Missing 1 (1.98%)	No 26 (74.3%) Yes 9 (25.7%)	No 21 (58.3%) N/A 1 (2.78%) Yes 10 (27.78%) Missing 3 (8.33%)	No 11 (78.6%) Yes 2 (14.3%) Missing 1 (7.1%)
I am receiving counseling or taking medication for depression symptoms.	No 42 (82.35%) N/A 1 (1.96%) Yes 7 (13.72%)	No 29 (82.9%) Yes 6 (17.1%)	No 27 (75.0%) N/A 1 (2.78%) Yes 5 (13.9%) Missing 2 (5.55%)	No 11 (78.6%) Yes 2 (14.3%) Missing 1 (7.1%)
I have relied on my spouse/partner/children /caregiver on a ____ basis	Daily 6 (11.7%) Multi/wk 4 (7.8%) N/A 17 (32.8%) Occasional 23 (43.0%)	Daily 6 (17.1%) Multi/wk 2 (5.7%) N/A 10 (28.6%) Occasional 15 (42.9%) Weekly 2 (5.7%)	Daily 3 (8.33%) Multi/wk 3 (8.33%) Weekly 1 (2.78%) n/a 11 (30.5%) occasional 15(41.7%)	Daily 1 (7.1%) Multi/wk 2 (14.3%) N/A 2 (14.3%) Occasional 8 (57.1%) Missing 1 (7.1%)

Over a quarter of respondents across risk groups reported that they have reduced their daily activities due to UM, with individuals in the "unknown" risk group most frequently reporting this impact (35.3%). Among individuals with metastatic disease, only one respondent reported an OM-related decrease in daily activities, and none reported an impact on employment. Those with metastatic UM have already experienced the impacts of primary treatment and "wait and see" uncertainty on daily activities. Therefore, this may serve as the baseline from which these respondents perceive and reported on the relatively incremental impact of metastatic disease. Importantly, vision changes due to UM do not appear to have a significant impact on patient ability to live independently, even when metastatic disease is present.

Individuals with, and at high risk of, metastatic disease reported experiencing a sense of uncertainty in planning for the future (50% and 60%, respectively). The only subgroup for which a majority of patients reported that uncertainty on disease was not a concern was, somewhat paradoxically, the unknown-risk population (60.8% responding "No" to inquiry). Knowledge of risk, however, does appear to reduce the sense of uncertainty about disease progression for individuals at low risk in comparison to those at high risk for metastatic disease (31.42% vs. 60% respectively responding "Yes" to inquiry about uncertainty leading to *less ability* to plan for the future).

Participant responses to the inquiry on treatment for anxiety indicate that UM patients experience anxiety symptoms across risk subpopulations ((28.57% [low risk]; 25.7% [high risk]; 19.61% [unknown risk) The 14.3% of metastatic disease respondents reporting treatment for anxiety was lower than rates reported across UM risk groups.

For UM patients struggling with anxiety and/or depression, the impact on quality of life can be profound. Several participants reported an unmet need with respect to addressing the psychosocial impact of their disease.

RESPONDENT COMMENTS ON THE PSYCHOSOCIAL IMPACT OF OM

"OM patients should not have to wait for results of scans. I am beyond anxiety after 7 years of mets but early on the waiting was unbearable." *(72-year-old metastatic patient)*

"Working with a social worker and being referred to a young adult cancer support group" *(26-year-old patient, describing helpful support interventions)*

"I think mental health support should be part of the treatment from day 1. Losing a major organ like and eye is very traumatic. Would help deal with day to day living including work. In the end I was treated for depression a few year later." *(72-year-old patient)*

"My greatest anxiety was being 6 yrs shy of Medicare age and having a serious illness. . . . My brother died of Multiple Myeloma when he was my age now. He often said he felt like digging a hole and burying himself with all his medical bills. I can see now how he felt. It breaks my heart." *(64-year-old patient)*

Patient Preferences on Primary Tumor Treatment, Genetic Testing, and Subsequent Treatment Options

Preferences for Treatment of Primary Tumors

The highest priority for patients choosing a primary treatment to address their tumor was that the tumor is eradicated or removed, followed by clinician recommendation on course of treatment (Table 8).

A majority of participants highly valued alternatives to removal of their eye and maintaining visual acuity, with 60.9% and 65.6% of overall responses, respectively, categorizing the goals as "very important." (Table 8) The treatment attributes most frequently viewed as "not important" were ability to avoid travel (35.2%) and not having to undergo multiple treatment sessions (32.8%). Respondents also identified low out-of-pocket costs as an important attribute for their primary UM treatment. Although respondents indicated that it is important to minimize pain and discomfort associated with primary treatment for the UM tumor, they were less likely to characterize this attribute as "very important," indicating that patients place higher value on attributes related to treatment effectiveness and a clinician-guided treatment plan.

Table 8. Importance of factors when considering treatment for the primary tumor in OM.

	High Risk (N=35)	Low Risk (N=36)	Neither (N=5)	Unknown (N=51)	Overall (N=128)
Allows me to keep my eye					
Not important	5 (14.3%)	1 (2.8%)	0 (0%)	5 (9.8%)	11 (8.6%)
Somewhat important	8 (22.9%)	10 (27.8%)	1 (20.0%)	10 (19.6%)	29 (22.7%)
Very important	21 (60.0%)	22 (61.1%)	3 (60.0%)	32 (62.7%)	**78 (60.9%)**
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Allows me to keep as much visual acuity as possible					
Not important	5 (14.3%)	2 (5.6%)	0 (0%)	2 (3.9%)	9 (7.0%)
Somewhat important	7 (20.0%)	7 (19.4%)	1 (20.0%)	10 (19.6%)	25 (19.5%)
Very important	22 (62.9%)	24 (66.7%)	3 (60.0%)	35 (68.6%)	**84 (65.6%)**
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Effectively eradicates or removes the primary tumor					
Not important	1 (2.9%)	0 (0%)	0 (0%)	3 (5.9%)	4 (3.1%)

	High Risk (N=35)	Low Risk (N=36)	Neither (N=5)	Unknown (N=51)	Overall (N=128)
Somewhat important	2 (5.7%)	1 (2.8%)	0 (0%)	2 (3.9%)	5 (3.9%)
Very important	31 (88.6%)	32 (88.9%)	4 (80.0%)	42 (82.4%)	**109 (85.2%)**
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Does not require travel overnight					
Not important	13 (37.1%)	15 (41.7%)	1 (20.0%)	16 (31.4%)	45 (35.2%)
Somewhat important	15 (42.9%)	13 (36.1%)	2 (40.0%)	21 (41.2%)	51 (39.8%)
Very important	6 (17.1%)	5 (13.9%)	1 (20.0%)	10 (19.6%)	22 (17.2%)
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Lacks bothersome side effects					
Not important	2 (5.7%)	2 (5.6%)	1 (20.0%)	6 (11.8%)	11 (8.6%)
Somewhat important	19 (54.3%)	18 (50.0%)	1 (20.0%)	19 (37.3%)	57 (44.5%)
Very important	13 (37.1%)	13 (36.1%)	2 (40.0%)	22 (43.1%)	50 (39.1%)
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Does not involve repeat administration or clinic visits					
Not important	10 (28.6%)	15 (41.7%)	1 (20.0%)	16 (31.4%)	42 (32.8%)
Somewhat important	20 (57.1%)	13 (36.1%)	2 (40.0%)	22 (43.1%)	57 (44.5%)
Very important	4 (11.4%)	5 (13.9%)	1 (20.0%)	9 (17.6%)	19 (14.8%)
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Does not involve pain/discomfort					
Not important	3 (8.6%)	8 (22.2%)	1 (20.0%)	8 (15.7%)	20 (15.6%)
Somewhat important	22 (62.9%)	14 (38.9%)	2 (40.0%)	22 (43.1%)	60 (46.9%)
Very important	9 (25.7%)	11 (30.6%)	1 (20.0%)	17 (33.3%)	38 (29.7%)
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Has low out-of-pocket expense					
Not important	4 (11.4%)	5 (13.9%)	1 (20.0%)	9 (17.6%)	19 (14.8%)
Somewhat important	16 (45.7%)	11 (30.6%)	2 (40.0%)	12 (23.5%)	**41 (32.0%)**
Very important	14 (40.0%)	17 (47.2%)	1 (20.0%)	26 (51.0%)	**58 (45.3%)**
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Was recommended by my doctor					
Not important	0 (0%)	0 (0%)	0 (0%)	2 (3.9%)	2 (1.6%)
Somewhat important	8 (22.9%)	2 (5.6%)	0 (0%)	7 (13.7%)	17 (13.3%)
Very important	26 (74.3%)	31 (86.1%)	4 (80.0%)	38 (74.5%)	**99 (77.3%)**
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)

Several respondents directed their open-ended responses to their experience with primary treatment for UM. These responses underscored the importance of clear, consistent communication among providers and from provider(s) to patient, as well as specific concerns that younger UM patients might have when enucleation is the recommended approach.

RESPONDENT COMMENTS ON PRIMARY UM TREATMENT

"My treatment was approximately 29 years ago. Initially I had radiation treatment and really wanted to keep my eye. Eventually I had my eye removed and wear a prosthetic. In hindsight I should have had my eye removed initially but as a 21 yr old I was trying to keep my eye and regain 20/20 vision." *(50-year-old patient)*

"It's important to have different dr's at the same hospital be on the same page. The first dr. I met with said that if we moved quickly we'd be able to save my eye, while the surgeon I saw the next day would only recommend enucleation. That was pretty crushing. Even if enucleation is the only option, give patients a better understanding of the challenges of monocular vision & wearing an occular prosthetic. Particularly, how little the prosthetic will move in comparison to a real eye. Having to wear a prosthetic has been the hardest part of this whole thing & has ruined my self-confidence. Most OM patients are older people but I could see this being particularly hard on younger folks, like myself." *(28-year-old patient)*

"[m]y original eye surgeon did not do follow up scans and give me no choice about enucleation. Said it would save me life, but he didn't tell me about the chance of metastasis." *(72-year-old patient; metastatic disease diagnosed 1-3 years after primary treatment)*

"Ease of getting in for an appointment in timely way and not having to wait so long was very important to me when first diagnosed. There happened to be a cancellation so was able to get into see ocular oncologist the following week after diagnosed and that was perfect." *(59-year-old patient)*

Preferences for Prognostic Tests for UM

Responses to survey inquiries on patient preferences were stratified by metastatic risk to ascertain differences in priorities based on whether patients are at high- or low-risk or are unaware of their risk ("Unknown"; or answered "No/No" for high- or low-risk, classified as "Neither") of metastatic disease (Table 9).

As expected, there was near-unanimous agreement among participants on the importance of reliability in tests used to predict disease progression or likely response to treatment – the only individual characterizing this attribute as "not important" was within the unknown-risk subgroup and had expressed a "personal preference" for declining genetic testing. After test

reliability, the attribute most frequently characterized as "important" was a low risk of side effects, with 94.3% of high-risk participants, 86.3% of individuals at unknown-risk, 80.6% of individuals at neither high nor low risk, 86.1% of those with low risk, and 85.9% of overall participants assessing this as an important factor.

Survey participants indicated that, when considering testing, it is important to be able to have procedures performed locally, and that they be performed by a clinician with expertise in OM. Respondents at high risk of metastatic disease were most likely to value both the ability to have the testing performed without the need for travel (88.6%) and that the procedures be performed by a disease-specific expert (80%). While the majority of individuals with unknown risk view local care (68.6%) and OM expertise (74.5%) as "important," respondents in this group are more likely than those in the remaining risk groups to view those attributes as "unimportant" (local care (23.5%); OM expertise (17.6%)).

Table 9. Importance of factors when considering a test for metastatic risk or treatment for metastatic disease

	High Risk (N=35)	Low Risk (N=36)	Neither (N=5)	Unknown (N=51)	Overall (N=128)
Low out-of-pocket expense					
Important	30 (85.7%)	28 (77.8%)	2 (40.0%)	37 (72.5%)	97 (75.8%)
Not important	4 (11.4%)	3 (8.3%)	2 (40.0%)	9 (17.6%)	18 (14.1%)
Missing	1 (2.9%)	5 (13.9%)	1 (20.0%)	5 (9.8%)	13 (10.2%)
Reliably predicts response to treatment or progression of disease					
Not important	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)	1 (0.8%)
Important	**34 (97.1%)**	**33 (91.7%)**	**4 (80.0%)**	**45 (88.2%)**	**116 (90.6%)**
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	5 (9.8%)	11 (8.6%)
Can be performed by local clinics, does not require travel					
Not important	3 (8.6%)	7 (19.4%)	0 (0%)	**12 (23.5%)**	22 (17.2%)
Important	**31 (88.6%)**	26 (72.2%)	4 (80.0%)	35 (68.6%)	96 (75.0%)
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Can only be performed by experts in my cancer					
Not important	6 (17.1%)	4 (11.1%)	0 (0%)	**9 (17.6%)**	19 (14.8%)
Important	28 (80.0%)	29 (80.6%)	4 (80.0%)	38 (74.5%)	99 (77.3%)
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)
Low risk of side effects					
Not important	1 (2.9%)	4 (11.1%)	0 (0%)	3 (5.9%)	8 (6.2%)

	High Risk (N=35)	Low Risk (N=36)	Neither (N=5)	Unknown (N=51)	Overall (N=128)
Important	**33 (94.3%)**	**29 (80.6%)**	**4 (80.0%)**	**44 (86.3%)**	**110 (85.9%)**
Missing	1 (2.9%)	3 (8.3%)	1 (20.0%)	4 (7.8%)	10 (7.8%)

UM patients at all levels of risk for metastatic disease can face a decade or more of follow-up visits and imaging studies. Individuals at highest risk of metastatic disease may require these visits up to 4 times a year for the first 6 years. Pre-survey assumptions focused on a likely patient preference for early detection of metastatic disease, minimal inconvenience in maintaining surveillance schedule, and ability to maintain a high quality of life. Survey responses largely confirmed these assumptions. Respondents across risk subgroups reported a preference for surveillance intensity and frequency matched to their patient-specific risk of developing metastatic disease (Table 10).

Participants also prioritized having imaging performed with sufficient frequency to reduce anxiety and maintaining a high quality of life. Although travel burden can be significant for UM patients, minimizing travel was a relatively low priority across risk subgroups. Respondents also placed less importance on expense and side effects associated with testing during "wait and see."

Table 10. Rank of factors when considering the blood tests and scans that are performed during the "wait and see" period. (*Range: 1=most important and 6=least important)

	High Risk (N=35)	Low Risk (N=36)	Neither (N=5)	Unknown (N=51)	Overall (N=128)
Tailored to my disease & risk					
Median [Min, Max]	1.00 [1.00, 5.00]	1.50 [1.00, 6.00]	1.00 [1.00, 2.00]	2.00 [1.00, 6.00]	1.00 [1.00, 6.00]
Missing	1 (2.9%)	2 (5.6%)	1 (20.0%)	4 (7.8%)	9 (7.0%)
Maintain QOL					
Median [Min, Max]	3.00 [1.00, 6.00]	2.00 [1.00, 6.00]	3.00 [3.00, 4.00]	2.00 [1.00, 6.00]	2.00 [1.00, 6.00]
Missing	1 (2.9%)	2 (5.6%)	1 (20.0%)	4 (7.8%)	9 (7.0%)
Frequency to minimize anxiety					
Median [Min, Max]	2.50 [1.00,	3.00 [1.00, 6.00]	2.00 [1.00, 5.00]	3.00 [1.00, 6.00]	3.00 [1.00, 6.00]

	High Risk (N=35)	Low Risk (N=36)	Neither (N=5)	Unknown (N=51)	Overall (N=128)
	6.00]				
Missing	1 (2.9%)	2 (5.6%)	1 (20.0%)	4 (7.8%)	9 (7.0%)
Minimize travel					
Median [Min, Max]	5.00 [1.00, 6.00]	5.00 [2.00, 6.00]	4.00 [4.00, 6.00]	5.00 [1.00, 6.00]	5.00 [1.00, 6.00]
Missing	1 (2.9%)	2 (5.6%)	1 (20.0%)	4 (7.8%)	9 (7.0%)
Minimize expense					
Median [Min, Max]	5.00 [2.00, 6.00]	5.00 [1.00, 6.00]	5.00 [3.00, 6.00]	5.00 [1.00, 6.00]	5.00 [1.00, 6.00]
Missing	1 (2.9%)	2 (5.6%)	1 (20.0%)	4 (7.8%)	9 (7.0%)
Little or no Side effect					
Median [Min, Max]	5.00 [1.00, 6.00]	4.00 [1.00, 6.00]	5.50 [2.00, 6.00]	4.00 [2.00, 6.00]	5.00 [1.00, 6.00]
Missing	1 (2.9%)	2 (5.6%)	1 (20.0%)	4 (7.8%)	9 (7.0%)

Open-ended responses directed to the “wait and see” period focused on patient interest in receiving information at each visit that includes new treatment options as well as patient-specific information and prioritized the need to ensure management through the surveillance period by a clinician with disease-specific expertise.

RESPONDENT COMMENTS ON MONITORING DURING "WAIT AND SEE"

"Updated information on latest treatments, etc. at each monitoring appointment relative to my specific condition and indications." *(61-year-old patient)*

"I live in AK and there are no specialists with ocular melanoma experience and knowledge. I frequently am educating my revolving ophthalmologists about proper follow up scans and care. They don't know how to read test results which is very stressful. Please work to educate doctors on OM and proper follow up care." *(59-year-old patient)*

"Experience of doctor access for this specific disease of MOST importance." *(54-year-old patient)*

"It is important to have consistency in seeing the same physician on an ongoing basis as much as possible." *(75-year-old patient)*

Preferences for Treatment of Metastatic disease

Treatment preferences for metastatic disease aligned with those for primary treatment of the UM tumor. Responses to treatment and process attributes in metastatic UM (Table 11) indicate a very clear patient preference, across risk groups, for access to a metastatic disease treatment as early as possible.

Respondents also felt it was very important that treatment for metastatic disease allow them to maintain independence. Respondents within the high- and low- risk groups valued access to clinical trials higher than those in the unknown-risk group, with 91.4% of high-risk respondents and 88.9% of low-risk respondents (compared to 76.4% of those at unknown risk) indicating that this attribute is either somewhat or very important. Respondents indicated a willingness to travel and participate in clinical trials (avoiding travel and clinical trial are viewed as "not important" to 29.7% and 44.5% of overall respondents, respectively). The majority of respondents across risk groups also identified low out-of-pocket costs as either somewhat or very important. It is worth noting that for some patients, a preference for lower out-of-pocket costs will neither drive treatment decisions nor impede access to preferred treatment options. However, patients with limited financial means, inadequate insurance coverage, and/or limited provider networks, can find that their options on choosing an expert clinician and obtaining early access to promising therapies are driven primarily, or even completely, by financial considerations.

Table 11. Importance of factors in considering treatment options for metastatic OM.

	High Risk (N=35)	Low Risk (N=36)	Unknown (N=51)	Overall (N=128)
Has low out-of-pocket expense				
Not important	3 (8.6%)	6 (16.7%)	7 (13.7%)	16 (12.5%)
Somewhat important	17 (48.6%)	13 (36.1%)	17 (33.3%)	50 (39.1%)
Very important	13 (37.1%)	14 (38.9%)	21 (41.2%)	49 (38.3%)
Missing	2 (5.7%)	3 (8.3%)	6 (11.8%)	13 (10.2%)
Lacks bothersome side effects				
Not important	2 (5.7%)	2 (5.6%)	5 (9.8%)	10 (7.8%)
Somewhat important	20 (57.1%)	14 (38.9%)	21 (41.2%)	56 (43.8%)
Very important	11 (31.4%)	17 (47.2%)	19 (37.3%)	49 (38.3%)
Missing	2 (5.7%)	3 (8.3%)	6 (11.8%)	13 (10.2%)
Does not require out-of-town travel				
Not important	9 (25.7%)	13 (36.1%)	14 (27.5%)	38 (29.7%)
Somewhat important	16 (45.7%)	14 (38.9%)	23 (45.1%)	53 (41.4%)
Very important	8 (22.9%)	6 (16.7%)	8 (15.7%)	24 (18.8%)
Missing	2 (5.7%)	3 (8.3%)	6 (11.8%)	13 (10.2%)
Does not require clinical trial enrollment				
Not important	19 (54.3%)	14 (38.9%)	22 (43.1%)	57 (44.5%)
Somewhat important	11 (31.4%)	13 (36.1%)	15 (29.4%)	40 (31.2%)
Very important	3 (8.6%)	6 (16.7%)	8 (15.7%)	18 (14.1%)
Missing	2 (5.7%)	3 (8.3%)	6 (11.8%)	13 (10.2%)
Available at first detection of metastasis				
Somewhat important	2 (5.7%)	3 (8.3%)	5 (9.8%)	11 (8.6%)
Very important	**31 (88.6%)**	**30 (83.3%)**	**39 (76.5%)**	**103 (80.5%)**
Not important	0 (0%)	0 (0%)	1 (2.0%)	1 (0.8%)
Missing	2 (5.7%)	3 (8.3%)	6 (11.8%)	13 (10.2%)
Access new treatments in clinical trials				
Not important	1 (2.9%)	1 (2.8%)	6 (11.8%)	8 (6.2%)
Somewhat important	11 (31.4%)	9 (25.0%)	17 (33.3%)	38 (29.7%)
Very important	21 (60.0%)	23 (63.9%)	22 (43.1%)	69 (53.9%)
Missing	2 (5.7%)	3 (8.3%)	6 (11.8%)	13 (10.2%)

	High Risk (N=35)	Low Risk (N=36)	Unknown (N=51)	Overall (N=128)
Maintain independence				
Not important	0 (0%)	1 (2.8%)	1 (2.0%)	2 (1.6%)
Somewhat important	7 (20.0%)	5 (13.9%)	3 (5.9%)	15 (11.7%)
Very important	26 (74.3%)	27 (75%)	41 (80.4%)	98 (76.6%)
Missing	2 (5.7%)	3 (8.3%)	6 (11.8%)	13 (10.2%)

Several participants submitted open-ended responses that discussed their experience addressing metastatic disease. Their statements echo the priorities expressed by participants discussing the "wait and see" period – a robust bi-directional communication channel between the patient and provider, and disease-specific clinician expertise are of paramount importance.

RESPONDENT COMMENTS ON METASTATIC OM

"Communication is paramount - particularly [in regard to] outcome (probabilities of stability or regression) and side effects (both long and short term). Additionally, listening to the patient is critical and running necessary tests if symptoms warrant." *(30-year-old metastatic patient)*

"It is very important to me that my testing (scans) is done on in such a way as to keep on top of the progression of my disease." *(72-year-old metastatic patient)*

"My first oncologist was horrible (did not specialize in OM). Since then, I've had an amazing team of doctors who all speak to each other (UCHealth, UMPC, Columbia, MSK). Of course, Hovland being the first coach involved and continued support. I feel so lucky to have gotten the care I have and to still be here today. I so appreciate the communication that goes on between all the doctors out there trying to treat this disease." *(38-year-old metastatic patient)*

"I don't want participate in a treatment that will make me miserable for the last part of my life." *(50-year-old patient*)

Discussion

Respondent demographics diverged from that of the general UM patient population in that a majority of survey participants were women (65.6%), and age at diagnosis was approximately 10 years earlier among respondents than that found in SEER data (52.8 versus 62 years of age) (Table 2). The disproportionate responses from female patients may reflect a generalized tendency for women to be more likely than men to contribute information through survey responses that has been noted across survey populations, including patients, workers, and

faculty members (Smith 2008).

The predictions for UM patient preferences were that all patients would value preserving their vision, obtaining as much information on their disease and its likely progression as possible; and maintaining a good quality of life throughout the primary treatment, "wait and see" surveillance, and metastatic disease phases of UM. UM patient responses supported these hypotheses.

UM Patients continue to struggle with coverage for "prognostic" genetic testing. It is important to note that describing UM metastatic risk assessment testing as "prognostic" may have a meaning, or at least a connotation, which diverges from the "medical necessity" determinations driving coverage. Using the term in connection with genetic testing for UM metastatic risk may have obscured the clinical utility of an accurate, validated test in guiding the surveillance and follow-up plan for these patients. One respondent described difficulties in obtaining coverage for the genetic testing, including the need for multiple levels of reconsideration and appeal.

RESPONDENT COMMENT ON COVERAGE FOR GENETIC TESTING

"I had to fight very hard for my insurance to cover my genetic biopsy. It was denied and appealed 3 times and sent to arbitration before they would cover it. The biopsy results were the guiding principles to my treatment." (*58-year-old metastatic patient)*

While only two respondents cited out-of-pocket costs as a contributing factor in deciding to decline testing, coverage uncertainties can often deter providers from recommending procedures that may result in unexpected out-of-pocket costs for the patient or that have the potential for coverage denial. Educating payers on the primary purpose and clinical utility of these tests could enable patients and their providers to avoid burdensome and time-intensive payer processes. It is also important to note that the relative low priority patients assigned to out-of-pocket costs associated with testing does not mean that overall treatment costs do not impact access. Patients generally construe "out-of-pocket costs" as their financial responsibilities within their insurance plan, i.e., deductibles and copayments. When "costs" are viewed more broadly to include out-of-town travel to receive care, including within a clinical trial, or out-of-network care, the impact on patient decisions and access is likely quite high.

Although genetic testing for metastatic risk was clinically available for all but one of the 24 participants who were age 65 or over when first diagnosed with OM, 10 (41.67%) of these patients were unaware of their risk of metastatic disease (calculated from raw data on file). Medicare Administrative Contractors (MACs) have issued local coverage determinations (LCDs) providing ***conditional*** coverage for this testing performed with Castle Bioscience's DecisionDx-UM, an RNA gene expression classifier that is based on the expression levels of 15 mRNA transcripts (3 control and 12 discriminating genes). Results of the test are reported as a 5-year risk classification for metastasis: low risk (Class 1A), intermediate risk (Class 1B), or high risk (Class 2). Although the MACs recognize that "[i]n both prospective and retrospective

multicenter studies, DecisionDX-UM has been shown to be a more accurate prognostic indicator of metastasis compared to any other factor" (Noridian LCD, 2019), coverage is described as "limited" and requires use of a registry with retrospective MAC review of registry data to demonstrate real-world clinical utility:

> Registry endpoints will demonstrate that ≥ 80% of class 2 patients are referred to medical oncology for management, and that Class 1A/1B patients do not undergo more intensive surveillance testing compared to Class 2 patients. Continued coverage of this assay will depend on semi-annual review of interim data and publications demonstrating the above clinical utility (Noridian LCD, 2019).

For patients and their providers, coverage clarity through a Medicare LCD can serve to expand access to services. There may, however, be unintended consequences associated with the conditional coverage of DecisionDX-UM, including:

- Provider hesitance due to the administrative burden of documenting referrals and participating in the mandatory registry.

- Constricted access to the full team of specialists that their particular cancer requires, including BOTH a medical oncologist and an ocular oncologist, and surveillance frequency and intensity based on decisions between the patient and their clinician(s).

    - MRF's treatment center finder: https://melanoma.org/treatment-center-finder/ enables patients to access an expert clinician directory. This list of UM specialists includes medical oncologists, as well as a significant number of identified expert clinicians listed as ocular oncologists.

    - Medicare patients may receive follow-up surveillance based on the LCD rather than on considerations that more closely align with patient preferences.

Finally, payers may require documentation that a patient is at high risk for metastatic disease as a condition to coverage of imaging studies and other follow-up for early detection of metastatic disease. This could impact care decisions and access for patients identified as intermediate and low risk for metastatic disease, as well as those for whom genetic testing for risk assessment was not performed.

Patient decisions on whether to have prognostic testing may be based on factors unrelated to risk and should not drive follow-up surveillance for metastatic disease. In the unknown risk group, 13.72% of participants report either that imaging studies were not performed or that they were unsure; 11.43% of those within the low-risk group stated that they had not undergone imaging studies (compared to 2.86% in the high-risk group who did not undergo scans to monitor for metastases) (data on file). Increasing acceptance of stratified approaches

to “wait and see” among providers and payers could have the potential to drive care gaps for UM patients who fail to have their metastatic risk assessed.

Given that the standard of care suggests that the frequency of imaging studies and other tests for early detection of metastasis should be driven by patient-specific risk, patients for whom metastatic risk has not been assessed -and, from a payer perspective, cannot be documented- could face coverage hurdles as they seek follow-up care. It is, therefore, important that patients with a personal preference against knowing their metastatic risk, concerns about cost, or other reasons for declining genetic testing, or who may not have been offered the testing, are able to access the follow-up care they need. Defaulting these patients to surveillance intensity and frequency indicated for low-risk UM patients could compromise outcomes and reduce access to promising new treatment options targeted to UM status and/or risk profile.

UM patients have limited access to emerging treatment options within clinical trials. Although existing FDA-approved treatments have yet to demonstrate significant improvement in overall survival, promising new treatments therapies are in development. Patients, advocacy organizations, and clinicians specializing in UM will need to take a proactive approach in ensuring that patients struggling with metastatic disease have access to the treatment most likely to be of benefit. During a January 2020 FDA Patient-Led Listening Session organized by the MRF’s CURE OM initiative, UM patients emphasized the “financial toxicity” associated with navigating care to include clinical trial participation and/or expanded access to promising therapies in development (FDA Listening Session). Continued engagement with FDA and manufacturers that focuses on leveraging some of the lessons learned from the COVID-19 pandemic, including remote and virtual monitoring, could increase access to clinical trial participation. Although expanded access programs are designed to get treatments demonstrating safety and efficacy in clinical trials to the patients needing them, patient awareness of, and therefore access to, these programs often depend upon clinician expertise in the disease. Patient advocacy organizations can play a pivotal role in alerting patients to therapeutic advances and providing the key information patients need to navigate access.

UM patients experience and seek treatment for anxiety, but not depression, more frequently than the general population. Participant responses to the inquiry on treatment for anxiety indicate that UM patients experience anxiety symptoms with a greater frequency and severity than the general population. Although anxiety disorders are the most common mental illness in the U.S., affecting 18.1% of the adult population each year, only 36.9% of impacted individuals (therefore 6.68% of the adult population) receive treatment (Anxiety and Depression Association of America, 2021). Survey participants in the unknown, high- and low-risk groups reported that they had received treatment for anxiety (28.57% [low risk]; 25.7% [high risk]; 19.61% [unknown risk]) with greater frequency than the overall US adult population. The 14.3% of metastatic disease respondents reporting treatment for anxiety was lower than rates reported across UM risk groups, but more than double that of the US adult population (6.68% [general population]; 14.3% [metastatic UM disease]).

UM patients reported receiving counseling and/or medication for depression with a frequency

that is consistent with statistics for the general population (13.72% [unknown risk]; 17.1 [high risk]; and 14.3% [low risk and metastatic disease]). According to data from the National Health and Nutrition Examination Survey compiled from 2015–2018, 13.2% of adults aged 18 and over used antidepressant medications in the past 30 days. Antidepressant use increased with age and was higher among the non-Hispanic white (16.6%) adults that comprise the vast majority of UM patients, compared with non-Hispanic black (7.8%), Hispanic (6.5%), and non-Hispanic Asian (2.8%) adults (Centers for Disease Control and Prevention, 2020).

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In addition, the immediate post-diagnosis period presents unique stressors for patients, as they face decisions that may require balancing quick action addressing the primary tumor with patient interest in selecting a clinician with UM-specific expertise and gathering the information needed to make an informed decision. Once UM is diagnosed, patients appreciate timely referral to a UM expert so that the tumor can be removed or eradicated with expertise.

Conclusions

UM is a rare cancer that is a distinct disease from cutaneous melanoma with differences in rate of metastasis and treatment approaches. Although most patients are diagnosed before metastatic disease is detectable, and primary treatment for the UM tumor is successful in controlling local eye disease in the overwhelming majority of cases, approximately half of UM patients will go on to develop metastatic disease (Krantz 2017). The survey of UM patients revealed multiple factors that are important to patients when making decisions about treatments and “wait and see” surveillance for UM:

- Successful removal of the UM tumor through an effective primary treatment.
- Reliable, accurate genetic biomarker testing that can be performed locally by clinicians experienced in treating UM.
- Follow-up to primary treatment with surveillance regimen tailored in frequency and intensity to the patient’s risk of metastatic disease; and
- Effective treatments for metastatic UM that can be prescribed or administered at first detection of metastasis.

Other key findings include:

- Newly-diagnosed UM patients may not understand all primary treatment options, or that UM is a rare disease and treatment is best handled by an experienced clinician with disease-specific expertise ***(open-ended responses).***
- Newly-diagnosed UM patients are not always informed that genetic biomarker testing is available.
- Even when genetic biomarker testing is performed, patients may not understand the results of the test or their risk of metastatic disease.

UM patients live with the uncertainty burden of this cancer and may have to travel out-of-town to ensure that their cancer is treated, managed, and monitored by a clinician with UM expertise. Significant out-of-town travel may be required to receive care from an UM expert or participate in a clinical trial. This is relatively common and for many patients can become a long-term necessity due to lack of local expertise. Genetic testing has enabled clinicians to assess 5-year risk of metastatic disease and to direct follow up frequency and intensity in the adjuvant setting to match the level of risk. Individuals at high-risk for metastatic disease have the ability to make treatment decisions, including clinical trial participation, and, if available, use of adjuvant treatment regimens outside the clinical trial setting.

Recent advancements in the understanding of UM, as well as the ability to accurately assess metastatic risk, offer hope for improved outcomes in the approximately 50% of UM patients who will develop metastatic disease. There are, however, potential hurdles to ensuring that all UM patients have the primary UM treatment, genetic testing, follow-up imaging and treatment to address patient-specific risks, and a metastatic disease treatment that offers the best chance for improved survival.

- Coverage for biomarker testing may vary by payer and require patients to go through multiple appeals processes to secure coverage.
- Medicare covers the DecisionDX-UM test but requires use of a registry and clinician referral of high-risk patients to a medical oncologist, and implies oversight on the intensity of surveillance in patients at low risk of metastatic disease. This coverage mechanism could have the unintended consequence of deterring clinicians from offering the test and reduce Medicare patient access to follow-up surveillance based on individual patient/clinician decisions.
- Stratifying follow-up surveillance by risk could also have the unintended consequence of reducing access to appropriate follow-up and surveillance for patients unable or unwilling to have genetic biomarker testing performed.
- Adjuvant treatment options within clinical trials are unavailable to the vast majority of high-risk UM patients due to the limited number of studies and sites, as well as clinical trial inclusion and exclusion criteria limiting enrollment to patients within a 6-month window following primary treatment; and
- Although clinical trial participation is recommended for patients with metastatic UM, the small set of interventional studies recruiting US patients are clustered in a limited

number of sites. Patients unable to afford traveling from home multiple times or for extended periods will not have access to this level of care.

Finally, open-ended responses and survey results indicated that many patients struggle to acquire and/or fully understand UM and their diagnostic and treatment options throughout the patient journey. Ensuring that all UM patients are aware of, and have access to, the resources they need to make informed decisions, engage with other patients, and access supportive services as needed. The MRF and its CURE OM initiative have developed a comprehensive set of informational and supportive resources for UM patients.

- CURE OM landing page (www.cureom.org) with information about OM as well as the CURE OM brochure and the ocular melanoma fact sheet. This page also defines terms that patients are likely to encounter.
  .
- The Just Diagnosed OM Patient Guide is a helpful resource for patients struggling with a newly-diagnosed UM. https://melanoma.org/patients-caregivers/ocular-melanoma/diagnosis-ocular/

- Information on UM treatment options can augment clinician/patient discussions. https://melanoma.org/patients-caregivers/ocular-melanoma/treatment-ocular/

- Additional resources include links to support groups and a set of questions that patients might wish to ask their providers. https://melanoma.org/patients-caregivers/ocular-melanoma/resources-ocular/

- CURE OM's Global VISION Registry page: www.visionregistry.org

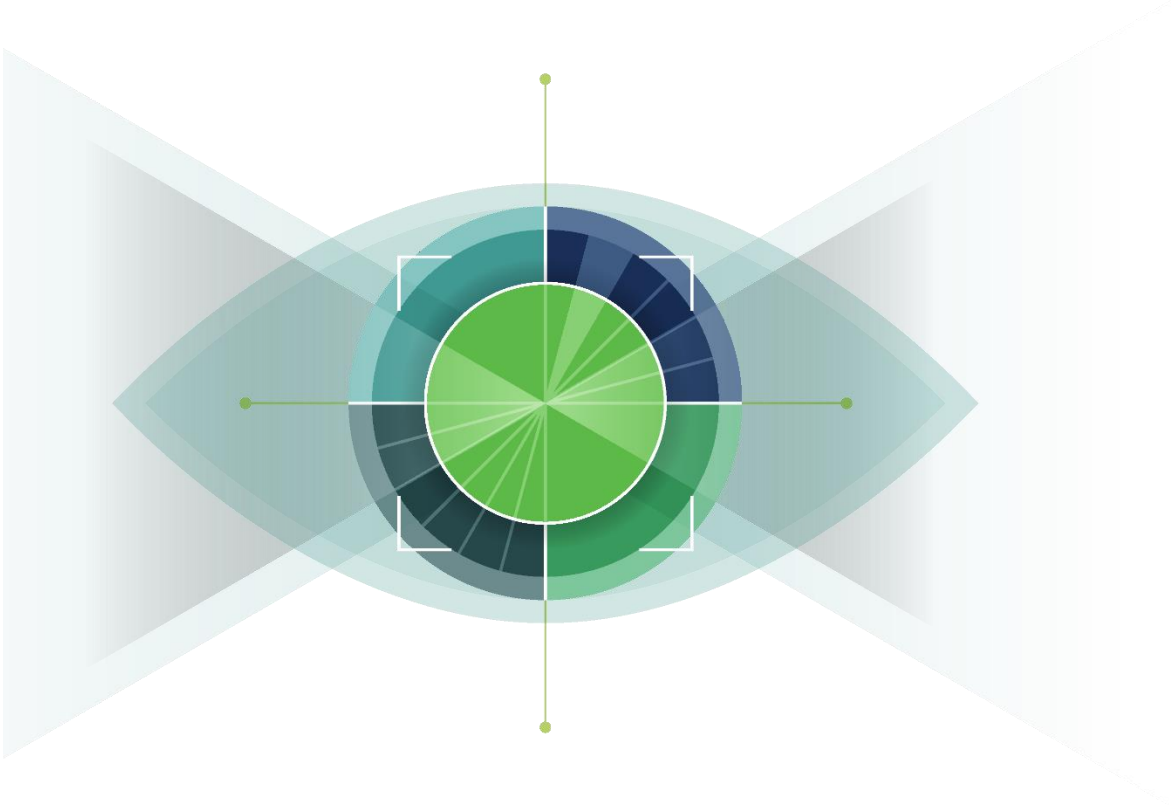
Strengths and Limitations

The survey instrument was the sole source of patient-derived data. Post-survey follow-up with respondents to seek clarity or granularity may have enabled expanded or more in-depth response acquisition.

The survey was conducted from late September to late October 2020, when individuals in the US faced uncertainties associated with the COVID-19 pandemic as well as social isolation due to social distancing requirements. It is unclear how these ambient factors might have impacted participant responses on disease burden, mental health impact, quality of life, travel to health care providers, and reliance on caregivers. With respect to the mental health burden of UM, participants may have followed the overall trend in the US population and experienced mental health concerns with greater frequency or intensity. UM patients may, alternatively, have felt desensitized to disease-specific anxiety and depression, or attributed these symptoms to the pandemic.

Survey responses related to specifics on the medical care participants received are not likely to be impacted by the pandemic, and the set of patients responding to the survey were

representative of patients at the various disease stages, including individuals living with UM for multiple decades as well those facing metastatic disease within a year of first diagnosis. We also believe that patient preferences in this population, including those driving decisions to choose a particular treatment or test, are informed by participant's knowledge of the disease and its risks as well as their healthcare experience, and likely reflect real-world experience with the benefits and shortcomings of existing options.



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