Ontario Health
Cancer Care Ontario

Guideline Endorsement C50-CIDAP-1

A Quality Initiative of the
Cancer Care Integration and Disease Advisory Program (CIDAP), Ontario Health (Cancer Care Ontario)

An Endorsement of the 2021 Cancer Care Alberta Clinical Practice Guideline on Uveal Melanoma

F.C. Wright, M. Butler*, R. Beecroft, A. Cyr, I. King, H. Krema, N. Laperriere, G. Martel, M. Ong, S. Courtney, and the Uveal Melanoma Guideline Endorsement Working Group*

Report Date: March 19, 2024

This document describes the Ontario Health (Cancer Care Ontario) Cancer Care Integration and Disease Advisory Program endorsement of the 2021 Cancer Care Alberta Clinical Practice Guideline on Uveal Melanoma. The original publication is available at https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cu015-uveal-melanoma.pdf.

*Co-first authors
For information about this document, please contact Dr. F.C. Wright at: Phone: 416-480-4210 Fax: 416-480-6002 E-mail: frances.wright@sunnybrook.ca

Please visit the Ontario Health (Cancer Care Ontario) website at https://www.cancercareontario.ca/en/guidelines-advice for the most up-to-date version of all reports.

Report Citation (Vancouver Style): Wright FC, Butler M, Beecroft R, Cyr A, King I, Krema H, Laperriere N, Martel G, Ong M, Courtney S. An endorsement of the 2021 Cancer Care Alberta clinical practice guideline on uveal melanoma. Toronto (ON): Ontario Health (Cancer Care Ontario); *2024 March 19*. Ontario Health (Cancer Care Ontario) Guideline Endorsement No.: C50-CIDAP-1.

Table of Contents

An Endorsement of the 2021 Cancer Care Alberta Clinical Practice Guideline on Uveal Melanoma

Section 1: Guideline Endorsement

GUIDELINE OBJECTIVES

The objectives of this guideline are to provide recommendations on the diagnosis and management of uveal melanoma. The recommendations are based on version 2 of the Cancer Care Alberta Clinical Practice Guideline on Uveal Melanoma [1].

TARGET POPULATION

Patients with suspected or confirmed uveal melanoma diagnosis.

INTENDED USERS

The guideline document will support providers in the diagnosis and management of patients with uveal melanoma.

ENDORSEMENT

The Uveal Melanoma Guideline Development Group (GDG) of Ontario Health (Cancer Care Ontario) endorses the majority of recommendations of the Cancer Care Alberta (CCA) Clinical Practice Guideline on Uveal Melanoma, available at https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cu015-uveal-melanoma.pdf, as modified by the endorsement process described in this document. These recommendations are reprinted below with permission from CCA, with modifications noted. \

Fourteen of the thirty-one recommendations were endorsed without modifications or comments. Seventeen of the thirty-one recommendations were endorsed with comments, which are the consensus opinion of the working group, as listed in Table 1-1.

Table 1-1. CCA uveal melanoma clinical practice guideline recommendations [1]

Recommendations	Assessment
Diagnosis and Work-Up	
1. All intraocular malignancies and indeterminate lesions should be evaluated by a provider trained in all aspects of care (i.e., medical, oncologic, surgical, radiotherapy [RT], laser therapy [e.g., transpupillary thermotherapy]) to determine appropriate follow-up and/or treatment. (Level of Evidence: V24-26, Strength of Recommendation: B) **Comment:** Intraocular malignancies and indeterminate lesions should be assessed by an ophthalmologist with expertise in uveal melanoma. Once an intraocular malignancy has been diagnosed, a multidisciplinary team should assess the patient.	**Endorsed with comment**
2. Complete history including ophthalmic and medical history.	**Endorsed**

3. Complete ophthalmic examination and fundoscopy. • A baseline fundus photograph of adequate quality and an objective assessment of lesion height is required for all melanocytic lesions.	**Endorsed**
4. Ocular ultrasonography by a certified ophthalmic ultrasonographer or ophthalmologist with training in ultrasound (U/S). • A-scan U/S can demonstrate initial prominent spike followed by low-to-medium internal reflectivity or a decrescendo pattern and can be used to measure tumour height. (Level of Evidence: IV27, Strength of Recommendation: B) • B-scan U/S can allow for tumour measurement (height), and tumour characteristics including solidity/hollowness, vascularity, shape, and extra-scleral (extraocular) extension. (Level of Evidence: IV27, Strength of Recommendation: B) • U/S biomicroscopy (UBM) is a high frequency U/S providing high resolution imaging of the anterior segment of the eye. It is used to visualize ciliary body and iris tumours. (Level of Evidence: IV28, 29, Strength of Recommendation: B)	**Endorsed**
5. Ancillary ocular studies, if ophthalmic examination is inconclusive, sometimes due to media opacity. (Level of Evidence V30-32, Strength of Recommendation: B) • Fluorescein and/or Indocyanine green angiography of the retina and choroidal vasculature is helpful in select cases (requires clear media for visualization). • Computed tomography (CT) of the eye is rarely needed. • Magnetic resonance imaging (MRI) of the eye is rarely needed. **Comment:** Optical Coherence Tomography can differentiate amelanotic melanoma from simulating lesions, can detect subtle subretinal fluid, and retinal changes over choroidal tumours.	**Endorsed with comment**

6. Staging work-up to rule out metastases for patients diagnosed with uveal melanoma.
• Serum testing
  o Complete blood count (CBC)
  o Liver function tests (LFTs)
• Diagnostic imaging should aim to reduce unnecessary radiation.
  o All patients should receive a baseline Primovist-enhanced abdominal MRI and ultrasound (U/S) of the liver and non-contrast enhanced CT scan of the chest.
  o Or whole-body positron emission tomography (PET)/CT scan and ultrasound of the liver. (Level of Evidence: III33 IV34, Strength of Recommendation: B)
  o If there is a suspicion of metastases, refer to a tertiary cancer centre.
 	
<u>Comment</u>: After treatment of the primary lesion, all patients should receive baseline imaging, including a computed tomography (CT) of the chest and contrast-enhanced magnetic resonance imaging (MRI) of the liver. If MRI is not possible, ultrasound of the liver by trained personnel may be performed.
 	
If there is suspicion of metastases, patients should be referred to a tertiary cancer centre with expertise in uveal melanoma.
	Endorsed with comment

Primary Management	
Melanocytic Choroid Tumours	

1. Small (<3 mm in thickness) tumours (i.e., 'nevi', 'indeterminate melanocytic lesions', and small melanomas)
• Small lesions are observed for growth or treated based on risk factors for growth and the associated risk of visual loss with treatment.
  ○ Most lesions with no risk factors are observed until growth is documented. Once growth is documented the lesion is labeled a melanoma and is treated. (Level of Evidence: IV35-39, Strength of Recommendation: B)
  ○ All lesions are evaluated based on their risk factors for future growth.
  ▪ Risk factors for future growth include tumour thickness >2 mm, subretinal fluid, symptoms of visual acuity loss to 20/50 or worse, orange pigment, hollow acoustic density and tumour largest basal diameter >5 mm. *(Level of Evidence: IV40, Strength of Recommendation: B)*
  ▪ High-risk lesions (≥ 3 risk factors) are often offered treatment, biopsy, or close observation based on discussions with the patient regarding visual loss, since the risk of future growth is greater than 50%. *(Level of Evidence: IV41 V31, Strength of Recommendation: B)*
  ▪ When indicated, treatment is most commonly ocular brachytherapy. *(Level of Evidence: III42 IV43, Strength of Recommendation: B)*
	Endorsed

2. Medium/intermediate (3-12 mm in thickness) tumours are typically treated with ocular brachytherapy. (Level of Evidence: I44-48, Strength of Recommendation: A) • Enucleation is sometimes chosen by patients who cannot make the follow-up visits required post brachytherapy. **<u>Comment</u>:** Tumours that significantly encroach over the optic disc can be treated with external beam radiotherapy.	**Endorsed with comment**

3. Large (>12 mm in thickness) tumours • Due to the risk of severe vision loss and neovascular glaucoma secondary to radiation complications with large lesions, large lesions are offered enucleation or brachytherapy (if standard dosing can be achieved with brachytherapy). o Many centres offer enucleation for very large tumors greater than 12 mm in thickness and 18 mm in maximal width. (Level of Evidence: IV49-52, Strength of Recommendation: B) o Brachytherapy for very large lesions (>12 mm thick or >18 mm in maximal basal dimension) is sometimes performed in select cases such as contralateral vision loss or in patients who insist on avoiding enucleation. (Level of Evidence: V24, Strength of Recommendation: C) • Neo-adjuvant pre-enucleation radiation does not provide a clinically or statistically meaningful difference in mortality rates. (Level of evidence: I53, Strength of recommendation: E) **<u>Comment</u>:** Tumour resection followed by low-dose brachytherapy may be indicated for large tumours involving single eyed patient to avoid the sight damaging effect of high dose brachytherapy. In extremely rare situations, enucleation may be chosen by patients who cannot attend brachytherapy follow-up visits.	**Endorsed with comment**
Ciliary Body Lesions	
1. Ciliary body lesions <12 mm thick and that do not have an extensive circumferential growth pattern are most commonly treated with brachytherapy. (Level of Evidence: IV54 V55, Strength of Recommendation: C)	**Endorsed**
2. Ciliary body lesions are amenable to surgical excision (i.e., iridocycletcomy) in select cases. (Level of Evidence: IV56 V23, Strength of Recommendation: C)	**Endorsed**
Iris Lesions	
1. Iris lesions are typically observed for growth before brachytherapy treatment is offered. (Level of Evidence: IV57, Strength of Recommendation: C)	**Endorsed**
2. Iris lesions are amenable to surgical excision (i.e., iridectomy) in select cases. (Level of Evidence: V23, 58, Strength of Recommendation: C)	**Endorsed**
3. Iris lesions are often also amenable to brachytherapy. (Level of Evidence: V23, 59, Strength of Recommendation: C)	**Endorsed**
Principles of Complete Assessment	

1. Lesions being observed require a complete assessment of: • The current risk factors for growth • Adequate baseline photographic imaging of the lesion • An objective assessment of the lesion's thickness to allow assessment for growth • Intermittent follow-up imaging is also required to document change or stability of the lesion.	**Endorsed**
2. Adequate photographic imaging requires: • The entire lesion and the adjacent normal structures need to be photographed. Otherwise, growth cannot be truly assessed. ○ In addition, a photograph of the entire lesion including the fovea and the optic nerve is recommended (but not required) to ensure reproducibility of the landmarks adjacent to the lesion. • Some very anterior choroidal lesions and ciliary body lesions cannot be photographed in the entirety due to technical limitations in current imaging technology. • The lesion needs to be in focus, and appropriate exposure levels in the baseline and follow-up imaging allowing for assessment of change over time need to be obtained. • If adequate imaging cannot be obtained, referral to a specialist capable of performing a complete assessment is required. • If two or more risk factors are present or any change or growth is noted, referral to a subspecialist ocular oncologist is recommended. **<u>Comment</u>:** A referral should be made to an ophthalmologist with expertise in ocular malignancy.	**Endorsed with comment**
Principles of Enucleation	
1. Enucleation involves surgical removal of the eye.	**Endorsed**
2. Typically, lesions >12 mm in thickness and/or >18 mm in diameter are offered enucleation.	**Endorsed**

3. For patients undergoing enucleation, in accordance with the College of American Pathologists' Protocol for the Examination of Specimens from Patients with Uveal Melanoma, review of specimens should include reporting of the following elements: • Specimen laterality • Tumour site: iris, ciliary body, choroid • Largest basal diameter and thickness • Scleral and optic nerve invasion • Extraocular extension • Histologic type: spindle, mixed, epithelioid • Mitotic count • Vascular invasion • Extravascular matrix pattern • Inflammatory cells/tumour infiltrating lymphocytes and macrophages • Invasion of Bruch's membrane • Margins • Regional lymph nodes • Pathologic stage classification (pTNM, AJCC 8th Edition) Molecular results (if known): o Chromosome 3 and 8 loss/gain o BAP1 status o Gene expression profile (GEP) o Multiplex ligation dependent probe amplification (MLPA) analysis • Additional pathologic findings **Comment:** Further molecular profiling results may aid diagnosis, risk assessment and management. Additional molecular results may also include reporting of GNAQ, GNA11, SF3B1, EIF1AX, PLCB4, CYSLTR2 and MBD4 tumour variants, if available. There is limited evidence comparing the different approaches to molecular risk stratification of uveal melanoma. Implementation should be done in conjunction with available evidence and clinical expert opinion.	**Endorsed with comment**
Principles of Primary Radiotherapy (RT)	
1. Episcleral brachytherapy is the most commonly utilized treatment for uveal melanoma worldwide and is the treatment of choice in Alberta. **Comment:** Episcleral brachytherapy is the most commonly utilized treatment for uveal melanoma worldwide and is the treatment of choice in Ontario.	**Endorsed with comment**
2. Other RT modalities include charged-particle external beam RT (EBRT) (i.e., protons, carbon ions, or helium ions), and photon-based radiosurgery (i.e., linear accelerator, gammaknife, or cyberknife).	**Endorsed**

Adjuvant Local Therapy	
1. Positive margins post excision: • If margins are positive or indeterminate after resection, adjunctive plaque brachytherapy RT of the surgical margins is often utilized. **Comment:** After resection, irrespective of margins, all patients should receive adjunctive plaque brachytherapy RT.	**Endorsed with comment**
2. Transpupillary thermotherapy (TTT): • TTT uses an infrared laser administered through a dilated pupil for choroidal lesions. • TTT as a primary treatment has been associated with a relatively high rate of local recurrence, especially when the tumour abuts the optic nerve and overhangs the optic disc. Therefore, TTT is not recommended as monotherapy for uveal melanoma in the standard case. (Level of Evidence: II61 IV62, Strength of Recommendation: D) • TTT can be offered as an adjunctive treatment to reduce the risk of local recurrence following RT or as a primary treatment for medium risk nevi in select cases. (Level of Evidence: IV63, 64, Strength of Recommendation: C) • TTT is used in some centers to treat marginal recurrence post brachytherapy. (Level of evidence: IV64, Strength of Recommendation: C) • TTT can cause retinal vascular damage and retinal traction and subsequent secondary visual loss. **Comment:** In Ontario, TTT is not recommended as a primary treatment for medium risk benign nevi.	**Endorsed with comment**
3. Radiation retinopathy: • Intravitreal anti-vascular endothelial growth factor (VEGF) agents are often utilized to prevent and/or reduce the severity of radiation retinopathy and its associated visual loss. (Level of Evidence: ranibizumab II65, 66 bevacizumab IV67-70, Strength of Recommendation: B) **Comment:** Continuous anti-VEGF should be started at the earliest sign of radiation retinopathy.	**Endorsed with comment**
Genetic Prognostic Testing	

1. All patients should be offered GEP or monosomy 3 and 8 testing to provide information on survival prognosis. This will also guide systemic follow-up and consideration for inclusion in clinical trials for patients at high risk of metastases (Figure 2, Table 2). (Level of Evidence: III71, 72 IV22, 73-75, Strength of Recommendation: B) **Comment:** If known (i.e., biopsy performed on original lesion), tumour variants in genes with established prognostic significance (BAP1, SF3B1 and EIF1AX) should be reported. Additionally, tumour variants in GNAQ, GNA11, CYSLTR2, PLCB4, and MBD4 may be reported. There is limited evidence comparing the different approaches to molecular risk stratification of uveal melanoma. Implementation should be done in conjunction with available evidence and clinical expert opinion. According to the Ontario Hereditary Cancer Testing Eligibility Criteria, patients with a history of uveal melanoma should be referred to genetics for familial melanoma genetic testing.	**Endorsed with comment**
Management of Patients with Metastatic Disease and High-Risk Patients	
1. Currently there is no strong evidence to treat high-risk patients (monosomy 3 and 8q gain, GEP 2, or tumours >9 mm thick) without identified metastasis with adjuvant treatments to reduce the risk of disease recurrence. However, the use of systemic therapy as adjuvant treatment to enucleation or definitive radiation is an active focus of research, and consideration for enrollment in clinical trials is warranted where possible. (Level of Evidence: IV76, Strength of Recommendation: B) **Comment:** High-risk patients include monosomy 3 and 8q gain, GEP 2, tumours >9 mm thick, and stage III or higher. Mutational analysis by NGS should also be considered. If known, GNAQ, GNA11, CYSLTR2, PLCB4, BAP1, SF3B1, MBD4 and EIF1AX mutations found in metastatic lesions should be reported.	**Endorsed with comment**

2. Systemic therapy for the management of metastases: • When possible, enrollment in a clinical trial is recommended. • A phase III clinical trial comparing treatment with tebentafusp against investigator's choice chemo-/immunotherapy in advanced uveal melanoma patients with positive HLA-A 02:01 haplotype achieved its primary end point of OS in the intent-to-treat population with a hazard ratio (HR) of 0.51 (95% CI, 0.36-0.71; p<0.0001), favouring tebentafusp over investigator's choice of therapy (1-year OS 73 vs 59% median OS 22 vs 16 months) (Level of Evidence: I20, Strength of Recommendation: A) A prospective, non-comparative phase II clinical trial demonstrated an overall response rate (ORR) of 18% and a median OS of 19.1 months in a cohort of patients treated with the combination of ipilimumab and nivolumab. (Level of Evidence: ipilimumab and nivolumab II77, Strength of Recommendation: B) • Objective tumour responses have been documented with the use of pembrolizumab and nivolumab as monotherapy. (Level of Evidence: pembrolizumab III78 nivolumab II79, Strength of Recommendation: B) • Outside of a clinical trial, the routine use of palliative cytotoxic chemotherapy is not recommended; the use of chemotherapy for the treatment of patients with metastatic ocular melanoma is associated with very low objective response rates and has never been shown to extend OS. (Level of Evidence: I80, 81 II82-98, Strength of Recommendation: D) **Comment:** Review by a multidisciplinary team, including medical oncology, radiation oncology, surgery, pathology, and interventional radiology familiar with the best treatment recommendations for uveal melanoma, including available clinical trials.	**Endorsed with comment**
3. Surgical resection of solitary/oligo liver metastasis may offer benefit in highly selected patients; most patients who present with metastatic disease present with diffuse involvement of the liver and therefore, do not qualify for surgical resection. (Level of Evidence: III99 IV100, 101, Strength of Recommendation: C) **Comment:** Surgical options should be discussed at a multidisciplinary case conference with a liver surgeon, interventional radiologist, medical oncologist, and radiation oncologist present.	**Endorsed with comment**

4. Ablative techniques (i.e., thermoablation, radioembolization) are used in the setting of metastatic uveal melanoma, with higher-quality evidence in support of radioembolization. (Level of Evidence: II102 IV103 V104, 105, Strength of Recommendation: C) **Comment:** Loco-regional therapy options, including ablation, trans-arterial therapies, and radiotherapy should be discussed at a multidisciplinary case conference with a liver surgeon, interventional radiologist, medical oncologist, and radiation oncologist present.	**Endorsed with comment**
Surveillance Following Definitive Local Therapy	
1. Patients with GEP class 1a or 1b, or disomy 3 (monosomy 3 negative or undetected) OR patients with no genetic assessment and tumour ≤9 mm thick: (Level of Evidence: V, Strength of Recommendation B) • Liver U/S: annually for up to 10 years. • Physical exam: annually, for up to 10 years. • Follow-up may be transitioned to the family physician at 5 years. **Comment:** Low-risk patients include patients with GEP class 1a or 1b, or disomy 3 (monosomy 3 undetected), no 8q gain OR patients with no genetic assessment and stage I or II. Patients should receive a liver ultrasound or MRI annually for 10 years and then as clinically indicated.	**Endorsed with comment**
2. Patients with GEP class 2, monosomy 3 (monosomy 3 positive or detected), OR tumours >9 mm thick with no genetic assessment: (Level of Evidence: V, Strength of Recommendation B) • Physical exam: annually, indefinitely • Imaging every six months consisting of an annual liver U/S alternating with annual MRI liver for ten years. If body habitus limits U/S, consideration for other modalities should be given. • Follow-up may be transitioned to the family physician at 5-10 years. **Comment:** High-risk patients include patients with GEP class 2, monosomy 3 (monosomy 3 detected), 8q gain, OR stage III or IV with no genetic assessment. Patients should receive a liver MRI every 3-6 months for the first 5 years, and then every 6-12 months for the next 5 years, and then as clinically indicated.	**Endorsed with comment**

An Endorsement of the 2021 Cancer Care Alberta Clinical Practice Guideline on Uveal Melanoma

Section 2: Endorsement Methods Overview

BACKGROUND FOR GUIDELINE

Uveal melanoma, which includes melanoma of the iris, ciliary body, and choroid, is the most prevalent intraocular malignancy and second most prevalent location for melanoma [2,3]. The risk factors include Caucasian race, light eye and skin colour, cutaneous and iris nevi and freckles, an inability to tan, and exposure to arc welding and tanning beds [4-9]. Uveal melanoma has a 5-year survival rate of 62% and 10-year survival rate of 47% [10,11].

There is currently no Ontario-specific guideline in this area. The purpose of this endorsement document is to provide clinicians with evidence-based recommendations on the diagnosis and treatment of uveal melanoma.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Uveal Melanoma Guideline Development Group (GDG) (Appendix 1), which was convened at the request of the Cancer Care Integration and Disease Advisory Program (CIDAP) Program at Ontario Health (Cancer Care Ontario). The project was led by a small Working Group of the Uveal Melanoma GDG, which was responsible for reviewing the evidence base and recommendations in version 2 of the CCA Clinical Practice Guideline on Uveal Melanoma in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in ocular oncology, surgical oncology, medical oncology, radiation oncology, interventional radiology, pathology, and patient advocacy. Other members of the Uveal Melanoma GDG served as the External Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1 and were managed in accordance with the Ontario Health (Cancer Care Ontario) Conflict of Interest Policy.

ENDORSEMENT METHODS

CIDAP endorses guidelines using the process outlined in OH (CCO)'s Guideline Endorsement Protocol [12]. This process includes selection of a guideline, assessment of the recommendations (if applicable), drafting the endorsement document by the Working Group, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

CIDAP assesses the quality of guidelines using the AGREE II tool [13]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

Selection of Guidelines

As a first step in developing this document, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. A literature search in Google was performed in February 2022 with the search terms "guideline + uveal melanoma + Canada". Only one organizational guideline was found.

Assessment of Guideline

The working group selected the 2021 CCA Uveal Melanoma Guideline as it provides evidence-based recommendations for the diagnosis, treatment, and follow-up of uveal melanoma [1]. In addition, the rigour of development domain, which assesses the methodological quality of the guideline, had a high score.

Details of the AGREE II assessment can be found in Appendix 2. The overall quality of the guideline was rated a 6 on a scale from 1 to 7 by both appraisers. Both appraisers recommended this guideline for use. The AGREE II average quality ratings for the individual domains were varied; scope and purpose received a score of 100%, stakeholder involvement received a score of 61%, rigor of development received a score of 72%, clarity of presentation received a score of 81%, applicability received a score of 56%, and editorial independence received a score of 92%.

DESCRIPTION OF ENDORSED GUIDELINE

The 2021 CCA Clinical Practice Guideline on Uveal Melanoma provides updated recommendations on the diagnosis, treatment, and follow-up of patients with uveal melanoma. The guideline was updated by the Alberta Provincial Cutaneous Tumour Team, which included representation from surgical oncology, radiation oncology, medical oncology, dermatology, nursing, pathology, and pharmacy [1].

For the Alberta guideline update, PubMed was searched for literature published after the release of the first version of the guideline (2014 to March 2021) [1]. The results were limited to clinical trials (phase II and III), prospective studies, systematic reviews, meta-analyses, and clinical practice guidelines in humans 19 years of age and older published in English. Evidence was selected and reviewed by a working group made up of members of the Provincial Cutaneous Tumour Team, external participants identified by the working group, and a methodologist. Additional details about the development and update of guidelines can be found at albertahealthservices.ca.

ENDORSEMENT PROCESS

The Working Group reviewed each recommendation from the 2021 CCA Uveal Melanoma Guideline to determine whether it could be endorsed, endorsed with changes, or rejected. This determination was based on the agreement of the Working Group with the interpretation of the available evidence presented in the guideline, and whether the recommendation was applicable and acceptable to the Ontario context, whether it was feasible for implementation, and whether new evidence reported since the guideline was developed might change any of the recommendations.

For reach recommendation, the Working Group considered the following issues:

1) Does the Working Group agree with the interpretation of the evidence and the justification of the original recommendation?
2) Are modifications required to align with the Ontario context?
3) Is it likely there is new, unidentified evidence that would call into question the recommendation?
4) Would additional statements of qualification/clarification be valuable in Ontario?

ENDORSEMENT REVIEW AND MODIFICATIONS

Thirteen of the thirty-one recommendations were endorsed without modifications or comments. Eighteen of the thirty-one recommendations were endorsed with comments, as listed in Table 2-1 (see Section 1, Table 1-1 for a list of all 31 recommendations).

Table 2-1. AHS uveal melanoma guideline recommendations [1]

Recommendations	Assessment
Diagnosis and Work-Up	
1. All intraocular malignancies and indeterminate lesions should be evaluated by a provider trained in all aspects of care (i.e., medical, oncologic, surgical, radiotherapy [RT], laser therapy [e.g., transpupillary thermotherapy]) to determine appropriate follow-up and/or treatment. (Level of Evidence: V24-26, Strength of Recommendation: B) **Comment:** Intraocular malignancies and indeterminate lesions should be assessed by an ophthalmologist with expertise in uveal melanoma. Once an intraocular malignancy has been diagnosed, a multidisciplinary team should assess the patient.	**Endorsed with comment**
3. Complete ophthalmic examination and fundoscopy. • A baseline fundus photograph of adequate quality and an objective assessment of lesion height is required for all melanocytic lesions.	**Endorsed**
5. Ancillary ocular studies, if ophthalmic examination is inconclusive, sometimes due to media opacity. (Level of Evidence V30-32, Strength of Recommendation: B) • Fluorescine and/or Indocyanin green angiography of the retina and choroidal vasculature is helpful in select cases (requires clear media for visualization). • Computed tomography (CT) of the eye is rarely needed. • Magnetic resonance imaging (MRI) of the eye is rarely needed. **Comment:** Optical Coherence Tomography can differentiate amelanotic melanoma from simulating lesions, can detect subtle subretinal fluid, and retinal changes over choroidal tumours.	**Endorsed with comment**

6. Staging work-up to rule out metastases for patients diagnosed with uveal melanoma.
• Serum testing
  o Complete blood count (CBC)
  o Liver function tests (LFTs)
• Diagnostic imaging should aim to reduce unnecessary radiation.
  o All patients should receive a baseline Primovist-enhanced abdominal MRI and ultrasound (U/S) of the liver and non-contrast enhanced CT scan of the chest.
  o Or whole-body positron emission tomography (PET)/CT scan and ultrasound of the liver. (Level of Evidence: III33 IV34, Strength of Recommendation: B)
  o If there is a suspicion of metastases, refer to a tertiary cancer centre.
 	
Comment: After treatment of the primary lesion, all patients should receive baseline imaging, including a computed tomography (CT) of the chest and contrast-enhanced magnetic resonance imaging (MRI) of the liver. If MRI is not possible, ultrasound of the liver by trained personnel may be performed.
 	
If there is suspicion of metastases, patients should be referred to a tertiary cancer centre with expertise in uveal melanoma.
	Endorsed with comment

Primary Management	
Melanocytic Choroid Tumours	
2. Medium/intermediate (3-12 mm in thickness) tumours are typically treated with ocular brachytherapy. (Level of Evidence: I44-48, Strength of Recommendation: A) • Enucleation is sometimes chosen by patients who cannot make the follow-up visits required post brachytherapy. **Comment:** Tumours that significantly encroach over the optic disc can be treated with external beam radiotherapy.	**Endorsed with comment**

3. Large (>12 mm in thickness) tumours • Due to the risk of severe vision loss and neovascular glaucoma secondary to radiation complications with large lesions, large lesions are offered enucleation or brachytherapy (if standard dosing can be achieved with brachytherapy). o Many centres offer enucleation for very large tumors greater than 12 mm in thickness and 18 mm in maximal width. (Level of Evidence: IV49-52, Strength of Recommendation: B) o Brachytherapy for very large lesions (>12 mm thick or >18 mm in maximal basal dimension) is sometimes performed in select cases such as contralateral vision loss or in patients who insist on avoiding enucleation. (Level of Evidence: V24, Strength of Recommendation: C) • Neo-adjuvant pre-enucleation radiation does not provide a clinically or statistically meaningful difference in mortality rates. (Level of evidence: I53, Strength of recommendation: E) **Comment:** Tumour resection followed by low-dose brachytherapy may be indicated for large tumours involving single eyed patient to avoid the sight damaging effect of high dose brachytherapy. In extremely rare situations, enucleation may be chosen by patients who cannot attend brachytherapy follow-up visits.	**Endorsed with comment**
Principles of Complete Assessment	
2. Adequate photographic imaging requires: • The entire lesion and the adjacent normal structures need to be photographed. Otherwise, growth cannot be truly assessed. o In addition, a photograph of the entire lesion including the fovea and the optic nerve is recommended (but not required) to ensure reproducibility of the landmarks adjacent to the lesion. • Some very anterior choroidal lesions and ciliary body lesions cannot be photographed in the entirety due to technical limitations in current imaging technology. • The lesion needs to be in focus, and appropriate exposure levels in the baseline and follow-up imaging allowing for assessment of change over time need to be obtained. • If adequate imaging cannot be obtained, referral to a specialist capable of performing a complete assessment is required. • If two or more risk factors are present or any change or growth is noted, referral to a subspecialist ocular oncologist is recommended. **Comment:** A referral should be made to an ophthalmologist with expertise in ocular malignancy.	**Endorsed with comment**
Principles of Enucleation	

3. For patients undergoing enucleation, in accordance with the College of American Pathologists' Protocol for the Examination of Specimens from Patients with Uveal Melanoma,60 review of specimens should include reporting of the following elements: • Specimen laterality • Tumour site: iris, ciliary body, choroid • Largest basal diameter and thickness • Scleral and optic nerve invasion • Extraocular extension • Histologic type: spindle, mixed, epithelioid • Mitotic count • Vascular invasion • Extravascular matrix pattern • Inflammatory cells/tumour infiltrating lymphocytes and macrophages • Invasion of Bruch's membrane • Margins • Regional lymph nodes • Pathologic stage classification (pTNM, AJCC 8th Edition) Molecular results (if known): o Chromosome 3 and 8 loss/gain o BAP1 status o Gene expression profile (GEP) o Multiplex ligation dependent probe amplification (MLPA) analysis • Additional pathologic findings **Comment:** Further molecular profiling results may aid diagnosis, risk assessment and management. Additional molecular results may also include reporting of GNAQ, GNA11, SF3B1, EIF1AX, PLCB4, CYSLTR2 and MBD4 tumour variants, if available. There is limited evidence comparing the different approaches to molecular risk stratification of uveal melanoma. Implementation should be done in conjunction with available evidence and clinical expert opinion.	**Endorsed with comment**
Principles of Primary Radiotherapy (RT)	
1. Episcleral brachytherapy is the most commonly utilized treatment for uveal melanoma worldwide and is the treatment of choice in Alberta. **Comment:** Episcleral brachytherapy is the most commonly utilized treatment for uveal melanoma worldwide and is the treatment of choice in Ontario.	**Endorsed with comment**
Adjuvant Local Therapy	

1. Positive margins post excision: • If margins are positive or indeterminate after resection, adjunctive plaque brachytherapy RT of the surgical margins is often utilized. **Comment:** After resection, irrespective of margins, all patients should receive adjunctive plaque brachytherapy RT.	**Endorsed with comment**
2. Transpupillary thermotherapy (TTT): • TTT uses an infrared laser administered through a dilated pupil for choroidal lesions. • TTT as a primary treatment has been associated with a relatively high rate of local recurrence, especially when the tumour abuts the optic nerve and overhangs the optic disc. Therefore, TTT is not recommended as monotherapy for uveal melanoma in the standard case. (Level of Evidence: II61 IV62, Strength of Recommendation: D) • TTT can be offered as an adjunctive treatment to reduce the risk of local recurrence following RT or as a primary treatment for medium risk nevi in select cases. (Level of Evidence: IV63, 64, Strength of Recommendation: C) • TTT is used in some centers to treat marginal recurrence post brachytherapy. (Level of evidence: IV64, Strength of Recommendation: C) • TTT can cause retinal vascular damage and retinal traction and subsequent secondary visual loss. **Comment:** In Ontario, TTT is not recommended as a primary treatment for medium risk benign nevi.	**Endorsed with comment**
3. Radiation retinopathy: • Intravitreal anti-vascular endothelial growth factor (VEGF) agents are often utilized to prevent and/or reduce the severity of radiation retinopathy and its associated visual loss. (Level of Evidence: ranibizumab II65, 66 bevacizumab IV67-70, Strength of Recommendation: B) **Comment:** Continuous anti-VEGF should be started at the earliest sign of radiation retinopathy.	**Endorsed with comment**
Genetic Prognostic Testing	

1. All patients should be offered GEP or monosomy 3 and 8 testing to provide information on survival prognosis. This will also guide systemic follow-up and consideration for inclusion in clinical trials for patients at high risk of metastases (Figure 2, Table 2). (Level of Evidence: III71, 72 IV22, 73-75, Strength of Recommendation: B) **Comment:** If known (i.e., biopsy performed on original lesion), tumour variants in genes with established prognostic significance (BAP1, SF3B1 and EIF1AX) should be reported. Additionally, tumour variants in GNAQ, GNA11, CYSLTR2, PLCB4, and MBD4 may be reported. There is limited evidence comparing the different approaches to molecular risk stratification of uveal melanoma. Implementation should be done in conjunction with available evidence and clinical expert opinion. According to the Ontario Hereditary Cancer Testing Eligibility Criteria, patients with a history of uveal melanoma should be referred to genetics for familial melanoma genetic testing.	**Endorsed with comment**
Management of Patients with Metastatic Disease and High-Risk Patients	
1. Currently there is no strong evidence to treat high-risk patients (monosomy 3 and 8q gain, GEP 2, or tumours >9 mm thick) without identified metastasis with adjuvant treatments to reduce the risk of disease recurrence. However, the use of systemic therapy as adjuvant treatment to enucleation or definitive radiation is an active focus of research, and consideration for enrollment in clinical trials is warranted where possible. (Level of Evidence: IV76, Strength of Recommendation: B) **Comment:** High-risk patients include monosomy 3 and 8q gain, GEP 2, tumours >9 mm thick, and stage III or higher. Mutational analysis by NGS should also be considered. If known, GNAQ, GNA11, CYSLTR2, PLCB4, BAP1, SF3B1, MBD4 and EIF1AX mutations found in metastatic lesions should be reported.	**Endorsed with comment**

2. Systemic therapy for the management of metastases: • When possible, enrollment in a clinical trial is recommended. • A phase III clinical trial comparing treatment with tebentafusp against investigator's choice chemo-/immunotherapy in advanced uveal melanoma patients with positive HLA-A 02:01 haplotype achieved its primary end point of OS in the intent-to-treat population with a hazard ratio (HR) of 0.51 (95% CI, 0.36-0.71; p<0.0001), favouring tebentafusp over investigator's choice of therapy (1-year OS 73 vs 59% median OS 22 vs 16 months) (Level of Evidence: I20, Strength of Recommendation: A) A prospective, non-comparative phase II clinical trial demonstrated an overall response rate (ORR) of 18% and a median OS of 19.1 months in a cohort of patients treated with the combination of ipilimumab and nivolumab. (Level of Evidence: ipilimumab and nivolumab II77, Strength of Recommendation: B) • Objective tumour responses have been documented with the use of pembrolizumab and nivolumab as monotherapy. (Level of Evidence: pembrolizumab III78 nivolumab II79, Strength of Recommendation: B) • Outside of a clinical trial, the routine use of palliative cytotoxic chemotherapy is not recommended; the use of chemotherapy for the treatment of patients with metastatic ocular melanoma is associated with very low objective response rates and has never been shown to extend OS. (Level of Evidence: I80, 81 II82-98, Strength of Recommendation: D) **Comment:** Review by a multidisciplinary team, including medical oncology, radiation oncology, surgery, pathology, and interventional radiology familiar with the best treatment recommendations for uveal melanoma, including available clinical trials.	**Endorsed with comment**
3. Surgical resection of solitary/oligo liver metastasis may offer benefit in highly selected patients; most patients who present with metastatic disease present with diffuse involvement of the liver and therefore, do not qualify for surgical resection. (Level of Evidence: III99 IV100, 101, Strength of Recommendation: C) **Comment:** Surgical options should be discussed at a multidisciplinary case conference with a liver surgeon, interventional radiologist, medical oncologist, and radiation oncologist present.	**Endorsed with comment**

4. Ablative techniques (i.e., thermoablation, radioembolization) are used in the setting of metastatic uveal melanoma, with higher-quality evidence in support of radioembolization. (Level of Evidence: II102 IV103 V104, 105, Strength of Recommendation: C) **Comment:** Loco-regional therapy options, including ablation, trans-arterial therapies, and radiotherapy should be discussed at a multidisciplinary case conference with a liver surgeon, interventional radiologist, medical oncologist, and radiation oncologist present.	**Endorsed with comment**
Surveillance Following Definitive Local Therapy	
1. Patients with GEP class 1a or 1b, or disomy 3 (monosomy 3 negative or undetected) OR patients with no genetic assessment and tumour ≤9 mm thick: (Level of Evidence: V, Strength of Recommendation B) • Liver U/S: annually for up to 10 years. • Physical exam: annually, for up to 10 years. • Follow-up may be transitioned to the family physician at 5 years. **Comment:** Low-risk patients include patients with GEP class 1a or 1b, or disomy 3 (monosomy 3 undetected), no 8q gain OR patients with no genetic assessment and stage I or II. Patients should receive a liver ultrasound or MRI annually for 10 years and then as clinically indicated.	**Endorsed with comment**
2. Patients with GEP class 2, monosomy 3 (monosomy 3 positive or detected), OR tumours >9 mm thick with no genetic assessment: (Level of Evidence: V, Strength of Recommendation B) • Physical exam: annually, indefinitely • Imaging every six months consisting of an annual liver U/S alternating with annual MRI liver for ten years. If body habitus limits U/S, consideration for other modalities should be given. • Follow-up may be transitioned to the family physician at 5-10 years. **Comment:** High-risk patients include patients with GEP class 2, monosomy 3 (monosomy 3 detected), 8q gain, OR stage III or IV with no genetic assessment. Patients should receive a liver MRI every 3-6 months for the first 5 years, and then every 6-12 months for the next 5 years, and then as clinically indicated.	**Endorsed with comment**

EXTERNAL EXPERT PANEL REVIEW AND APPROVAL

Feedback on the approved draft endorsement document was obtained from content experts from across Canada. The endorsement document was evaluated by an GDG Pan-Canadian Expert Panel of clinical content experts representing ocular oncology, medical oncology, radiation oncology, and pathology (Appendix 1).

For the endorsement document to be approved, 75% of the content experts who comprise the GDG Pan-Canadian Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. The Pan-Canadian Expert Panel may specify that approval is conditional, and that changes to the document are required.

Of the 5 members of the GDG Pan-Canadian Expert Panel, 5 members voted and 0 abstained, for a total of 100% response in June 2023. Of those who voted, 5 approved the document (100%). The main comments from the Pan-Canadian Expert Panel and the Working Group's responses are summarized in Table 2-2.

Table 2-2. Summary of the Working Group's responses to comments from the External Expert Panel

Comments	Responses
1. For comments, do we need to indicate strength of recommendations?	Guideline endorsements do not typically indicate strength of recommendations in the endorsement comments.
2. For initial diagnosis, patients are generally only seeing ophthalmologist with expertise in uveal melanoma, do we need more clarity for what's considered multidisciplinary team?	We reworded the comment to include an ophthalmologist with expertise in uveal melanoma. Multidisciplinary team has been left broad as it will vary by centre.
3. As the comment from diagnosis and work-up recommendation 3 is mentioned in recommendation 4, not sure it is needed.	We removed the comment, and the recommendation was endorsed as-is.
4. How important is the timing of the baseline imaging after treatment of the primary lesion? I feel it is ok to have the imaging done around the time of diagnosis or after initial treatment.	We did not change the comment as baseline imaging is completed after primary treatment because very few patients have metastatic disease at initial presentation.
5. For baseline imaging, should we just say contrast enhanced MRI of liver (Primovist is better than Gadolinium, but more difficult to access)?	We updated the comment to contrast-enhanced MRI of the liver rather than specifying gadolinium-enhanced MRI of the liver.
6. Do we have reference that baseline PET is not useful? Or is this statement due to radiation/resources?	We removed the sentence about PET from the comment because we felt that it does not offer optimal imaging.
7. For the primary management of melanocytic choroid tumours, tumours that significantly encroach over the optic disc can be treated with external beam proton or photon radiotherapy.	We did not amend the comment to specify proton or photon radiotherapy as the provincial government does not cover proton radiotherapy.
8. Patients with large (>12 mm in thickness) melanocytic choroid tumours may be candidates for proton therapy (or photon stereotactic) actually more than brachytherapy.	We did not change the comment as brachytherapy is better tolerated than proton or photon radiotherapy.
9. Selected patients with ciliary body lesions <12 mm thick and that do not have an extensive circumferential growth pattern can be considered for photon or proton external beam radiotherapy.	We did not change the comment as brachytherapy is better tolerated than proton or photon radiotherapy.
10. Patients with iris lesions are good candidates for proton therapy at centers with dedicated eye lines.	We did not change the comment as brachytherapy is better tolerated than proton or photon radiotherapy.

11. Not clear who is considered ocular oncologist? Most patients see ophthalmology with ocular malignancy expertise.	We added a comment updating the term ocular oncologist to "an ophthalmologist with expertise in ocular malignancy". The recommendation was changed from "endorsed" to "endorsed with comment".
12. Mitotic count, extravascular matrix pattern, inflammatory cells/tumour infiltrating lymphocytes and macrophages, invasion of Bruch's membrane are optional to report as per CAP.	We did not add a comment stating that mitotic count, extravascular matrix pattern, inflammatory cells/tumour infiltrating lymphocytes and macrophages, invasion of Bruch's membrane are optional as the working group felt they should be reported as they define the risk for metastasis.
13. I must say I do not understand this recommendation. In theory there are no primary endoresections in Canada. If resection post radiation, would not give radiation a second time to all patients. I do not see where in the recommendation positive margins post enucleation are addressed. Positive margin in the orbit post enucleation would typically be considered for adjuvant external radiotherapy.	We did not modify the comment because although rarely done in Canada, upfront resections are occasionally done for small anterior lesion in the USA.
14. For radiation retinopathy, add comment about continuous anti-VEGF. Patients with sub foveal melanomas carry the highest risk for radiation maculopathy and vision loss due to tumor location associated high radiation doses.	We added a comment clarifying that continuous anti-VEGF should be started at the earliest sign of radiation retinopathy.
15. Do we need to indicate when tissue should be available for genetic prognostic testing? Or this implies to discuss biopsy around the time of radiation procedure?	We did not change the comment because we felt it already covered this.
16. For genetic prognostic testing, the reality is that there is risk associated with biopsy and there are no adjuvant trials in Canada and there is no proven impact to changing the follow-up schedule. It would make more sense to have a recommendation such as "testing should be discussed with all patients" rather than "testing should be offered".	We did not amend the comment as there are neoadjuvant and adjuvant clinical trials starting that will impact how patients are followed.
17. I presume that it is normal that there is no cost-benefit consideration throughout the guidelines?	Most guidelines, including this one, does not incorporate cost-benefit considerations.
18. There is no statement as to when a patient should be tested for HLA haplotype?	We did not include specific treatment recommendations in the comment as they should be discussed during the multidisciplinary review.

19. The B recommendation for prospective, non-comparative phase II clinical trial on combination of ipilimumab and nivolumab seems like a higher grade than justified by the evidence for the HLA A0201 negative patients. It would be interesting to comment on the need (or lack there of) of BRAF testing.	We did not include BRAF testing to the comment because it is not currently mandated by the province and specific diagnostic tests can be discussed during the multidisciplinary review.
20. While routine use of chemotherapy in the palliative population is not recommended, it can be discussed in some patients following failure of immunotherapy if the patient understands the limitation of this approach.	We did not include specific treatment recommendations in the comment as they should be discussed during the multidisciplinary review.
21. Should we consider consult or multidisciplinary review for the management of metastases?	We updated the comment to "review by a multidisciplinary team, including medical oncology, radiation oncology, surgery, pathology and interventional radiology familiar with the best treatment recommendations".
22. Systematic testing for HLA0201 should be offered if tebentafusp is accessible and available as a therapeutic option.	We did not include specific treatment recommendations in the comment as they should be discussed during the multidisciplinary review.

DISSEMINATION AND IMPLEMENTATION

The endorsement document will be published on the OH (CCO) website. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice.

UPDATING THE ENDORSEMENT

CIDAP at Ontario Health (Cancer Care Ontario) will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for us in Ontario.

ACKNOWLEDGEMENTS

The Uveal Melanoma GDG would like to thank the following individuals for their assistance in developing this report:

- Sheila McNair from the Program in Evidence-Based Care (PEBC) for assisting the CIDAP with the guideline endorsement process
- CCA for collaborating with CIDAP to facilitate endorsement of the guideline

CONCLUSION

The final endorsed recommendations contained in Section 1 reflect the integration of feedback obtained through the internal review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel.

References

1. Weis E, Cheng T, Salopek T, Temple-Oberle C, Walker J, Surgeoner B. Uveal melanoma. Edmonton (AB): Cancer Care Alberta; 2021 Jun. Report No.: CU-015. Available from: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cu015-uveal-melanoma.pdf
2. Singh AD, Topham A. Survival rates with uveal melanoma in the United States: 1973-1997. Ophthalmology. 2003;110(5):962-5. Available from: https://doi.org/10.1016/s0161-6420(03)00077-0
3. Egan KM, Seddon JM, Glynn RJ, Gragoudas ES, Albert DM. Epidemiologic aspects of uveal melanoma. Surv Ophthalmol. 1988;32(4):239-51. Available from: https://doi.org/10.1016/0039-6257(88)90173-7
4. Gallagher RP, Elwood JM, Rootman J, Spinelli JJ, Hill GB, Threlfall WJ, et al. Risk factors for ocular melanoma: Western Canada Melanoma Study. J Natl Cancer Inst. 1985;74(4):775-8.
5. Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association of cutaneous and iris nevi with uveal melanoma: a meta-analysis. Ophthalmology. 2009;116(3):536-543.e2. Available from: https://doi.org/10.1016/j.ophtha.2008.10.008
6. Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association between host susceptibility factors and uveal melanoma: a meta-analysis. Arch Ophthalmol. 2006;124(1):54-60. Available from: https://doi.org/10.1001/archopht.124.1.54
7. Shah CP, Weis E, Lajous M, Shields JA, Shields CL. Intermittent and chronic ultraviolet light exposure and uveal melanoma: a meta-analysis. Ophthalmology. 2005;112(9):1599-607. Available from: https://doi.org/10.1016/j.ophtha.2005.04.020
8. Canadian Cancer Society. Eye Cancer. n.d. Available from: https://cancer.ca/en/cancer-information/cancer-types/eye
9. Weis E, Aghazadeh H, Roelofs K, Agi J. Sunlamp use is a risk factor for uveal melanoma: a meta-analysis. Can J Ophthalmol. 2021;57(2):105-111. Available from https://doi.org/10.1016/j.jcjo.2021.02.041
10. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci. 2003;44(11):4651-9. Available from: https://doi.org/10.1167/iovs.03-0538
11. Kath R, Hayungs J, Bornfeld N, Sauerwein W, Höffken K, Seeber S. Prognosis and treatment of disseminated uveal melanoma. Cancer. 1993;72(7):2219-23. Available from: https://doi.org/10.1002/1097-0142(19931001)72:7%3C2219::aid-cncr2820720725%3E3.0.co;2-j
12. Program in Evidence-Based Care. OH(CCO) guideline endorsement protocol; 2022 [updated 2022 Apr 22; cited 2023 May 10]. Available from: http://pebctoolkit.mcmaster.ca/doku.php?id=projectdev:cco_endorsement_protocol
13. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-E42. Available from: https://doi.org/10.1503/cmaj.090449

Appendix 1: Affiliations and Conflict of Interest Declarations

Table 1: Members of the Uveal Melanoma Guideline Development Group

Name	Affiliation	Conflict of Interest
Working Group		
Frances Wright Surgical Oncologist Ontario Skin Cancers Lead	Sunnybrook Health Sciences Centre Ontario Health (Cancer Care Ontario) Toronto, ON	Melanoma talk at William Osler. Funds donated to University of Toronto (U of T) from Novartis. Received donation from Merck for U of T endowed fund for General Surgical Oncology fellowship program.
Marcus Butler Medical Oncologist	Princess Margaret Cancer Centre Toronto, ON	Advisory board participation is reimbursed. Merck, Bristol-Myers Squibb, Immunocore, and Medison are marketing drugs that are the subject of this study. Novartis, Adaptimmune, EMD Serono, GSK, Genzyme, Sanofi, La Roche-Posay, Sun Pharma, Instil Bio, Iovance, Pfizer market products that are not the subject of this study. Safety Review Committees with Adaptimmune and GSK are concerning cell therapy products and are not the subject of this study. Honoraria for lectures from Merck, BMS, Novartis, Sanofi, Pfizer. Merck and BMS market products (pembrolizumab, nivolumab, ipilimumab) that are used for the treatment of metastatic uveal melanoma.
Robert Beecroft Interventional Radiologist	University Health Network Toronto, ON	None declared.
Annette Cyr Patient Advisor	Melanoma Network of Canada Oakville, ON	None declared.
Ian King Clinical Molecular Geneticist	University Health Network Toronto, ON	None declared.
Hatem Krema Ocular Oncologist	University Health Network Toronto, ON	None declared.
Norm Laperriere Radiation Oncologist	University Health Network Toronto, ON	None declared.
Guillaume Martel Surgical Oncologist	The Ottawa Hospital Ottawa, ON	None declared.
Michael Ong Medical Oncologist	The Ottawa Hospital Ottawa, ON	Received a consultation honorarium for ipilimumab and nivolumab for cutaneous melanoma from Bristol-Myers Squibb.

Sarah Courtney Senior Specialist, Care Integration and Disease Advisory Program (CIDAP)	Ontario Health (Cancer Care Ontario) Toronto, ON	None declared.
Expert Panel		
Rahima Jamal Medical Oncologist	University of Montreal Hospital Centre Montreal, QC	Participation on Iovance, Medison Pharma, Immunocore, Bristol-Myers Squibb, Merck advisory boards. PI on melanoma investigator-initiated trials with Merck and Iovance.
Zaid Saeed Kamil Dermatopathologist	University Health Network Toronto, ON	None declared.
Luis Guillermo Riveros Ocular Oncologist	Horizon Health Network Fredericton, NB	None declared.
David Roberge Radiation Oncologist	University of Montreal Hospital Centre Montreal, QC	Honoraria for presentations and advisory board participation with Accuracy. Honoraria, advisory board participation, and research support from AstraZeneca, Roche, Varian, Novocure, KK Pharma, and Recordati.
Xinni Song Medical Oncologist	The Ottawa Hospital Ottawa, ON	Advisory board meetings with Bristol-Myers Squibb, Novartis, Merck, and Medison.

Appendix 2: AGREE II Score Sheet

Domain	Item	Appraiser 1 Ratings[1]	Appraiser 2 Ratings[1]
1) Scope and Purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	7
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	7
Domain score[2] =	(42-6/42-6)*100 = 36/36*100 = 1*100 = **100%**	Score =	42
2) Stakeholder Involvement	4. The guideline development group includes individuals from all relevant professional groups.	5	7
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	2	2
	6. The target users of the guideline are clearly defined.	6	6
Domain score[2] =	(28-6/42-6)*100 = 22/36*100 = 0.6111*100 = **61.1%**	Score =	28
3) Rigor of Development	7. Systematic methods were used to search for evidence.	6	6
	8. The criteria for selecting the evidence are clearly described.	6	6
	9. The strengths and limitations of the body of evidence are clearly described.	6	5
	10. The methods for formulating the recommendations are clearly described.	6	5
	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	5	4
	12. There is an explicit link between the recommendations and the supporting evidence.	6	4
	13. The guideline has been externally reviewed by experts prior to its publication.	6	3
	14. A procedure for updating the guideline is provided.	6	7
Domain score[2] =	(86-16/112-16)*100 = 70/96*100 = 0.7292*100 = **72.3%**	Score =	86
4) Clarity of Presentation	15. The recommendations are specific and unambiguous.	6	5
	16. The different options for management of the condition or health issue are clearly presented.	6	4
	17. Key recommendations are easily identifiable.	7	7
Domain score[2] =	(35-6/42-6)*100 = 29/36*100 = 0.8056*100 = **80.6%**	Score =	35

5) Applicability	18. The guideline describes facilitators and barriers to its application.	2	2
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	7	6
	20. The potential resource implications of applying the recommendations have been considered.	3	3
	21. The guideline presents monitoring and/or auditing criteria.	6	6
Domain score[2] =	(35-8/56-8)*100 = 27/48*100 = 0.5625*100 = **56.3%**	Score =	35
6) Editorial Independence	22. The views of the funding body have not influenced the content of the guideline.	6	6
	23. Competing interests of guideline development group members have been recorded and addressed.	7	7
Domain score[2] =	(26-4/28-4)*100 = 22/24*100 = 0.9167*100 = **91.7%**	Score =	26
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	6	6
Overall Guideline Assessment	2. I would recommend this guideline for use.	Yes, with modifications	Yes, with modifications

[1]Rated on a scale from 1 to 7

[2]Domain score = (Obtained score – Minimum possible score) / (Maximum possible score – Minimum possible score)